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# Homologous recombination deficiency represents a new therapeutic strategy for breast cancer brain metastases

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BACKGROUND: Brain metastatic disease occurs in 10-30% of metastatic breast cancer cases. The incidence of brain metastases is increasing, yet overall survival remains < 2 years. Treatment of brain metastases is limited with current clinical practice centered on radiation, chemotherapy and surgery. Although these treatments may prolong survival in the short term, targeting oncogenic alterations in brain metastases may deliver a more sustained clinical benefit. In this multicenter study, we comprehensively characterized DNA and RNA alterations that aberrantly drive specific oncogenic pathway activity pertinent to breast cancer brain metastases (BCBM).
METHODS: RNA sequencing was performed on a cohort of patient-matched primary and resected brain metastatic tumours (45 patients; N=90 samples). Whole exome DNA sequencing (WXS) was performed for 18/45 patients (54 trios consisting of primary tumor, brain metastasis and matched normal tissue). An independent brain metastatic WXS cohort (N=21 patients) (PMID: 26410082) was also analysed resulting in a total of 39 patient samples. Recurrent somatic copy number alterations (SCNA), somatic single nucleotide variants (SNVs) and mutational signatures were identified from WXS data. Expressed gene fusions were detected computationally from RNA-Seq (N=45 cases)
RESULTS: Of the 45 BCBM patients, median age at diagnosis was 51 years [25, 67], median overall survival 57 months (range 18-255) with median brain metastases free survival 34 months (range 5-216).Clinical molecular subtype of the primary tumour included 13 ER+/HER2- (29%), 16 HER2+ (35.5%) and 16 TNBC (35.5%). Regions of significant recurrent amplifications and deletions in BCBM (N=39 patients) were identified in 4q12, 10q11.21, 8p11.23, 8q23.3 and 17q12 (FDR < 0.10). Recurrent expressed gene fusions identified in known cancer driver genes were associated with chromatin modification, MAPK and HER signaling pathways. Mutational signature analysis of SNVs identified signatures associated with ageing, mismatch repair and homologous recombination deficiency (HRD) mutational processes. The relative contribution of the HRD signature was significantly increased in brain metastases compared to matched primary tumour ($p < 0.05$). Concordantly increased HRD in the brain metastatic transcriptome was confirmed in these patients by gene set variation analysis (GSVA) of homologous recombination pathway genes from KEGG database in RNA-Seq data. Moreover, in the extended BCBM RNA-Seq (N=45 patients) GSVA pathway scores were elevated in brain metastases relative to primary tumours, validating the functional significance of altered DNA repair defects in brain metastases
CONCLUSIONS: Here, we report recurrent genetic drivers, supported by altered functional transcriptome, unique to brain metastasis that may have clinical implications for prognosis and treatment choice. Specifically, targeting defects in the homologous recombination repair mechanism may represent new therapeutic strategies and management opportunities for breast cancer brain metastases patients.

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# Where you live matters: Impact of economic, racial/ethnic, and racialized economic residential segregation on breast cancer survival

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**Background:**Racial and economic residential segregation remains a problem within the United States (US). Although advances in screening, detection, diagnosis, and treatment have reduced overall breast cancer mortality, well-documented socioeconomic and racial/ethnic survival disparities persist. The objective of this study was to analyze the effect of economic and racial/ethnic residential segregation as measured by the Index of Concentration at the Extremes (ICE) on breast cancer survival in South Florida.
**Methods:**Patients treated at our medical campus with stage I-IV breast cancer from 2005-2017 were identified from our local tumor registry. Census tracts were used as neighborhood proxies. Using 5-year estimates from the American Community Survey, 5 ICE variables were computed: economic (high vs. low), race/ethnicity (non-Hispanic White (NHW) vs. non-Hispanic Black (NHB) and NHW vs. Hispanic) and racialized economic (low-income NHB vs high-income NHW and low-income Hispanics vs. high-income NHW) segregation. ICE captures spatial socioeconmic and racial/ethnic segregation by literally mapping a critical dimension of social inequality not otherwise captured by metrics that characterize areas solely in terms of the proportion of the population at a specified socioeconomic level or identified as belonging to a particular racial/ethnic group. Random effects frailty models were conducted for all patients and then stratified by race/ethnicity controlling for sociodemographics, tumor characteristics, and NCCN-guideline appropriate treatment.
**Results:**The study population included 6,145 breast cancer patients. 52.6% were Hispanic, 26.3% were NHW, and 17.2% were NHB. After controlling for multiple covariates, those living in extreme economically disadvantaged neighborhoods had a statistically significant increased mortality compared to those living in more economically advantaged neighborhoods (HR: 1.58 95%CI: 1.29, 1.92, p<0.001), Table 1. Patients living in an economically disadvantaged NHB neighborhood also had a statistically significant increased mortality compared to those living in more economically advantaged NHW neighborhoods (HR: 2.0 95% CI: 1.54, 2.60, p<0.001). In race-stratified analyses, an NHW person living in a predominantly economically disadvantaged NHB neighborhood had increased mortality compared to a NHW person living in an economically advantaged NHW neighborhood (HR: 2.02 95%CI: 1.19-3.41, p< 0.0071) controlling for tumor subtype and NCCN-guideline appropriate treatment.
**Conclusion:**This is the first study to evaluate breast cancer survival by ICE, which identifies inequitable associations by conveying extreme concentrations of both economic deprivation/privilege and racial/ethnic segregation. Our study suggests that breast cancer survival disparities is partly influenced by extreme racial/ethnic and economic segregation. Even when accounting for sociodemographics, tumor characteristics, and NCCN-guideline appropriate treatment, survival disparities remained, suggesting potential social and environmental factors impacting survival. To address these disparities, effective interventions are needed that account for the social and environmental contexts in which cancer patients live and are treated.

**Table 1: Breast Cancer Hazard Ratio by Economic, Racial/Ethnic, and Racialized Economic Residential Segregation Residential Segregation**

| Type of Segregation (ICE) | Quartile | Model 1 | Model 2 | Model3 |
|---|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Economic Segregation | Q1 | 1.83 (1.1, 3.03)* | 1.64 (0.89, 3.02) | 1.58 (1.29, 1.92)* |
| Economic Segregation | Q2 | 2.36 (1.48, 3.76)* | 2.45 (1.38, 4.34)* | 1.44 (1.16, 1.79)* |
| Economic Segregation | Q3 | 1.16 (0.72, 1.8) | 1.08 (0.61, 1.9) | 1.16 (0.94, 1.44) |
| Economic Segregation | Q4 | 1 | 1 | 1 |
| NHB Segregation | Q1 | 1.6 (0.9, 2.84) | 1.42 (0.72, 2.82) | 1.41 (0.96, 2.07) |
| NHB Segregation | Q2 | 0.92 (0.52, 1.6) | 0.91 (0.47, 1.77) | 1 (0.68, 1.48) |
| NHB Segregation | Q3 | 0.61 (0.29, 1.26) | 0.85 (0.37, 1.94) | 0.82 (0.52, 1.31) |
| NHB Segregation | Q4 | 1 | 1 | 1 |
| Hispanic Segregation | Q1 | 1.38 (0.83, 2.28) | 1.13 (0.61, 2.08) | 1.36 (1.12, 1.66)* |
| Hispanic Segregation | Q2 | 79 (0.47, 1.32) | 0.74 (0.4, 1.38) | 0.86 (0.67, 1.08) |
| Hispanic Segregation | Q3 | 0.94 (0.59, 1.49) | 0.98 (0.57, 1.67) | 1.05 (0.86, 1.29) |
| Hispanic Segregation | Q4 | 1 | 1 | 1 |
| NHB Economic Segregation | Q1 | 2.68 (1.6, 4.47)* | 2.02 (1.09, 3.74) | 2 (1.54, 2.6)* |
| NHB Economic Segregation | Q2 | 1.85 (1.15, 2.97)* | 1.39 (0.79, 2.44) | 1.56 (1.22, 2.02)* |
| NHB Economic Segregation | Q3 | 1.2 (0.69, 2.07) | 1.09 (0.58, 2.06) | 1.19 (0.88, 1.6) |
| NHB Economic Segregation | Q4 | 1 | 1 | 1 |
| Hispanic Economic Segregation | Q1 | 1.91 (1.19, 3.07)* | 1.45 (0.83, 2.54) | 1.64 (1.24, 2.15)* |
| Hispanic Economic Segregation | Q2 | 1.45 (0.8, 2.62) | 1.06 (0.52, 2.17) | 1.44 (1.06, 1.96)* |
| Hispanic Economic Segregation | Q3 | 1.26 (1.73, 2.18) | 0.95 (0.49, 1.84) | 1.11 (0.8, 1.54) |
| Hispanic Economic Segregation | Q4 | 1 | 1 | 1 |
| Model 1: Adjusted for ICE, race/ethnicity, age, insurance | | | | |
| Model 2: Adjusted for Model 1 covariates plus receptor status, clinical stage | | | | |
| Model 3: Adjusted for Model 1 and 2 covariates plus stage appropriate treatment | | | | |
| Q1: Most disadvantaged neighborhoods; Q4: Reference: most advantaged neighborhoods.*p < 0.05 | | | | |

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Pembrolizumab versus chemotherapy for previously treated metastatic triple-negative breast cancer (KEYNOTE-119): Efficacy in patients with lung or liver metastases

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**Background:** KEYNOTE-119 (NCT02555657) is a randomized, open-label phase 3 study of pembrolizumab (pembro) monotherapy vs single-agent chemotherapy (chemo) in patients with previously treated metastatic triple-negative breast cancer (mTNBC). The results showed directionally favorable improvement in overall survival (OS) with pembro compared to chemo in patients with PD-L1−positive tumors, although statistical superiority was not demonstrated. The pembro treatment effect increased with PD-L1 enrichment, as measured by the combined positive score (CPS). Since treatment outcomes may vary by location of metastasis, we performed a retrospective, exploratory analysis to evaluate the efficacy of pembro vs chemo among patients with lung or liver metastasis at baseline enrolled in KEYNOTE-119.
**Methods:** Patients with centrally confirmed TNBC, 1-2 prior systemic treatments for metastatic disease, documented progression on most recent therapy and prior treatment with an anthracycline and/or taxane were randomized 1:1 to pembro 200 mg Q3W or single-agent chemo per investigator's choice of capecitabine, eribulin, gemcitabine, or vinorelbine (60% enrollment cap for each). Patients were stratified by PD-L1 status (CPS <1 vs ≥1) and history of prior neoadjuvant/adjuvant treatment vs de novo metastatic disease at initial diagnosis. Primary study end points were OS in patients with PD-L1 CPS ≥10, patients with CPS ≥1, and all patients.
**Results:** Overall, 622 patients were randomized in KEYNOTE-119 (pembro, n=312; chemo, n=310); median follow-up was 31 months at the April 11, 2019 data cutoff date. At baseline, 403 (65%) patients had lung metastasis and 173 (28%) had liver metastasis. Pembro did not improve OS vs chemo in patients with lung or liver metastases in the ITT population, although the HRs decreased as tumor PD-L1 expression increased, with the greatest benefit observed in patients with PD-L1 CPS ≥20 tumors (**Table**). Similar trends were observed for progression-free survival, objective response rate, and duration of response. In both treatment groups, presence of liver metastases at baseline was associated with shorter OS as compared to absence of liver metastases at baseline; this trend was not observed for lung metastases. Results should be interpreted with caution due to modest patient sample size in some subgroups.
**Conclusion:** Among patients with previously treated mTNBC who had lung or liver metastases for whom prognosis is typically poor, pembro monotherapy showed a benefit vs single-agent chemo in patients with increasing PD-L1 tumor enrichment. These findings are consistent with the results from the global study population.
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Table. Analysis of Overall Survival

| | | **ITT** | | | **CPS ≥1** | | | **CPS ≥10** | | | **CPS ≥20** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **N** | **Median, mo (95% CI)** | **HR (95% CI)** | **N** | **Median, mo (95% CI)** | **HR (95% CI)** | **N** | **Median, mo (95% CI)** | **HR (95% CI)** | **N** | **Median, mo (95% CI)** | **HR (95% CI)** |
| **Patients With Lung Metastases** | Pembro | 200 | 9.8 (7.4-11.7) | 0.99 (0.80-1.23) | 127 | 10.6 (8.1-12.5) | 0.85 (0.65-1.10) | 56 | 12.8 (9.3-17.2) | 0.80 (0.53-1.18) | 31 | 17.0 (11.7-27.1) | 0.55 (0.32-0.95) |
| | Chemo | 203 | 11.4 (8.7-13.1) | | 131 | 10.4 (7.2-12.7) | | 63 | 11.9 (7.3-14.9) | | 34 | 13.0 (7.2-15.8) | |
| **Patients Without Lung Metastases** | Pembro | 112 | 10.3 (8.3-13.6) | 0.92 (0.69-1.23) | 76 | 10.8 (8.9-15.7) | 0.89 (0.63-1.26) | 40 | 12.1 (8.6-16.4) | 0.79 (0.47-1.31) | 26 | 12.8 (7.8-23.0) | 0.63 (0.32-1.24) |
| | Chemo | 107 | 10.2 (7.2-12.7) | | 71 | 9.9 (7.0-13.5) | | 35 | 11.3 (7.0-15.7) | | 18 | 10.5 (5.2-15.7) | |
| **Patients With Liver Metastases** | Pembro | 87 | 6.5 (4.7-9.3) | 1.04 (0.76-1.43) | 57 | 7.7 (4.2-9.9) | 1.02 (0.69-1.51) | 24 | 10.3 (6.2-16.4) | 0.78 (0.44-1.39) | 13 | 10.7 (6.2-19.0) | 0.69 (0.31-1.53) |
| | Chemo | 86 | 6.5 (5.4-8.4) | | 54 | 6.5 (5.4-7.8) | | 31 | 7.2 (5.2-11.6) | | 20 | 7.5 (2.9-14.7) | |
| **Patients Without Liver Metastases** | Pembro | 225 | 10.9 (9.2-12.6) | 0.95 (0.78-1.17) | 146 | 12.4 (10.5-14.2) | 0.82 (0.64-1.05) | 72 | 13.0 (10.1-17.2) | 0.80 (0.55-1.16) | 44 | 16.0 (11.4-27.1) | 0.57 (0.33-0.95) |
| | Chemo | 224 | 12.6 (10.6-13.9) | | 148 | 12.6 (9.8-13.6) | | 67 | 12.7 (9.8-15.8) | | 32 | 14.3 (8.3-16.8) | |

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# Towards personalized medicine - patient-derived breast tumor grafts as predictors of relapse and response to therapy. Preliminary results

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**Background:** Predicting the risk of relapse in patients with non-metastatic breast cancer is important for medical decisions and patient counseling. For patients who receive neoadjuvant chemotherapy, pathologic response and especially pathologic complete response (pCR) has been associated with risk of relapse; however this association is imperfect. Our prior work in patient-derived xenograft (PDX) models indicated that tumor engraftment in mice correlated with risk of recurrence. To understand further the prognostic utility of PDX, we designed a prospective clinical trial to determine the correlation between PDX generation with residual disease following neoadjuvant chemotherapy and relapse. Preliminary data are presented.
**Methods:** Women with newly diagnosed non-metastatic hormone receptor low-positive (HR-low, ER and/or PR ≤ 10%) or negative breast cancer planned to receive systemic chemotherapy prior to definitive surgery were eligible. Tumor tissue at diagnosis was orthotopically implanted in NOD/SCID mice. The primary objective of the study is to correlate the ability of a tumor to engraft in mice with pathologic responses and clinical outcomes.
**Results:** Between 12/2016 and 2/2020, 58 patients enrolled (triple negative breast cancer (TNBC), n=37; HR-low or negative/Her2+, n=11; or HR-low/Her2-, n=8; mixed, n=1). PDXs were successfully established from 16 patients. Patients uniformly received intensive preoperative chemotherapy per standard of care.
Among the 12 patients whose tumors engrafted in mice (PDX(+)) and underwent surgery, the pCR rate was 41.7%. In the subgroup of patients with postoperative follow up >6 months (n=9), 3 patients had achieved a pCR, 1 of whom recurred; and 6 patients had residual disease, 3 of whom recurred (overall relapse rate 44.4%). All patients who relapsed (TNBC n=3; HR-low/Her2- n=1), experienced a very early relapse (<12 months) after their definitive surgery. Disease progressed to metastatic during preoperative chemotherapy in one patient and 2 patients with residual disease relapsed while on adjuvant capecitabine. One patient experienced an early relapse despite having achieved a pCR. Patients who relapsed, died of breast cancer ≤1 year after diagnosis; the only surviving patient has not reached this landmark yet.
Among the 38 patients whose tumors did not engraft (PDX(-)) and underwent surgery, the overall pCR rate was 60.6%. In the subgroup of patients with postoperative follow up >6 months (n=30), 18 patients had achieved a pCR of whom none recurred, and 12 had residual disease of whom 1 patient (with TNBC) had locoregional recurrence 35.1 months after her definitive surgery (relapse rate 3.3%). She underwent repeat surgery followed by radiation therapy and 5.5 months after her recurrence, she remains disease-free.
Achievement of pCR was not statistically different between the PDX(+) and PDX(-) group. In the entire cohort, the presence of residual disease was associated with high risk of relapse (22.2%) as compared to the achievement of pCR (4.8%, $p = 0.16$). However, successful tumor engraftment was associated not only with a higher risk of relapse (44.4% vs 3.3%, $p = 0.0068$, odds ratio 20.45), but also an early and exceptionally aggressive relapse.
**Conclusion.** Our functional studies not only identify a patient population with a high risk of relapse with greater precision than the achievement of pCR, but also identify patients whose relapse has a particularly aggressive natural history. We established models that recapitulate this aggressive disease and in-depth genomic studies are underway. These studies will lead us to better patient stratification on the basis of risk of relapse and novel therapeutic strategies focused on patients with exceptionally aggressive breast cancers that our current diagnostic methods cannot identify.

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Comprehensive genomic profiling (CGP) of metastatic invasive lobular carcinomas reveals heterogeneity in immune biomarkers and resistance alterations across biopsy sites

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**Introduction** Metastatic breast cancer is a clinically challenging disease with poor outcomes. Invasive lobular carcinoma (ILC) is a rarer subtype of breast cancer with distinct patterns of metastasis, including frequent GI and female reproductive (FR) metastases (mets). Due to their relative rarity, little is known about the genomic characteristic of ILC across met sites. Here we explore the genomic landscape of 1909 ILC, stratified by met site, with an examination of immune checkpoint inhibitor (ICPI) biomarkers, therapeutic alterations, and resistance mutations.
**Methods** CGP was carried out at Foundation Medicine with hybrid capture for exons from up to 395 cancer-related genes plus select introns from up to 31 genes (PMID 24142049). Tumor mutational burden (TMB) was determined on 0.8-1.1 Mb (PMID: 28420421). Ventana PD-L1 IC staining (SP142; positive >= 1% staining) was available for a subset of samples. 1071 breast-biopsied and 1909 met-biopsied ILC and 6926 breast-biopsied and 1901 met-biopsied IDC were available for analysis.
**Results** High TMB (>= 10 muts/mb) and PD-L1 IC staining are associated with response to ICPI. ILC mets overall had a greater rate of high TMB relative to IDC mets (21% v 9%, p = 7E-25) and breast-biopsied (breast) ILC (21% v 10%; p = 9E-15) with the highest frequency in GI (23%) and skin (21%). PD-L1 IC+ rates were lower in ILC mets (18%) relative to IDC mets (34%) and breast ILC (31%), but were variable across sites, with relatively high rates of positivity in GI (48%), skin (29%), and FR (18%) mets, and no positive staining in bone mets (0/37).
Alterations in *PIK3CA* were higher in ILC mets (58%) relative to IDC mets (34%) and generally exhibited a similar frequency across ILC met sites, with modestly lower prevalence in skin (48%, p = 0.005). Pathogenic alterations in *BRCA1/2* were observed in 4.8% of ILC mets overall, with a lower frequency in GI mets (1.3%, p = 0.03).
A comparison of ILC breast biopsies to ILC mets revealed 19 genes with higher prevalence in at least one ILC met site, most with known roles in therapy resistance (eg *ESR1, NF1, RB1, KRAS, ERBB2, BRAF*), though significant heterogeneity was observed across sites. Met-enriched (ME) alterations were highest in ILC from the liver (71%) and lowest in FR (33%). *ERBB2* mutations, which are may be targetable with HER2 kinase inhibitors, were predominantly found in liver mets (21%) with significantly lower prevalence in skin (11%), bone (10%), GI (3%), and FR (3%). *ESR1* alterations were common in most ILC sites, with the highest prevalence in liver (26%) and low frequency in FR (4%). While FR ILC harbored few ME alterations, the rare alterations were primarily found in NF1 (5%) and NCOR1 (5%).
**Conclusions** CGP revealed significant heterogeneity in ILC mets across tissues. ICPI biomarkers were variable across sites with the highest frequency in ILC GI mets, offering additional potential treatment avenues for these tumors. Alterations in *PIK3CA* were common in ILC mets with high prevalence across sites, suggesting utility for *PIK3CA* inhibitors. Therapy-resistant alterations were common in ILC mets but varied across sites. Notably, *ERBB2 alterations* were most prevalent in ILC liver mets, but less common at other sites.
The high prevalence of therapeutic and resistance alterations suggests value in profiling metastatic lesions.

| | **breast_ILC** | **met_ILC** | **breast_IDC** | **met_IDC** | **gi_ILC** | **liver_ILC** | **female_repr_ILC** | **bone_ILC** | **skin_ILC** |
|---|---|---|---|---|---|---|---|---|---|
| sample count (N) | 1071 | 1909 | 6926 | 1901 | 154 | 639 | 114 | 268 | 199 |
| **ICPI biomarker** | | | | | | | | | |
| TMB-H (>=10muts/mb) | 10.2% | 21.0% | 4.4% | 9.2% | 23.4% | 18.9% | 14.0% | 19.0% | 21.1% |
| PDL1-IC+ SP142 (subset) | 31.5% (39/124) | 17.8% (38/213) | 57.3% (480/837) | 34.2% (54/158) | 47.6% (10/21) | 11.6% (8/69) | 18.2% (2/11) | 0% (0/37) | 28.6% (6/21) |
| **Therapy Associated** | | | | | | | | | |
| PIK3CA | 50.0% | 57.6% | 29.3% | 34.3% | 59.1% | 57.3% | 62.3% | 60.1% | 48.2% |
| BRCA1/2 | 4.9% | 4.8% | 9.2% | 7.7% | 1.3% | 4.1% | 7.0% | 5.2% | 5.5% |
| **Met-Enriched** | | | | | | | | | |
| ESR1_mut | 3.8% | 18.3% | 2.2% | 17.0% | 20.8% | 25.5% | 3.5% | 11.9% | 7.5% |
| ERBB2_mut | 9.7% | 12.5% | 2.0% | 2.7% | 3.2% | 20.7% | 2.6% | 9.7% | 11.1% |
| ARID1A_mut | 7.5% | 12.2% | 4.0% | 5.5% | 14.3% | 11.4% | 7.9% | 9.0% | 10.6% |
| NF1_mut | 4.4% | 8.7% | 3.5% | 4.2% | 5.8% | 8.5% | 5.3% | 10.4% | 8.0% |
| RB1_mut | 2.7% | 6.3% | 4.3% | 3.5% | 7.8% | 5.9% | 2.6% | 4.5% | 11.6% |
| KRAS | 2.3% | 5.5% | 3.9% | 3.6% | 5.2% | 6.7% | 2.6% | 6.3% | 2.0% |
| PTEN_del | 3.1% | 4.1% | 5.7% | 4.7% | 1.9% | 4.7% | 4.4% | 1.9% | 8.0% |
| FGFR2 | 0.7% | 3.1% | 2.9% | 2.6% | 1.3% | 4.1% | 1.8% | 4.1% | 2.0% |
| NCOR1_mut | 1.2% | 2.9% | 1.1% | 1.1% | 3.2% | 3.0% | 5.3% | 1.9% | 1.0% |
| SMAD4 | 2.0% | 2.9% | 1.2% | 1.9% | 1.9% | 4.7% | 1.8% | 2.6% | 1.5% |
| BRAF | 1.6% | 2.1% | 1.2% | 1.4% | 0.0% | 1.4% | 2.6% | 4.5% | 2.5% |
| FOXP1_mut | 0.4% | 1.6% | 0.3% | 0.3% | 2.6% | 1.1% | 0.0% | 1.9% | 1.0% |
| APC_mut | 0.9% | 1.4% | 1.1% | 1.1% | 0.6% | 0.6% | 1.8% | 3.4% | 2.0% |
| SOX9 | 0.3% | 1.3% | 0.5% | 0.4% | 0.0% | 1.1% | 0.0% | 1.5% | 0.5% |
| CASP8_mut | 0.0% | 0.8% | 0.5% | 0.5% | 0.0% | 1.1% | 0.9% | 1.1% | 1.0% |
| PTPN11_mut | 0.1% | 0.7% | 0.2% | 0.3% | 0.0% | 0.6% | 1.8% | 1.5% | 1.0% |
| TERT_mut | 0.2% | 0.6% | 0.4% | 0.7% | 2.6% | 0.0% | 0.0% | 1.1% | 0.5% |
| ALK_mut | 0.1% | 0.4% | 0.2% | 0.4% | 2.6% | 0.0% | 0.9% | 0.4% | 0.5% |
| KMT2D_RE | 0.1% | 0.3% | 0.4% | 0.3% | 1.9% | 0.2% | 0.0% | 0.0% | 0.5% |
| any_ME | 32.5% | 60.1% | 30.1% | 42.4% | 53.9% | 71.4% | 33.3% | 53.4% | 52.3% |

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# Magnetic resonance imaging insights from an active surveillance cohort of women with DCIS

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**Purpose:** Standard treatment for ductal carcinoma in situ (DCIS) involves surgical excision usually with radiation therapy or mastectomy and often endocrine therapy, treatments that are the same as for invasive cancer (IDC). It is clear, however that not all patients with DCIS will develop IDC and so the question is who benefits from early surgical intervention? Active Surveillance (AS) with endocrine risk reduction presents an opportunity to improve outcomes by identifying those lesions that can be managed with endocrine therapy alone without immediate surgical intervention. An active surveillance cohort of women who chose not to have surgery at diagnosis were followed with serial MRIs to identify the imaging features associated with successful AS and those with IDC. **Methods:** Patients with DCIS were enrolled in MRI surveillance studies between 2002 and 2019 and analyzed retrospectively with IRB approval. Per medical record review, these patients sought to avoid surgical intervention. Inclusion criteria included at least two breast MRIs performed for purposes of surveillance. The final cohort of patients included 64 cases with at least two breast MRIs, with 27 patients having more than 4 MRIs. All breast MRIs consisted of routine sequences, including both pre and post IV contrast images with at least 2 post-contrast time points. Lesion conspicuity, change in lesion, background parenchymal enhancement (BPE), change in BPE, and likelihood of invasive cancer at each MRI timepoint, were subjectively measured independently by two breast radiologists. A Likert scale was used to grade each imaging feature. Radiologists were blinded to the clinical outcome of whether the patient had IDC at surgery or not. Input variables included all imaging features collected and classification trees were trained and bootstrapped on 90% of the data using recursive partitioning to distinguish imaging features predictive of clinical outcome. Proportionality tests were conducted to test whether IDC was associated with age, menopausal status, and breast composition among other clinical variables.**Results:** Women in the cohort had a mean age of 53.6 years (range 29.8 to 78.9). 98.3% were HR+. Of the 64 cases in the cohort, 57 received endocrine therapy (89.1%). A total of 31 cases (48.4%) eventually had surgical excision and 33 (51.6%) remained on AS. At surgery, 17 patients had IDC (26.6%). Classification trees revealed that the most distinguishing features in the model correlating with IDC were if the lesion was distinct from background at MRI timepoint 1, an increase in BPE between MRI timepoints 1 and 2, and an increase in the lesion size or conspicuity between MRI timepoints 1 and 2. At diagnosis, 56.3% demonstrated a more diffuse pattern of enhancement where the DCIS lesion was not distinguishable above background. Of those with lesions that did not stand out above background at diagnosis and whose BPE did not increase, only 1 of 31 patients developed IDC (3%) with mean follow up of 4.62 years. Patients with IDC were proportionately older (>60) and post-menopausal (73% with IDC were postmenopausal), although only 57% were postmenopausal at diagnosis. Other variables such as breast composition were not enriched in either the IDC versus the non-IDC population. **Conclusion:** Our study suggests that imaging markers such as BPE and conspicuity of lesion enhancement may provide information to better understand and stratify the risk of DCIS and avoid overtreatment. Importantly, MRI may provide insight as to when a diagnosis of DCIS is more likely to be a global risk factor amenable to endocrine risk reduction, versus a lesion best treated with surgical excision. Pathology correlation is underway. We are currently developing methods to improve reproducibility and harmonization between radiologists, and performance on a validation set will be presented.

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Trends in genetic testing and results for women diagnosed with breast cancer or ovarian cancer, 2013-2017

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**Background:** Genetic testing is increasingly important for breast and ovarian cancer risk reduction and treatment. However, little is known about trends and disparities in receipt of testing in the community and test results after diagnosis. **Methods:** We linked records of all women with breast cancer or ovarian cancer diagnosed from 2013-2017 in Georgia and California and reported to Surveillance, Epidemiology and End Results (SEER) registries to genetic testing results from four laboratories that did most clinical testing in the studied regions (Ambry Genetics, GeneDx, Invitae, Myriad Genetics). We combined test results performed by all laboratories over 2012-2019 with SEER data. We measured use of any test, median number of genes tested, rates of variants of uncertain significance (VUS) and pathogenic variants (PVs). **Results:** A total of 25.2% of 187,535 breast cancer patients, and 34.3% of 14,689 ovarian cancer patients, had genetic testing. Testing increased annually by 2% while the median number of genes tested increased annually by 28%. Among tested patients diagnosed with breast cancer in 2017, 5.2% had *BRCA1/2* PVs while 4.9% had PVs in genes associated with a recognized cancer syndrome (*APC, CDH1, MLH1, MSH2, MSH6, NF1, PMS2, PTEN, RET* and *TP53*) or with emerging evidence for an increased risk of breast cancer and/or ovarian cancer (*ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, RAD51C* and *RAD51D*). Among tested patients diagnosed with ovarian cancer in 2017, 11.0% had *BRCA1/2* PVs while 2.3% had PVs in a syndromic gene (*APC, MLH1, MSH2, MSH6, NF1, PMS2,* and *TP53*) or an emerging breast/ovarian cancer gene (*ATM, BARD1, BRIP1, CHEK2, NBN, PALB2, RAD51C* and *RAD51D*). PVs in other tested genes were rare (generally <1%). VUS rates increased from patients diagnosed in 2013 (11.2% breast, 11.2% ovarian) to 2017 (26.4% breast, 26.8% ovarian) and were higher in racial/ethnic minorities (47.8% Asian, 46.0% Black, 40% Hispanic versus 24.6% non-Hispanic Whites diagnosed with ovarian cancer in 2017; p<.001). **Conclusions:** A substantial gap persists in testing ovarian cancer patients (34.5% versus nearly 100% recommended) while testing more genes was associated with a substantial racial/ethnic gap in VUS. Most clinically relevant PVs occurred in the 17 genes (ovarian cancer patients) to 20 genes (breast cancer patients) reported above; testing only these genes may optimize the clinically salient PV-to-VUS ratio, particularly for racial/ethnic minorities.

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# A trial of endocrine therapy after breast conserving surgery will aid in patient treatment decisions regarding choice of adjuvant therapy

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**Purpose/Objective(s):** In the United States, more than a quarter of a million women are diagnosed with breast cancer each year. Fortunately, advances in detection and therapies have decreased breast cancer mortality significantly. Focus has been placed on improving quality of life through safely de-escalating treatment. Adjuvant monotherapy with endocrine therapy is an acceptable alternative to adjuvant radiotherapy and endocrine therapy in elderly women with favorable early stage breast cancer. The decision to omit radiation in this low-risk cohort is based on the patient's commitment to 5 years of endocrine therapy. However, compliance is poor and studies demonstrate a premature discontinuance rate of 23-50% within 1-4 years. Of the factors that may lead to non-compliance, side effects of treatment appear to be the most significant. Primary objective:

1. To assess the tolerability of the anti-endocrine therapy following breast conserving surgery in breast cancer women patients

Secondary objective:

1. To identify factors associated with intolerance of treatment.

**Methods**: 40 women who are willing to trial an 8 week course of endocrine therapy will be enrolled after breast conserving surgery. The trial must start within 8 weeks of surgery. Questionnaires will be collected at the time of enrollment (baseline) and at the end of the trial (to assess tolerance). Additionally, a medication log will be collected to assess medication compliance.
**Inclusion-and exclusion criteria**: Inclusion criteria are 1) patients with pathological T1N0 invasive breast cancer following breast conserving surgery 2)70 years of age and older 3) estrogen receptor positive per ASCO/CAP guidelines and 4) negative margins Exclusion criteria are 1) patients who have undergone previous radiation therapy to the ipsilateral breast, chest wall, or axilla are excluded, 2) patients with evidence of metastatic disease and 3) previous or concurrent malignant disease.
**Statistical Plan**: We plan to recruit 40 patients in one year. This study is not powered based on a specific null hypothesis, but if 40 patients are followed, with two-sided type I error rate at 5%, we will have 91% power to observe a statistically significant difference between the alternative hypothesis to observing 75% women to continue treatment versus the null hypothesis of only 50% will continue.

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**Publication Number:** PS11-01

# Outcome without adjuvant systemic treatment in breast cancer patients included in the MINDACT trial

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**Background:** Adjuvant systemic treatments have played an important role in the decline of breast cancer mortality over the years. Because of the extensive short- and long-term toxicities associated with these treatments, careful selection of patients likely to benefit from them is needed. Studies have shown excellent survival in subgroups of patients receiving no adjuvant systemic treatments. Some national guidelines advise no adjuvant systemic treatments in specific groups of patients with clinical low risk breast cancer. The aim of this study is to investigate the survival of breast cancer patients who received no adjuvant treatment (chemotherapy nor endocrine therapy) using data from the EORTC 10041/BIG 3-04 MINDACT trial. **Material and methods:** Of the 6693 patients enrolled in the MINDACT trial, accrued 2007-2011, 509 patients with hormone receptor positive, HER2 negative, lymph node negative tumors <2cm received no adjuvant systemic treatment, mostly following local recommendations. Median follow-up was 8.7 years. Using propensity score matching and exact matching, we will identify groups of patients treated with adjuvant endocrine therapy and/or chemotherapy with similar tumor characteristics to the untreated patients. We will use the Kaplan-Meier method to estimate distant metastasis free interval and overall survival at 5 and 8 years for each group. Differences between groups will be evaluated using the log-rank test, and hazard ratios with 95% CI derived from Cox proportional hazards models. **Planned analyses:** The long-term data of the MINDACT trial has recently become available. The date of planned analysis is August 10$^{th}$ 2020.For this study, the primary clinical endpoint will be distant metastasis free interval, which will be assessed in the matched groups of untreated patients, patients who received endocrine therapy only, and patients who received chemotherapy with or without endocrine therapy. Kaplan-Meier estimates will be provided at 5 years, and at 8 years to assess the long-term outcomes in this population. A statistical plan for this analysis was specifically developed and approved prior to performing any analysis.

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# Glucocorticoid receptor expression in early-stage triple-negative breast cancer is associated with a high level of tumor immune cell infiltrates

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Background: Triple-negative breast cancer (TNBC) with high glucocorticoid receptor activity (GR-high) is associated with a high risk of relapse and chemotherapy resistance. Glucocorticoids (GC) are essential for the regulation of immune and inflammatory responses. Multiple mechanisms of GC-induced immunosuppression have been proposed, including suppression of T cell proliferation and dendritic cell antigen presentation and function. The importance of intact immune surveillance in controlling neoplastic transformation is well-established, and accumulating evidence demonstates a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / Foxp3+ regulatory T-cells (Tregs) appears to correlate with improved prognosis and long-term survival. We hypothesized that tumor GR activity would modulate the tumor immune microenvironment (TME), thereby suppressing anti-tumor immunity in TNBC.
Methods: We identified 46 patients with TNBC who received neoadjuvant chemotherapy at The University of Chicago between 2002-2014, and had pretreatment tissue available for study. Tumors were stained for GR expression using the anti-GR rabbit monoclonal XP antibody (Cell Signaling, 1:200 dilution). GR expression was determined independently by two pathologists. Using multiplex immunohistochemistry, six phenotypes for immune cell markers (BATF3+ dendritic cells, CD8+ T-cells, Foxp3+ Tregs, PD-L1+tumor, PD-L1-tumor, PD-L1+immune cells) were identified in the tumor and stroma of the pretreatment biopsy specimens. Absolute counts of each type of immune cell as well as ratios between immune cell types were compared in GR-low, GR-moderate, and GR-high expressing TNBC specimens using the Kruskal-Wallis test.
Results: There were 8 GR-low, 23 GR-moderate, and 15 GR-high expressing tumors in our cohort. When comparing GR-low to GR-moderate or GR-moderate to GR-high expressing tumors, there were no significant difference observed in immune cell types. However, when comparing GR-high to GR-low expressing TNBCs, there were significantly higher levels of CD8+ T-cells, Foxp3+ Treg cells, and BATF3+ dendritic cells in GR-high vs GR-low TNBC tumors (p=0.0004, p=0.011, and p=0.0072, respectively). When comparing the ratio of CD8+ T-cells to Foxp3+ Treg cells, PD-L1+ tumor or immune cells, no significant differences were observed by level of GR expression (p=ns for all comparisons).
Conclusions: We report for the first time that GR-high, treatment-naïve, primary TNBCs have significantly higher CD8+ T cells, Foxp3+ T cells, and BATF3+ dendritic cells compared to GR-low TNBCs, consistent with an inflamed TME. While historically a robust immune infiltrate in the TME in early TNBC has been associated with a better response to chemotherapy and a more favorable long-term outcome, high GR activity in early TNBC has been associated with a worse outcome. Our observation that GR-high tumors have an inflamed TME, suggests that checkpoint blockade to either suppress Foxp3+ Tregs or activate CD8+ T cells may be able to restore anti-tumor immunity.

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Clinical and genomic correlation of a CLIA certified organoid based functional test in breast cancer patients

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The goal of precision medicine is to match the right drug to the right patient. However, every individual cancer carries a unique and complex mosaic of genetic and molecular changes making it difficult to identify the right drug based solely on genomic analysis. We developed a CLIA-certified functional drug assay (PARIS® test) for solid tumors which provides an actionable report of tumor derived organoid sensitivities to targeted, endocrine and chemotherapy agents as a tool for clinical therapeutic decisions. **Objectives:**1.To establish the concordance between organoid drug sensitivity with well-known genomic or immunohistochemical IHC biomarkers 2.To correlate organoid drug sensitivity with clinical outcomes.**Methods:** From 2015 to 2020, organoids from 410 tumor samples were subjected to functional testing at SEngine Precision Medicine, including 61 breast tumor samples from 48 patients. Fresh samples of tumor cells from core biopsies, surgical excisions, or from fluids arrived <48 hrs following collection and were cultured as 3D organoids. Samples were evaluated using a multi-dose drug response format with a library of up to 130 oncology drugs. Drug sensitivity was quantified using the SPM score (1-15) that combines sensitivity and personalization of each patient's response relative to a reference population. Known genomic anchors and IHC subtypes were compared to drug sensitivity to determine concordance.**Results:** 61 breast cancer samples from 48 patients were analyzed. The median age of patients was 53.4 (r26-76). 65 drugs on average were tested per patient with a mean turnaround time of 21 days (r9 -37). A mean of 6 drugs per patient were identified as top scoring sensitive drugs. In 42 patients with genomic or IHC data, we found high concordance of drug sensitivity with known biomarkers (e.g., HER2+ or ERBB2 amplification:HER2 or EGFR inhibitor, BRCA1 mutation: PARP inhibitor, FGFR1-2 mutation or amplification: FGFR inhibitor, PIK3CA mutation:PI3K inhibitor), measured as sensitivity to the cognate targeted drugs. For PIK3CAmut we found an 80% correlation of organoid sensitivity to alpelisib and taselisib. For HER2/ EGFRinh the correlation was 100%. We also found organoid sensitivity to targeted agents in the absence of known genomic or IHC biomarkers, for example tamoxifen and fulvestrant sensitivity in triple negative breast tumors, or HER2 inhibitor sensitivity in HER2 IHC negative tumors or PARP inhibitor sensitivity with BRCA2 variant of unknown significance (VUS). In a cohort of 18 analyzable patients, the retrospective and prospective correlation between organoid based drug sensitivity and clinical outcome was >90%.**Conclusions:** Organoid based drug testing exhibits strong concordance with genomic or IHC biomarkers and clinical response. In addition, functional testing identifies candidate therapies in patients lacking biomarkers and can nominate variants of unknown significance as candidate biomarkers. This study highlights the utility of functional assays to support clinical decision making in a genetically heterogenous cancer such as breast cancer.

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# The breast pre-cancer atlas illustrates the molecular and micro-environmental diversity of ductal carcinoma in situ

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Background: With the implementation of widespread breast cancer screening, the diagnosis of Ductal Carcinoma In Situ (DCIS) has increased 5 fold. Most cases are treated with combinations of surgery, radiation and endocrine therapy, reducing the risk of second events, including ipsilateral invasive cancer. Without standard markers to confidently identify the most indolent lesions, a subset of cases are likely over-treated. The mutational landscapes of DCIS and invasive ductal carcinoma (IDC) are similar and not sufficient to identify higher risk lesions with recent studies suggesting that clonal selection plays a limited role in progression. Histological analysis highlighted the role of the extracellular matrix and immune-surveillance to maintain duct integrity and limit progression. Due to the small size, limited availability and quality of research specimens, few biomarker studies investigated pure DCIS with adequate follow-up or genome-wide methods, let alone integrated more than one type of biomarker. Unlike breast cancer, there is no comprehensive, systematic, multi-modal atlas of DCIS, limiting the ability to test broad and novel hypotheses and characterize processes maintaining breast tissue homeostasis.
Methods: Through sequential sectioning of pure DCIS archived specimens, a total of 70 histological regions from 40 cases were annotated and profiled using up to 3 platforms: multiplex immuno-histochemistry (mIHC), RNA-seq, and whole-exome sequencing. Stromal and epithelial spatial distribution of immune cells and states were quantified using mIHC. The epithelial compartments were microdissected and profiled using genome-wide gene expression, DNA mutations and copy number alterations.
Results: Epithelial regions were classified according to expression subtypes consistent with histological markers, highlighting associations with the lesion architecture and grade. Compared to solid pattern, cribriform pattern DCIS has induced EMT processes and repressed proliferation processes, a trend reminiscent of low-recurrence-risk expression signatures measured in IDC. The DNA copy number burden increased with grade and the mutational burden was the highest in solid DCIS. Both were higher in Her2+ cases. The clustering of mutations at chromosome 17p - attributed to the *APOBEC*-driven Kataegis phenomenon - was observed in a subset of regions, suggesting this event can occur in pre-invasive lesions. All DCIS had somatic alterations of at least one known driver gene with some associated with grade (*TP53*) or expression subtype (*ERBB2*). Multi-region profiling available in a subset of samples revealed genetic heterogeneity of likely-driver events between proximal regions of similar histological characteristics. The density and proliferative states of selected immune cells - including T-cells, B-cells and Macrophages - highlights the diversity of the tumor immune environment with the highest densities observed in Her2+ ducts and stroma, minimal ductal infiltration in other lesions, fewer dividing B- and T-cells around the more proliferative areas and a small number of regions depleted from any adaptive immune cells.
Conclusion: This first multi-modal profiling of pure DCIS reveals an unsuspected diversity of molecular and microenvironmental states and presents their association with progression risk factors. The observations support the need for stronger integration of molecular and clinicopathology features, especially at sub-histological levels, to ensure the findings can be interpreted in the correct clinical and phenotypic context. The compatibility of the approach with archived specimens supports the expansion to larger retrospective DCIS collections with outcomes.

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# Biomarkers of resistance to palbociclib in ER+ primary breast cancer in the PALLET trial

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**Background:** CDK4/6 inhibitors are being used in combination with aromatase inhibitors as therapy for advanced ER+ breast cancer (BC) and are being explored for use in primary BC. Few mechanisms driving resistance to added CDK4/6 inhibitors have been defined. The PALLET phase II randomized neoadjuvant trial of letrozole (LET) ± palbociclib (PALBO) in postmenopausal ER+HER2- primary BC reported that clinical response rate over 14wks was not significantly increased by adding PALBO to LET but suppression of Ki67 was significantly increased (Johnston *et al*, JCO 2018, 37, 178): after 14wks complete cell cycle arrest (CCCA, Ki67<2.7%) was present in 59% on LET and 90% on LET+PALBO. Here we sought to identify biomarkers of de novo resistance to allow selection of patients most likely to benefit from added PALBO.
**Methods:** 307 patients were randomized to LET (n=103) or LET+PALBO (n=204) for 14 wks. The first 2wks of LET+PALBO patients were randomised to LET, PALBO, or LET+PALBO. Biopsies were taken at baseline, 2wks and 14wks. Biomarker data are presented here for baseline only, other than Ki67 at both baseline and 14wks. IHC analyses were conducted on FFPE biopsies for ER, PgR, RB1, cyclin-E1, and cyclin-D1 (also FISH). RNA-seq was performed on fresh frozen biopsies. Association of each biomarker with CCCA was determined by logistic regression. Differentially expressed genes (DEGs) were identified between patients sensitive (CCCA) (n=94) and resistant (non-CCCA) (n=10) to treatments with or without PALBO at 14wks by DESeq2. Fifty hallmark gene sets were tested for significant enrichment with DEGs and differential gene sets were identified by using Gene Set Enrichment Analysis (GSEA).
**Results:** The association of IHC biomarkers with CCCA is shown in the table. Lower levels of ER, higher levels of cyclin-E1, and amplification of cyclin-D1 were each significantly associated with a greater chance of non-CCCA with LET+PALBO. High cyclin-E1 levels were also associated with reduced chance of CCCA with LET only. Patients with high baseline Ki67 also exhibited higher non-CCCA with LET+PALBO at 14wks (p=0.0002). In the RNAseq data we identified 1973 DEGs between the 14wk CCCA and non-CCCA patients for LET+PALBO. E2F and MYC targets, PI3K/AKT/MTOR signalling and interferon response gene sets were among the hallmark gene sets enriched for genes with higher expression in non-CCCA patients at 14wks for LET+PALBO (FDR<0.05). For LET-only, 311 DEGs were identified and the “Estrogen Response Early” gene set was significantly enriched in genes with higher expression in CCCA samples. At the individual gene level, genes significantly associated with non-CCCA after 14wks LET+PALBO included *CCNE1*, *CDK2* and several E2F-related genes (p<0.05). Their expression was not significantly different between non-CCCA and CCCA patients with LET alone.
**Conclusion:** Biomarkers associated with response/resistance to added PALBO were different from LET only. PALBO resistance was associated with higher baseline expression of cyclin-E1 (both IHC and RNA), CDK2, and genes related to E2F, MYC, interferon and MTOR signalling. These results suggest that multiple identifiable mechanisms of de novo resistance to PALBO are likely to exist in primary ER+ BC. On-going WES analyses will allow the significance of alterations at the DNA level to be presented.
**Table 1**.Continuous measurement in a logistic regression for CCCA at 14 weeks; Oddsratio calculated separately for group A and groups B,C,D and were adjusted forregion (UK vs NA); * amplified vsnon-amplified

Continuous measurement in a logistic regression for CCCA at 14 weeks

| **Biomarker** | | **LET** | | | **LET+PALBO** | |
|---|---|---|---|---|---|---|
| | **Odds ratio** | **95% CI** | ***p*** | **Odds ratio** | **95% CI** | ***p*** |
| **ER** | 1.12 | 0.36, 3.48 | 0.84 | 4.47 | 1.62, 12.38 | 0.004 |
| **PgR** | 4.38 | 1.03, 18.58 | 0.05 | 3.05 | 0.50, 18.56 | 0.23 |
| **RB1** | 3.01 | 0.24, 38.56 | 0.40 | 0.42 | 0.05, 38.49 | 0.83 |
| **Cyclin-E1** | 0.10 | 0.01, 0.84 | 0.03 | 0.02 | 0.00, 0.20 | 0.001 |
| **Cyclin-D1 IHC** | 3.09 | 0.51, 18.49 | 0.22 | 2.56 | 0.28, 23.33 | 0.40 |
| **CyclinD1 FISH*** | 1.47 | 0.43, 4.99 | 0.53 | 0.28 | 0.06, 0.86 | 0.03 |

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A sense-antisense RNA interaction drives metabolic reprogramming in metastatic breast cancer

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*Background:* Metabolic reprogramming is a hallmark of breast cancer progression. However, the underlying regulatory pathways that initiate and maintain this process remain largely unexplored. Recently, we have identified a novel antisense RNA that helps protect breast cancer cells against oxidative stress by reprogramming their metabolic redox state. Using cell line and patient-derived xenograft models, as well as direct measurements in clinical samples, we have demonstrated the unique regulatory functions of this antisense RNA in increasing the metastatic capacity of breast cancer cells. *Results:* Non-coding RNAs have emerged as major drivers of metastatic progression. We have recently demonstrated that specific classes of non-coding RNAs, such as tRNAs (Goodarzi et al, Cell, 2016) and tRNA fragments (Goodarzi et al, Cell, 2015), play major roles in breast cancer metastasis as post-transcriptional regulators of gene expression. However, these types of regulatory RNAs constitute only a fraction of the non-coding RNAs that are aberrantly expressed in highly metastatic cells. For example, antisense RNAs are a large but often ignored class of RNAs with poorly understood cellular functions. We recently developed a new computational algorithm to systematically annotate antisense RNAs and identify those that are associated with metastatic progression based on data from cell line and patient-derived xenograft models, as well as matched primary and metastatic tumors from triple-negative breast cancer patients. We identified a previously unknown antisense RNA, which is transcribed from a locus in the 3' UTR of the gene NQO1 (and is hence named NQO1-AS). Both NQO1-AS and NQO1 are significantly upregulated in highly metastatic breast cancer cells, and we have shown that the NQO1 sense mRNA is stabilized by the expression of NQO1-AS. Our results indicate that NQO1-AS forms a stable duplex with the 3' UTR of NQO1 and induces the expression of a longer and more stable isoform of NQO1 mRNA. Metabolomic measurements in NQO1 knockdown and control cells revealed that increased NQO1 activity enables cancer cells to better tolerate the oxidative stress experienced during metastasis. We demonstrated this by performing lung metastasis assays in xenograft models. To confirm the clinical relevance of these findings, we performed comprehensive clinical association studies, and also used quantitative PCR and immunohistochemistry to measure NQO1 levels across all disease stages. We observed a highly significant association between higher NQO1 and NQO1-AS expression and metastatic relapse. *Methods:* We developed a method named iRAs to annotate and quantify antisense RNAs. We used global run-on assays (GRO-seq) and RNA sequencing in poorly and highly metastatic breast cancer cells to identify NQO1-AS as a novel pro-metastatic antisense RNA. We used both Gapmers and CRISPR-i to knock down NQO1-AS and to measure its impact on NQO1 mRNA stability and expression. We used CRISPRi to silence NQO1 in both MDA-231 and HCC-1806 breast cancer lines, and measured the metabolic consequences of NQO1 knockdown by measuring NADPH flux as well as performing general metabolomic profiling. We also used *in vivo* lung colonization assays (n=5 mice in each arm) to measure the metastatic capacity of NQO1 knockdown cells. Log-rank test (univariate) and Cox Proportional Hazard Models (multivariate) were used to perform survival analyses in METABRIC and the kmplot aggregate dataset. Mann-Whitney or ANOVA was used to compare expression of NQO1 and NQO1-AS across samples stratified based on sub-type and tumor grade/stage in public datasets as well as our own measurements in clinical samples (n=96; 5 healthy, 23 stage I, 30 stage II, 29 stage III, and 9 stage IV). IHC was performed on tissue microarrays from CHTN (Breast Progression), and blinded scoring was used to assess NQO1 levels.

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Combined analysis of the WORTH 1 and WORTH 2 studies of ipsilateral breast tumor recurrence after breast conservative surgery without radiotherapyusing the “5-mm thick slice and 5-mm free margin method”

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**Background**: Breast conserving surgery with radiotherapy is one of the standard treatment methods for early breast cancer. However, it is regarded as an option to treat elderly patients with small hormone receptor positive breast cancer with breast conserving surgery and hormone therapy without radiotherapy. Two sequential prospective studies were conducted to examine the efficacy of breast conserving surgery without radiotherapy from 2002. **Patients and Methods**: Primary breast cancer patients were divided into the WORTH 1 (n=123) group (Oct. 2002 and Mar. 2005) and the WORTH 2 (n=198) group (Dec. 2006 and Nov. 2011) and the data was retrospectively combined and analyzed. The eligibility criteria of the two sequential studies were a tumor ≥3cm determined by palpation, pathologically node negative by axillary dissection or sentinel node biopsy and M0, no preoperative treatment, postmenopausal patients ≥50 years of age at surgery, no tumor cells within 5 mm from the margins, no lymphatic invasion around the primary tumor, and estrogen receptor positive. The surgical specimens were sliced at 5 mm intervals and all the slices were examined microscopically. Postoperative radiotherapy was not conducted and adjuvant chemotherapy was optional. The patients were treated with tamoxifen or anastrozole in WORTH 1 and anastrozole in WORTH 2 for 5 years. Ipsilateral breast tumor recurrence (IBTR)-free survival and distant relapse-free survival (DRFS) were recorded as the interval from initial surgery until IRTR or distant relapse. The factors related to IBTR were evaluated using the proportional hazard model. Patients who did not develop IBTR or distant relapse were statistically censored at the time of the last follow-up or death. Survival rates were calculated using the Kaplan-Mayer method. Statistical analyses were conducted using the log rank test. Values < 0.05 were considered statistically significant. **Results**: The median age at surgery was 65 (range 50-84). The median tumor size was 1.5 cm (range 0-4.0 cm). The median follow-up period for IBTR was 95 months (range 4-192 months). Only 3 patients were treated with adjuvant chemotherapy. The 5- and 10-year overall survival rates were 98.7% and 95.1%, respectively and the 5- and 10-year distant DRFS rates were 99.3% and 96.3%, respectively. The 5- and 10-year IBTR free rates were 97.0% and 89.7%, respectively. Older patients had significantly less IBTR rates (5-year IBTR free rates: 95.8% for ≤64 vs. 98.1% for ≥65, p=0.019). There was no difference in IBTR rates between the large and small tumors (5-year IBTR free rates: 96.9% ≤1.4 cm vs. 96.8% for ≥1.5 cm, p=0.094). PR positivity had a significantly lower IBTR free rates (5-year IBTR free rates: 98.3% for PR positive vs. 91.5% for PR negative, p=0.009). The age at surgery (≤64, p=0.017, Hazard ratio 3.07, 95% CI 1.22-7.70) and the PR status (PR negative, p=0.024, Hazard ratio 2.54, 95% CI 1.13-5.69) independently affected the IBTR rates. Both the 5- and 10-year IBTR free rates of the patients who were ≥65 at surgery and had PR positive tumors (n=136) were 98.4%. **Conclusions**: The findings suggest that the “5-mm thick slice and 5-mm free margin” method may be effective in selecting patients who can be treated with breast conserving surgery and hormone therapy without radiotherapy.

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# How low is low risk: MINDACT updated outcome and treatment benefit in patients considered clinical low risk and stratified by genomic signature, age and nodal status

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**Background** With 8.7 years follow-up, the prospective phase III randomized MINDACT trial (EORTC 10041/BIG3-04) continues to meet its primary objective, i.e. 95.1% (95%CI 93.1-96.6), 5-year distant metastasis-free survival (DMFS) in clinical high (C-High)/genomic low (G-Low) risk patients who did not receive adjuvant chemotherapy (ACT) (Cardoso et al., ASCO 2020). In addition, about half of the MINDACT patients had a low clinical risk (C-Low) defined by pre-specified clinical-pathological characteristics. Here, we evaluated the outcome of this C-Low population stratified by the 70-gene signature (MammaPrint®) (G-Low or G-High) for outcome considering age, and present data on the total G-low population (C-Low and C-High combined). **Methods** Of 6693 patients enrolled in the MINDACT trial between 2007 and 2011, 3337 were C-Low, characterized as mainly T1, grade 1 or 2, and node negative. We evaluated the pre-specified DMFS, distant metastasis free interval (DMFI), and overall survival (OS) rates at 5 and 8 years in the C-Low population: i) in patients with genomic low risk (C-Low/G-Low, n=2744) who were recommended to receive endocrine therapy only (for 99% HR+), and ii) in C-Low/G-High who received ACT or not following randomization (ITT, n=690, 81% HR+). Exploratory analyses by age, ≤50 and >50, were conducted for ACT vs no ACT received in C-Low/G-High. In parallel we estimated survival rates for all G-low patients if all would have followed the genomic low risk assignment and received no ACT (C-Low/G-Low, and C-High/G-Low randomized to no ACT double weighted, n=4130). We used Kaplan-Meier estimates for time to event endpoints and hazard ratios with 95%CI from Cox-regression models adjusted for stratification factors used for the randomization. **Results** C-low/G-low patients who were recommended endocrine therapy only (compliance > 79%, based on local guidelines) have excellent 5 and 8 year survival rates for all endpoints (Table 1). The estimated survival rates for all G-Low patients, if all would have followed the genomic low risk assignment and received no ACT, is excellent as well (Table 1), albeit this population includes both C-Low and C-High patients. The survival estimates for C-Low/G-High patients are for all endpoints a few percentage points lower than for the C-Low/G-Low group (Table 1). At 8 years of follow-up, in the relatively small subset of 690 patients with C-Low/G-High tumors assigned to ACT or not by randomization (ITT), a 1.5% (SE ±2.3%) higher DMFS is seen in the ACT group, and a 2.9% (SE ±2.0%) higher DMFI. This suggested benefit is mostly seen in patients under 50 years of age (absolute Δ in DMFS for ACT vs no ACT at 8 years: 5.4% for age ≤50 vs -0.3% for age >50). **Conclusion** Patients with a 70-gene G-Low risk tumor have an excellent 8 year outcome in the context of C-Low characteristics when recommended for endocrine therapy only, very close to the outcome in the larger group of all G-Low patients regardless of clinical risk. Stratification of C-Low patients in to G-Low and G-high provides meaningful information. The benefit of ACT in C-Low patients with a 70-gene G-High risk tumor needs further confirmation, especially relevant in younger women.

**Table1**

| | ***All Patients Population*** | ***Patients*** | ***Observed events*** | ***% at 5 years (95% CI)*** | ***% at 8 years (95% CI)*** |
|---|---|---|---|---|---|
| **DMFS** | **C-Low / G-Low** | 2744 | 170 | 97.3 (96.6-97.9) | 94.7 (93.8-95.6) |
| **C-Low / G-High** | 593 | 61 | 94.2 (92.0-95.9) | 91.1 (88.4-93.3) | |
| **DMFI** | **C-Low / G-Low** | 2744 | 103 | 98.5 (97.9-98.9) | 96.7 (95.9-97.3) |
| **C-Low / G-High** | 593 | 46 | 95.8 (93.8-97.2) | 93.5 (91.0-95.3) | |
| **OS** | **C-Low / G-Low** | 2744 | 122 | 98.2 (97.6-98.7) | 96.5 (95.7-97.2) |
| **C-Low / G-High** | 593 | 44 | 96.8 (94.9-98.0) | 93.1 (90.5-95.0) | |
| | ***Patients G-low (C-Low & C-High)*** | ***Patients*** | ***Estimated events*** | ***% at 5 years*** | ***% at 8 years*** |
| **DMFS** | **All G-Low - no ACT** | 4130 | 339 | 96.4 | 92.8 |
| **DMFI** | **All G-Low - no ACT** | 4130 | 244 | 97.4 | 94.6 |
| **OS** | **All G-Low - no ACT** | 4130 | 223 | 97.9 | 95.7 |

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# Results from CONTESSA: A phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, hormone receptor + (HR+) metastatic breast cancer (MBC) who have previously received a taxane

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**Objectives:** The key objectives of CONTESSA are to evaluate the efficacy and safety of tesetaxel plus a reduced dose of capecitabine as an all-oral regimen versus capecitabine alone in patients with HER2-, HR+ MBC previously treated with a taxane.
**Rationale:** Tesetaxel is a novel, oral taxane with several properties that make it unique, including: oral administration with a low pill burden; a long (8-day) terminal plasma half-life in humans, enabling infrequent, once-every-3 weeks (Q3W) dosing; no observed hypersensitivity reactions; and significant activity against chemotherapy-resistant breast cancer cell lines. More than 1,000 patients have been treated with tesetaxel in clinical studies. Tesetaxel had encouraging monotherapy activity in a Phase 2 study in 38 patients with HER2-, HR+ MBC, with a confirmed objective response rate (ORR) per RECIST 1.1 of 45% and median progression-free survival (PFS) of 5.4 months (Seidman et al, 2018 ASCO Annual Meeting).
**Methodology:** CONTESSA is a multinational, multicenter, randomized (1:1), Phase 3 registration study comparing tesetaxel (27 mg/m$^2$ on Day 1 of a 21-day cycle) plus a reduced dose of capecitabine (1,650 mg/m$^2$/day on Days 1-14 of a 21-day cycle) to the approved dose of capecitabine alone (2,500 mg/m$^2$/day on Days 1-14 of a 21-day cycle) in patients with HER2-, HR+ MBC who have received no more than one chemotherapy regimen for advanced disease and have received a taxane in the (neo)adjuvant setting. There was no restriction on the disease-free interval following taxane therapy. The primary endpoint is PFS assessed by an Independent Radiologic Review Committee (IRC). CONTESSA was designed with 90% power to detect a 2.5-month improvement in median PFS (HR=0.71). Secondary endpoints are overall survival (OS), ORR and disease control rate.
**Results:** CONTESSA, which enrolled 685 patients, met the primary endpoint of improved PFS as assessed by the IRC. Median PFS was 9.8 months for tesetaxel plus a reduced dose of capecitabine versus 6.9 months for capecitabine alone, an improvement of 2.9 months [HR=0.716 (95% CI: 0.573-0.895); p=0.003]. ORR was 57% for tesetaxel plus a reduced dose of capecitabine versus 41% for capecitabine alone (p=0.0002). OS data are immature. Tesetaxel plus capecitabine was associated with a manageable side effect profile consistent with previous clinical studies. Grade ≥3 treatment-emergent adverse events (TEAEs) that occurred in ≥5% of patients (tesetaxel plus capecitabine vs. capecitabine alone) were: neutropenia (71.2% vs. 8.3%); diarrhea (13.4% vs. 8.9%); hand-foot syndrome (6.8% vs. 12.2%); febrile neutropenia (12.8% vs. 1.2%); fatigue (8.6% vs. 4.5%); hypokalemia (8.6% vs. 2.7%); leukopenia (10.1% vs. 0.9%); and anemia (8.0% vs. 2.1%). TEAEs resulting in treatment discontinuation in ≥1% of patients (tesetaxel plus capecitabine vs. capecitabine alone) were: neutropenia or febrile neutropenia (4.2% vs. 1.5%); neuropathy (3.6% vs. 0.3%); diarrhea (0.9% vs. 1.5%); and hand-foot syndrome (0.6% vs. 2.1%). Treatment discontinuation due to any adverse event occurred in 23.1% of patients treated with tesetaxel plus capecitabine versus 11.9% of patients treated with capecitabine alone. Grade 2 alopecia occurred in 8.0% of patients treated with tesetaxel plus capecitabine versus 0.3% of patients treated with capecitabine alone. Grade ≥3 neuropathy occurred in 5.9% of patients treated with tesetaxel plus capecitabine versus 0.9% of patients treated with capecitabine alone.
**Conclusion:** An all-oral regimen of tesetaxel plus a reduced dose of capecitabine significantly improved PFS versus capecitabine alone. Neutropenia was the most frequent Grade ≥3 TEAE. Rates of clinically significant alopecia and neuropathy were low.

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# A metabolomic signature as screening method for breast cancer diagnosis

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**Introduction:** There is a close relationship between metabolism and cancer, which modifies its metabolic network to support cell survival. This may be reflected in a release of metabolites into the circulating blood, which may allow the identification of a signature associated with a tumor. Here we analyze a metabolomic profile of non-metastatic breast cancer patients and healthy controls to identify a diagnostic signature. **Materials and methods:** We prospectively enrolled 350 subjects in our study. A blood sample withdrawal at breast cancer diagnosis or the day of the screening mammography for the control group was done. After centrifugation, plasma was collected and stored at -80 °C. A panel of 61 metabolites was tested on a TQ5500 tandem mass spectrometer in triplicate for each sample and with internal standard and inter-run calibrators. ComBat tool from GenePattern platform was used to remove the batch effect. After outliers removal with Tukey's method and mean value calculation for each replicate, a Z-standardization was done. A 10-fold cross-validation (CV) was used to find the best representative validation set containing 106 subjects (78 cancerous and 28 healthy), which represents 30% of the dataset. The remaining 70% was used as a training set, containing 244 subjects (126 cancerous and 118 healthy). After feature selection, the best signatures were identified on the training set with Random Forest method and validated on the validation set. Statistical analysis was performed with R-studio software. **Results:** We enrolled in our study 350 subjects, 204 breast cancer patients and 146 healthy controls. The median age in the breast cancer group was 56 years (range 26-86), and in the healthy controls group was 53 years (range 40-74). Breast cancer patients were all at an early stage: 44 at stage I (21.5%), 111 at stage II (54.4%), and 49 at stage III (24%). The breast cancer patients were of all subtypes: 61 luminal A (29.9%), 90 luminal B (44.1%), 14 hormone receptor-negative/HER2-positive (6.9%), and 39 triples negative (19.1%). A feature selection was performed on the training set using Random Forest method, and 10 metabolites were identified as the most important in discriminating cancerous from healthy subjects. From this reduced set, 1023 combinations were generated and evaluated for their AUC performance using 10-CV on the same training set. A total of 512 combinations were identified with an AUC $\geqq$ 0.90. To predict breast cancers, the best signature comprised 4 variables (C6-Carnitine, C3/C2, C2-Carnitine, C8/C2), with an AUC of 0.996 (SD 0.0073) in the training set and of 0.998 (SD 0.0002) for the validation set, at a specificity of 99.4% and a sensitivity of 98.7%. **Conclusions:** With our work, we identified a metabolite-based predictive signature of breast cancer with a validation performance of AUC 0.99 (specificity of 99.4% and sensitivity of 98.7%), thus outperforming the mammography screening test. Furthermore, the signature-based test is fast, cheap, and does not expose patients to ionizing radiation. Our study's limitation is a difficult application to clinical practices due to the statistical technique used. Thus, a refinement of the analysis technique and a validation on a larger and independent cohort are mandatory. Also, there are some differences in metabolism related to genetic, environmental factors, and feeding. Therefore, this result should be confirmed on different ethnicities, geographical regions, and the timing of blood withdrawal should be standardized.

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# 5-year outcomes in the NBRST trial: Preoperative MammaPrint and BluePrint breast cancer subtype is associated with neoadjuvant treatment response and survival

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**Background:** MammaPrint (MP) is used to identify breast cancer (BC) patients who can safely forego adjuvant chemotherapy. MP combined with the BluePrint (BP) molecular subtyping signature identifies BC subtypes with distinct therapeutic response rates and survival outcomes. In the Neoadjuvant Breast Symphony Trial (NBRST), MP and BP (MP/BP) predicted rates of pathologic complete response to neoadjuvant chemotherapy (NCT) and partial response to neoadjuvant endocrine therapy (NET). Here, we report 5-year overall survival (OS) and distant metastasis-free survival (DMFS) in patients from the NBRST registry according to MP/BP molecular classification. **Methods:** The NBRST trial (NCT01479101) prospectively enrolled 1072 patients from 2011 to 2014, who received MP and BP testing. Patients were assigned to receive NCT or NET according to NCCN guidelines and consented to 5 years post-surgery follow-up (FU). Clinical outcomes were available for 913 patients from 67 US institutions. Median FU for OS and DMFS was 5 and 4.6 years, respectively. Tumors classified by MP as High Risk (HR) or Low Risk (LR) were further stratified into four molecular subtypes by BP: Luminal A, Luminal B, HER2, and Basal. Differences in OS and DMFS at 3 and 5 years were assessed by Kaplan Meier analysis and log-rank test. **Results:** MP results from neoadjuvant patients (N=913) classified 16% of tumors as MP LR and 84% as MP HR. MP and BP classified 15.7% (143/913) of tumors as Luminal A, 32.5% (297/913) as Luminal B, 17.1% (156/913) as HER2, and 34.7% (317/913) as Basal. The 5-year OS and DMFS probabilities were significantly lower in HR compared to LR patients ($p < 0.001$ for OS and DMFS), and lowest in Basal and Luminal B compared to Luminal A and HER2 subtypes ($p < 0.001$ for OS and DMFS). Most DMFS events in BP Basal tumors occurred within the first 3 years. Of 841 patients that received NCT with or without HER2-targeted therapy, 12.2% (103/841) were LR and 87.8% (738/841) were HR. MP and BP classified 11.9% (100/841) of these patients as Luminal A, 32.6% (274/841) as Luminal B, 8.3% (154/841) as HER2 subtype, and 37.2% (313/841) as Basal. The 5-year OS and DMFS probabilities were lowest in HR, Basal or Luminal B patients ($p < 0.001$). In 59 patients who received NET alone, 5-year OS and DMFS were significantly worse in HR patients that had Luminal B or HER2 tumors compared to LR Luminal A patients. In the 39 patients with Luminal A tumors, response to NET at the time of surgery was: 46.2% partial response, 41.0% stable disease, 5.1% progressive disease, 2.6% not reported. Five year DMFS in patients with Luminal A tumors treated with NCT or NET was not significantly different ($p$=0.67).**Conclusions:** MammaPrint remained prognostic in BC patients undergoing neoadjuvant therapy. Long -term prognosis was excellent in LR groups who received NCT or NET alone. MP and BP can accurately classify patients into specific subtypes with distinct OS and DMFS outcomes at five years, with BP Basals having the worst outcomes, followed by Luminal B, HER2, and Luminal A subtypes. BP Basal patients had the highest frequency of events within the first 3 years post-surgery, suggesting a genomic risk timeline distinct from other BP subtypes and a potential benefit from a secondary therapeutic immediately post-surgery. Additionally, Luminal A patients had a very low risk of progressive disease while on NET alone prior to surgery, with similar DMFS outcomes to Luminal A-types who received NCT.

| | Number of patients | Observed events | % at 5 year (95% CI) | p-value |
|---|---|---|---|---|
| **All patients - MammaPrint Risk Group** | | | | |
| **OS** | 913 | 134 | | p<0.001 |
| Low Risk | 146 | 7 | 94.7 (88.4-97.6) | |
| High Risk | 767 | 127 | 81.1 (77.7-84.0) | |
| **DMFS** | 913 | 182 | | p<0.001 |
| Low Risk | 146 | 11 | 91.2 (84.2-95.2) | |
| High Risk | 767 | 171 | 75.5 (71.9-78.7) | |
| **All patients - MammaPrint + BluePrint Subtype** | | | | |
| **OS** | 913 | 134 | | p<0.001 |
| Luminal A | 143 | 7 | 94.6 (88.3-97.6) | |
| Luminal B | 297 | 44 | 84.5 (80.0-88.7) | |
| Basal | 317 | 74 | 72.2 (66.2-77.3) | |
| HER2 | 156 | 9 | 93.4 (87.1-96.7) | |
| **DMFS** | 913 | 182 | | p<0.001 |
| Luminal A | 143 | 11 | 91.1 (82.1-94.3) | |
| Luminal B | 297 | 69 | 75.2 (68.0-80.4) | |
| Basal | 317 | 85 | 70.4 (64.6-75.5) | |
| HER2 | 156 | 17 | 87.2 (79.7-92.0) | |
| **NCT patients - MammaPrint Risk Group** | | | | |
| **OS** | 841 | 121 | | p<0.001 |
| Low Risk | 103 | 3 | 97.4 (90.1-99.4) | |
| High Risk | 738 | 118 | 81.7 (78.3-84.7) | |
| **DMFS** | 841 | 167 | | p<0.001 |
| Low Risk | 103 | 7 | 92.6 (84.1-96.6) | |
| High Risk | 738 | 160 | 76.2 (72.5-79.4) | |
| **NCT patients - MammaPrint + BluePrint Subtype** | | | | |
| **OS** | 841 | 121 | | p<0.001 |
| Luminal A | 100 | 3 | 95.5 (86.2-98.6) | |

| | | | | |
|---|---|---|---|---|
| Luminal B | 274 | 39 | 78.9 (71.7-84.5) | |
| Basal | 313 | 71 | 68.7 (57.9-77.2) | |
| HER2 | 154 | 8 | 92.8 (85.9-96.4) | |
| **DMFS** | 841 | 167 | | p<0.001 |
| Luminal A | 100 | 7 | 92.4 (83.8-96.5) | |
| Luminal B | 274 | 63 | 75.7 (65.6-76.5) | |
| Basal | 313 | 81 | 71.4 (65.6-76.5) | |
| HER2 | 154 | 16 | 87.7 (80.2-92.5) | |
| **NET alone patients - MammaPrint** | | | | |
| **OS** | 59 | 7 | | p=0.01 |
| Low Risk | 39 | 2 | 93.0 (74.6-98.2) | |
| High Risk | 20 | 5 | 80.0 (55.1-92.0) | |
| **DMFS** | 59 | 8 | | p=0.003 |
| Low Risk | 39 | 2 | 93.0 (74.6-98.2) | |
| High Risk | 20 | 6 | 74.7 (49.4-88.6) | |
| **NET alone patients - MammaPrint +BluePrint Subtype** | | | | |
| **OS** | 59 | 7 | | p=0.008 |
| Luminal A | 39 | 2 | 93.0 (74.6-98.2) | |
| Luminal B | 18 | 4 | 83.3 (56.8-94.3) | |
| Basal | 0 | 0 | N/A | |
| HER2 | 2 | 1 | N/A | |
| **DMFS** | 59 | 8 | | p=0.005 |
| Luminal A | 39 | 2 | 93.0 (74.6-98.2) | |
| Luminal B | 18 | 5 | 77.4 (50.3-90.9) | |
| Basal | 0 | 0 | N/A | |
| HER2 | 2 | 1 | N/A | |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** SS2-01

# Impact of the COVID-19 pandemic on the multidisciplinary management of breast cancer: Initial analysis of the american society of breast surgeons mastery COVID-19 registry

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**Background:** The COVID-19 pandemic rapidly altered health care worldwide. To save protective equipment and minimize exposures, many hospitals stopped some or all cancer surgery, leading oncologic providers to quickly adjust patient management. The goal of this study is to describe the breast cancer patient level changes which occurred during the initial months of COVID-19 in the United States. **Methods:** The American Society of Breast Surgeons developed a COVID-19 specific registry, within the established HIPPA compliant Mastery of Breast Surgery Program. Surgeons entered patient demographic data as well as their surgical and medical care (Neoadjuvant endocrine (NET) vs Neoadjuvant chemotherapy (NCT)). Data fields tracked whether decisions were usual for that practice, or modified due to COVID-19. **Results:** Between 3/1 and 6/17/2020, data from 1781 patients was entered by 154 surgeons. Mean age was 63, 78% Caucasian, 10% African American, 6% Hispanic; with geographic distribution ranging from 10.8% Northwest to 29.5% Northeast. Initial consultation took place in-person for 94.8% and only 5.2% (89) occurred via video/telephone. To date, just over 1% (14) of patients tested positive for COVID-19. Mean invasive tumor size was 21.2mm and 15.7% were node positive. Of 1445 invasive breast cancers 75% (1081) were ER +/HER2-, 13.5% (195) HER2+, 11.1% (160) triple negative (TNBC) (9/missing data). DCIS comprised 18.2% (325) of the cohort. Of 267 cases of ER+ DCIS, 49% (131) had primary surgery and 49% (130) received NET. The majority of NET use was due to COVID-19, 95% (124). Almost all (50/52) ER- DCIS underwent primary surgery (6/missing ER). Table 1 describes the management for the 1436 patients with invasive cancer with known biomarkers. NET due to COVID-19 was utilized in 45% (482), with only 5% (54) as part of usual practice. Increasing age was not a statistically significant factor in the use of NET (OR 0.99, 95% CI 0.97-1.01). In comparison to patients from the Northwest, patients from the Southwest and Northeast had the greatest use of NET(COVID-19) vs NET(usual) (ORs 14.4 and 4.6) Genomic assay testing was performed on the core biopsy in 216 patients, with 65% (141) due to COVID-19. Among the patients who had genomic testing due to COVID-19, 116 (82%) had NET, 18 (13%) had NCT, with the remaining having primary surgery. Of 472 patients treated with primary surgery for which the impact of COVID-19 was provided, surgery was delayed in 20% (96). Patients from the Northeast had a 2.1 x greater odds of having surgery delayed in comparison to those from the Midwest. Patients also experienced changes to their surgical plan with the most common changes being 6% (27) converting from mastectomy to breast conservation and 7% (34) from mastectomy with reconstruction to mastectomy without reconstruction. **Conclusion:** COVID-19 led to significant modifications in breast cancer treatment, including high rates of NET, genomic assay testing on core biopsies as well as delays in surgery; each of which were consistent with the prioritization and treatment recommendations from the COVID-19 Pandemic Breast Cancer Consortium. The majority of patients with TNBC and HER2+ disease received guideline concordant NCT. The ASBrS Mastery COVID-19 registry provides a snapshot into the rapid care changes caused by the pandemic, has ongoing data entry and analysis and will enable understanding of the impact on long term breast cancer outcomes.

Table 1: Biomarker specific treatments

| | ER+/HER2- (1081) | TNBC (160) | HER2+/any ER (195) |
|---|---|---|---|
| Mean Age | 65 | 61 | 59 |
| African American (%) | 97(9%) | 21(13%) | 27(14%) |
| Primary Surgery (usual) | 386 (36%) | 50 (31%) | 37 (19%) |
| Primary Surgery (COVID-19) | 28 (2.6%) | 6 (3.7%) | 6 (3.1%) |
| NET (usual) | 54 (5%) | NA | 1(0.5%) |
| NET (COVID-19) | 482 (45%) | NA | 6 (3.6%) |
| NCT (usual) | 90 (8.3%) | 98 (61%) | 137 (70%) |
| NCT (COVID-19) | 39 (3.6%) | 6 (3.7%) | 8 (4.1%) |

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# Radiation therapy improves survival in early-stage HER2-positive breast cancer with high-level of tumor infiltrating lymphocytes

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**Background:** Scientific evidence strongly indicates that locoregional control in early-stage breast cancer (BC) by lumpectomy with radiation therapy or by mastectomy yields similar disease-free survival (DFS) and overall survival (OS). A recent retrospective review of a Danish prospective database demonstrated strong favorable interaction between radiotherapy (RT) and all BC subtypes that contain high amount of tumor infiltrating lymphocytes (TILs).
**Objective:** We aim to compare DFS and OS in patients with early-stage HER2-positive BC, whose tumors demonstrate high involvement by TILs after locoregional treatment by either mastectomy or lumpectomy and whole breast radiotherapy.
**Methods:** We retrospectively reviewed the charts and histopathology slides of patients with HER2-positive BC with clinical stage $T_1$-$T_2$ $N_0$, who were treated in our center between January 2009 and December 2018. Locoregional management included either mastectomy (no radiation group) or lumpectomy with whole breast irradiation (radiation group). Stromal TILs were estimated using hematoxylin-eosin staining, according to the recommendations of the TILs working group 2014. This was performed by 3 independent pathologists who were blinded to the clinical course of the patients. A competing risk model, Kaplan-Meier analysis and multivariate Cox regression analysis were used to estimate correlations between TILs and clinical outcomes.
**Results:** A total of 110 charts were reviewed and 99 were included in the final analysis. Patients were dichotomized into groups of “low-TILs” and “high-TILs” using a 40% cut off. Approximately 25% of patients (26/99) were “high-TILs” and around 50% of the “high-TILs” and “low-TILs” patients received RT. In all groups, around 90% of patients received chemotherapy and anti-HER2 therapy. All hormone receptor-positive patients received adjuvant endocrine therapy. While RT did not result in significant DFS or OS advantage in the low-TILs group, patients with high-TILs had significant improvement of DFS and OS with the addition of RT. Table 1 depict the 5-year DFS and 5-year OS in "high-TILs" and "low-TILs" groups in relation to RT, respectively.
**Conclusion:** In this retrospective analysis, our findings indicate that in high-TILs early-stage HER2-positive BC, RT was associated with significant improvement of 5-year DFS and OS. The exact mechanism is not well understood. However, this observation is important and warrants confirmation in prospective clinical trials.

| | 5-year DFS | | 5-year OS | |
|---|---|---|---|---|
| | **High TILs** | **Low TILs** | **High TILs** | **Low TILs** |
| RT group | 100% | 90% | 100% | 83% |
| No RT group | 65% | 90% | 72% | 93% |
| p-value | ***0.027*** | 0.96 | ***0.025*** | 0.184 |

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# Adherence to the new WCRF cancer prevention recommendations associates with a decreased breast cancer risk

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Background: Breast cancer remains the leading cancer in women. In 2018, following its summary report, the World Cancer Research Fund (WCRF) issued its recommendations for cancer prevention based on the nutritional risk factors with a sufficient level of evidence, several of which being related to breast cancer. Our objective was to study whether adherence to these new recommendations was actually associated with reduced risk of breast cancer.
Methods: A total of 62,546 women from the NutriNet-Santé population-based cohort study (2009-2019) were included in our analyses. Adherence to the 2018 WCRF recommendations was assessed using the operationalized score on a 7-point scale, proposed by Shams-White et al (Nutrients 2019), including: weight, physical activity, fruit and vegetables, dietary fibers, ultra-processed foods, red and processed meat, sugary drinks and alcohol. Usual dietary intakes were assessed using repeated 24h-dietary records and physical activity level using the IPAQ questionnaire. Cox proportional hazard models were computed with adjustment for the following potential confounders: educational level, height, smoking status, number of 24h dietary records, family history of cancer, number of biological children, age at menarche, age at parity, menopausal status, use of oral contraception or hormonal treatment for menopause.
Results: During a median follow-up of 7.3 years, 745 women were diagnosed with a first incident breast cancer. The median WCRF 2018 adherence score was 3.75 (IQR: 3.25-4.50). An increase of 1-point increment in the score was associated with a decreased risk of breast cancer (HR=0.92; 95%CI 0.85-1.00; P=0.05), and especially of breast cancer post-menopause (n=456 cases, HR=0.88; 0.79-0.98; P=0.02). No association was observed for breast cancer pre-menopause (n=289, HR=0.99; 0.87-1.12; P=0.8). Sugary drink, alcohol and weight components of the score particularly contributed to the observed association.
Conclusions: Our results suggest that a higher adherence to the WCRF 2018 recommendations for cancer prevention is associated to a decreased risk of breast cancer. Considering that the WCRF cancer recommendations are consistent with overall food-based dietary guidelines, such recommendations should be promoted to the general public and transposed as public health actions to contribute to decrease the burden of cancer.

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# BluePrint performance in predicting pertuzumab benefit in genomically HER2-positive patients: A biomarker analysis of the APHINITY trial

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**BACKGROUND:**APHINITY is a phase III study (NCT01358877) which included 4805 patients (pts) with histologically centrally confirmed HER2+ early breast cancer (EBC) randomized to standard adjuvant chemotherapy (C) plus trastuzumab (T), plus either pertuzumab (P) or placebo[1] for 1 year. With median follow up of 45 months, the primary analysis showed significant invasive disease-free survival (iDFS) benefit at 3 years with a hazard ratio (HR) of 0.81 (95% CI: 0.66-1.00; $P = 0.045$) for the addition of P to C/T[1]. BluePrint (BP) is an 80-gene molecular subtyping test that classifies EBC into functional basal, luminal and HER2 BP-subtypes[3] according to gene expression. Previous studies showed that this genomic test can reclassify HER2+ EBC (as determined by IHC/FISH) into basal, luminal or HER2 BP-subtypes[4]. Recently, it was revealed that a smaller proportion of breast tumours may display two functionally activated BP pathways (BP dual activated subtypes, of which one is usually less pronounced), whereas the majority has clearly only one activated functional BP pathway (BP single activated subtypes)[5]. We hypothesized that BluePrint could identify a subgroup of patients within the APHINITY population who derived additional benefit from the addition of P to C/T.**METHODS:**Genomic results were obtained using RNA sequencing (RNAseq) data[6] from a subset of APHINITY pts (N=970) derived from a 1023 unique patients nested case-control (NCC) set where event and matched controls were selected (1 iDFS event matched to 3 controls from the primary analysis database with 45 months median follow-up). Raw read counts were $\log_2$ transformed followed by quantile normalization prior to genomic assessment. BP subtype scores were calculated equally to the standard microarray diagnostic testing and calibrated based on a bridge analysis with matched microarray and RNAseq data. IDFS outcome based on genomic subtype and the treatment arm (P+C/T *vs* placebo + C/T) was analysed. Results are reported descriptively with 95% CIs.**RESULTS:**From the patients within the NCC subset, BP subtype testing classified the 970 pts as basal, n=210 (22%); luminal, n=485 (50%) and HER2, 275 (28%) subtypes, an expected finding since the majority were hormone receptor positive (N=598/970, 62%). Further dissection of the BP results showed single activated subtype in 123 of 210 (59%) basal, 413 of 485 (85%) luminal and 139 of 275 (51%) of HER2 subtype cancers.
After NCC-inverse probability weighted corrected multivariate Cox regression analysis, no significant differences in iDFS were observed among the different genomic subtypes. A greater benefit with the addition of P to T/C was suggested in the 'single activated' HER2 BP-subtype compared with other groups (single HER2 HR=0.56, 95% CI 0.27-1.15, single basal HR=0.89, 95% CI 0.44-1.79 and single luminal HR=0.93, 95% CI 0.61-1.41).
**CONCLUSIONS:**In this exploratory analysis, HER2+ tumors with a single transcriptional HER2 activated pathway showed a trend for greater benefit from pertuzumab than tumors in which multiple mitogenic pathways are activated. Further research is ongoing to confirm these findings.
**References**1.von Minckwitz G et al, NEMJ, 20172.Piccart M et al, SABCS, 20193.Krijgsman O et al, BCRT, 20114.Whitworth P et al, ASO, 20145.Kuilman M et al, EBCC12, 20206.Krop IE et al, ASCO, 2020

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6-year absolute invasive disease-free survival (IDFS) benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: A STEPP analysis of the APHINITY (BIG 4-11) trial

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**Background:** The primary analysis of the randomized, double-blind, placebo-controlled APHINITY trial, published in 2017, including 4804 patients (pts) with HER2-positive, early breast cancer with 45.4 months' median follow-up, demonstrated that adjuvant pertuzumab (P) added to trastuzumab and chemotherapy, statistically significantly improved invasive disease-free survival (IDFS) compared with placebo (Pla) added to trastuzumab and chemotherapy overall and for pts with node-positive (N+) disease. In 2019, updated descriptive analyses of IDFS with 74.1 months' median follow-up, demonstrated sustained benefit of adding P both overall (HR, 0.76; 95% CI, 0.64-0.91), and for N+ disease (HR, 0.72; 95% CI, 0.59-0.87), while confidence intervals remained wide for the node-negative (N-) cohort (HR, 1.02; 95% CI, 0.69-1.53). There is great interest to explore how these significant overall results translate into absolute treatment benefits for different patient subpopulations.
**Methods:** Subpopulation Treatment Effect Pattern Plot (STEPP) is an exploratory, graphical method that plots estimates of treatment effect for overlapping patient subpopulations defined by a covariate of interest. Four continuous covariates of interest are considered for defining subpopulations in this report: i) a clinical composite risk score (see below), ii) TILs percentage, iii) HER2 FISH copy number, and iv) a clinical-biological composite risk score combining the previous three factors. Pts with lowest values for the covariate comprise the extreme left STEPP subpopulation, and pts with highest values comprise the extreme right subpopulation. The clinical composite risk score for IDFS based on the overall cohort was calculated using a Cox regression model including the following prespecified clinical characteristics: number of positive nodes, tumor size, age, and centrally-reviewed hormone receptor status. Composite risk scores were scaled between 0 and 100 with higher scores reflecting higher risk of an IDFS event. An example of low clinical risk factors would be T1N0 and aged 40-64; while high risk would be T3N2 or higher and ages <40 or ≥65. At 74.1 months' median follow-up, the composite risk of an IDFS event did not depend on hormone receptor status. Differences in Kaplan-Meier estimates of 6-year IDFS percents (P minus Pla) were used as estimates of treatment effect for each subpopulation. The overall analyses (N=4804) used 9 overlapping subpopulations with ~1000 pts in each, the N- analyses (N=1799) used 5 subpopulations with ~500 pts in each, and the N+ analyses (N=3005) used 7 subpopulations with ~750 pts in each. Intermediate (middle) subpopulations were the 5th, 3rd, and 4th, respectively.
**Results:** Table of 6-year IDFS percents (%) from Aphinity STEPPs, Overall and for N- and N+ cohorts. For each analysis, results are shown for the two subpopulations at either extreme of the STEPP (i.e. lowest and highest risk or values) as well as the intermediate STEPP subpopulation.
**Conclusions:** Based on the two extreme and one intermediate subpopulations of the STEPP analyses shown in the table, the intermediate clinical composite risk subpopulation and the highest TILs percentages had the largest absolute improvements in 6-year IDFS percents for P compared with Pla.

Table of 6-year IDFS percents (%) from Aphinity STEPPs, Overall and for N- and N+ cohorts.

| **6-year IDFS %** | **Overall (N=4804)** | | | **Node-Negative (N=1799)** | | | **Node-Positive (N=3005)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **P** | **Pla** | **Δ?SE** | **P** | **Pla** | **Δ?SE** | **P** | **Pla** | **Δ?SE** |
| **Overall Average Results** | 90.6 | 87.8 | **2.8?0.9** | 95.0 | 94.9 | **0.1?1.1** | 87.9 | 83.4 | **4.5?1.2** |
| **Clinical composite risk** | | | | | | | | | |
| Lowest risk (0 - 21) | 95.3 | 96.2 | **-0.9?1.3** | 96.1 | 96.5 | **-0.4?1.5** | - | - | - |
| Intermediate (39 - 63) | 92.6 | 87.3 | **5.3?1.9** | 95.0 | 91.0 | **4.0?3.0** | 93.6 | 86.7 | **6.9?2.3** |
| Highest risk (81 - 100) | 80.5 | 75.8 | **4.7?2.8** | - | - | - | 79.4 | 75.4 | **4.0?3.2** |
| **TILs percentage** | | | | | | | | | |
| Lowest values (0-9) | 90.4 | 87.8 | **2.6?2.0** | 94.7 | 95.2 | **-0.5?2.0** | 87.2 | 82.6 | **4.6?2.7** |
| Intermediate (13-21) | 89.4 | 87.7 | **1.7?2.1** | 94.2 | 94.1 | **0.1?2.2** | 85.4 | 84.8 | **0.6?2.7** |
| Highest values (≥31) | 95.6 | 89.3 | **6.3?1.7** | 98.1 | 94.9 | **3.2?1.7** | 92.3 | 84.9 | **7.4?2.4** |
| **HER2 copy number** | | | | | | | | | |
| Lowest values (1-8) | 87.1 | 86.4 | **0.7?2.2** | 92.7 | 94.8 | **-2.1?2.2** | 84.1 | 82.1 | **2.0?2.8** |
| Intermediate (9.5-11) | 91.8 | 89.0 | **2.8?1.9** | 94.9 | 96.1 | **-1.3?1.9** | 90.7 | 83.3 | **7.4?2.5** |
| Highest values (13-32) | 90.5 | 88.9 | **1.6?2.0** | 96.0 | 95.1 | **0.9?2.0** | 87.7 | 85.3 | **2.4?2.6** |
| **Clinical-biological composite risk** | | | | | | | | | |
| Lowest risk (0-21) | 96.7 | 96.4 | **0.3?1.2** | 98.2 | 95.7 | **2.5?1.6** | - | - | - |
| Intermediate (40-60) | 93.4 | 89.5 | **3.9?1.9** | 91.7 | 92.7 | **-1.0?2.5** | 94.2 | 88.8 | **5.4?2.2** |
| Highest risk (79-100) | 80.1 | 75.9 | **4.2?2.7** | - | - | - | 79.5 | 75.2 | **4.3?3.2** |

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# Snord67 promotes lymph node metastasis through U6-mediated alternative splicing in breast cancer

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**Background:** While the presence of lymph node (LN) metastases in solid tumor malignancies is clinically significant and associated with increased risk for distant metastases, there is little evidence that lymphatic metastasis is distinct from hematogenous dissemination. Recent studies showed that cancer cells in LNs can directly give rise to distant metastases, but the mechanisms behind how cancer cells exit lymph nodes to establish distant metastases is still unknown.
**Materials and Methods:** We developed an immunocompetent mouse model of lymph node metastasis using the 4T1 murine breast cancer cell line. In this model, 4T1 cells micro-surgically injected into axillary lymph nodes (AxLN) are capable of spontaneously establishing distant metastases. We then performed microarray analyses of subclones derived from MFP tumors, AxLN-injected tumors (AxLN), and lung metastases that arose from AxLN-injected tumors (AxLN-LuM) to evaluate for non-coding RNAs (ncRNAs) that were differentially expressed in AxLN tumors.
**Results:** Microarray analyses of ncRNAs expressed in MFP, AxLN, and AxLN-LuM subclones showed that a class of ncRNAs, small nucleolar RNAs (snoRNAs), were enriched in AxLN tumors compared to MFP and AxLN-LuM. We identified the snoRNA SNORD67 as a key regulator of LN metastasis. Knockout of SNORD67 by both CRISPR and antisense oligonucleotide (ASO) resulted in significantly decreased LN tumor growth and subsequent development of distant metastases. This was at least in-part due to loss of targeted 2'-O-methylation of the small nuclear RNA U6, a component of the spliceosome. RNA-Seq analyses revealed distinct alternative splicing in SNORD67 knockouts. Using rapid autopsy breast cancer cases, we found that matched primary tumor and LN metastases revealed similar alternatively spliced genes, including several genes with previously described cancer-promoting splice variants.
**Conclusions:** Small nucleolar RNAs (snoRNAs) have long been regarded as “housekeeping genes”, important for ribosomal biogenesis and protein synthesis. However, there is increasing evidence that this largely ignored class of non-coding RNAs (ncRNAs) also have wide-ranging, non-canonical functions in diseases, including cancer. SnoRNAs have been shown to have both oncogenic and tumor suppressor roles, yet whether snoRNAs regulate metastasis is unknown. Here we show that expression of certain snoRNAs are enriched in lymph node (LN) metastases in a micro-surgical, immune-competent mouse model of breast cancer. Moreover, our results show that SNORD67 is critical for growth of LN metastases and subsequent spread to distant metastases, and suggest that snoRNA-guided modifications of the spliceosome represent a previously unappreciated, yet targetable pathway in cancer.

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Characteristics and outcomes of SARS-CoV-2 infection in patients with invasive breast cancer (BC) from the COVID-19 and cancer consortium (CCC19) cohort study

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**Background:** Overall, patients with cancer experience a greater risk of adverse outcomes following SARS-CoV-2 infection; however, little is known for those with BC.
**Methods:** CCC19 (NCT04354701) is an international cohort study aimed at investigating the impact of COVID-19 in patients with a history of or active cancer using de-identified data on patient demographics, cancer history, clinical course and outcomes of COVID-19. The current analysis includes patients from U.S. and Canada with invasive BC and laboratory-confirmed SARS-CoV-2 entered between March 17, 2020 and July 2, 2020. Co-primary outcomes were hospitalization during COVID-19 illness and 30-day all-cause mortality. Frequencies for categorical variables and medians (range) for continuous variables were estimated. Final presentation will include bivariable and multivariable Cox proportional hazards regression analysis to identify risk factors (including BC subtypes and therapies, for which data collection is ongoing) associated with 30-day all-cause mortality and severe COVID-19 illness (composite of any hospitalization requiring supplemental oxygen, admission to an intensive care unit [ICU], use of mechanical ventilation, or death).
**Results:** During the study period, a total of 2683 patients with cancer and COVID-19 were accrued in the CCC19 registry including 529 (20%) with invasive BC. Among patients with BC, 352 (67%) were 60 years or older; 518 (98%) were women; 275 (52%) non-Hispanic White, 116 (22%) non-Hispanic Black, 70 (13%) Hispanic, 56 (11%) in other categorizations; 178 (34%) had a smoking history; 75 (14%) ECOG performance status ≥2; 191 (36%) with >2 active comorbidities; 64 (12%) with AJCC stage IV disease at BC diagnosis; and 267 (50%) were on anti-cancer treatment including systemic therapy, radiation, or surgery within 3 months of COVID-19 diagnosis. At least 323 (61%) patients with BC had 30-day follow-up after COVID-19 diagnosis, and 35 (7%) had 90-day follow-up. COVID-19 illness at initial diagnosis required outpatient care in 288 (54%), inpatient care in 193 (36%), and ICU care in 40 (8%). Overall, 247 (47%) were hospitalized and 30-day all-cause mortality was 9%. 30-day all-cause mortality rates by receipt of major BC treatment modalities (within past 3 months) were: 10% for those on cytotoxic systemic therapy vs 5% and 12% for noncytotoxic systemic therapy and local therapy, respectively. The table shows hospitalization and mortality outcomes by major demographic and BC treatment strata. The final presentation will incorporate the latest patient accrual and evaluate independent clinical risk factors associated with serious COVID-19 outcomes in patients with BC.
**Conclusions:** This represents the largest study to date of COVID-19 outcomes in patients with invasive BC. Nearly half of the patients with BC required hospitalization during their COVID-19 disease course and we observed a 9% 30-day all-cause mortality.
Submitted on behalf of the COVID-19 and Cancer Consortium (ccc19us.org)

**Table 1.** COVID-19 related hospitalization and 30-day all-cause mortality for all patients with invasive BC

| | **N** | **Any Hospitalization** | | **30-day all-cause Mortality** | |
|---|---|---|---|---|---|
| | | N | % [95% CI] | N | % [95% CI] |
| **Total population** | 529 | 247 | 47 [42-51] | 49 | 9 [7-12] |
| **Age** | | | | | |
| <60 | 177 | 44 | 25 [19-32] | 2 | 1 [0-4] |
| 60-69 | 115 | 51 | 44 [35-54] | 8 | 7 [3-13] |
| 70-79 | 120 | 66 | 55 [46-64] | 17 | 14 [8-22] |
| 80+ | 117 | 86 | 74 [65-81] | 22 | 19 [12-27] |
| **ECOG PS** | | | | | |
| 0-1 | 322 | 122 | 38 [33-43] | 16 | 5 [3-8] |
| 2+ | 75 | 61 | 81 [71-89] | 16 | 21 [13-32] |
| **Active Comorbidities** | | | | | |
| 0 | 74 | 10 | 14 [7-23] | 0 | 0 [0-5] |
| 1-2 | 223 | 94 | 42 [36-49] | 17 | 8 [5-12] |
| >2 | 191 | 129 | 68 [60-74] | 29 | 15 [10-21] |
| **Treatment Intent** | | | | | |
| Curative | 186 | 64 | 34 [28-42] | 9 | 5 [2-9] |
| Palliative | 74 | 39 | 53 [41-64] | 12 | 16 [9-27] |
| **Cancer Status** | | | | | |
| Remission/NED | 331 | 154 | 47 [41-52] | 24 | 7 [5-11] |
| Active disease, stable or responding to treatment | 119 | 48 | 40 [31-50] | 7 | 6 [2-12] |
| Active disease, progressing | 37 | 27 | 73 [56-86] | 11 | 30 [16-47] |
| **Treatment Modality (within 3 months)** | | | | | |
| Cytotoxic chemotherapy | 83 | 35 | 42 [31-54] | 8 | 10 [4-18] |
| Noncytotoxic therapy | 185 | 64 | 35 [28-42] | 10 | 5 [3-10] |
| Local therapy (surgery or radiation) | 34 | 17 | 50 [32-68] | 4 | 12 [3-27] |

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Additional efficacy endpoints from the phase 3 KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy for locally recurrent inoperable or metastatic triple-negative breast cancer

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**Background:** Pembrolizumab (pembro) monotherapy showed durable antitumor activity and manageable safety in patients (pts) with metastatic triple-negative breast cancer (TNBC) in the KEYNOTE-012, -086, and -119 studies. In a prespecified interim analysis of KEYNOTE-355 (NCT02819518), pembro combined with chemotherapy (chemo) showed a statistically significant improvement in PFS versus chemo alone in pts with previously untreated locally recurrent inoperable or metastatic TNBC whose tumors expressed PD-L1 CPS ≥10 (HR for progression or death, 0.65, 95% CI, 0.49-0.86; one-sided *P*=0.0012 [prespecified statistical criterion was alpha=0.00411 at this interim analysis]). Additionally, pembro + chemo was generally well tolerated, with no new safety signals. Here, we examine PFS outcomes for each chemo partner and present key secondary endpoints from KEYNOTE-355.
**Methods:** 847 pts with measurable disease per RECIST v1.1, ECOG PS 0-1, and ≥6 mo DFI were randomized 2:1 to pembro + chemo (nab-paclitaxel 100 mg/m$^2$ days 1, 8, and 15 every 28 days; paclitaxel 90 mg/m$^2$ days 1, 8, and 15 every 28 days; or gemcitabine 1000 mg/m$^2$ + carboplatin AUC 2 days 1 and 8 every 21 days) or pbo + chemo for up to 35 administrations of pembro/pbo or until progression/intolerable toxicity. Steroid premedication for paclitaxel was given according to local guidelines and practices, and was not restricted by the protocol. Crossover between arms was not allowed. Pts were stratified by chemo type (taxane vs gemcitabine/carboplatin), PD-L1 status (CPS ≥1 vs <1), and prior (neo)adjuvant treatment with same-class chemo (yes vs no). Dual primary endpoints are PFS (RECIST v1.1, blinded independent central review) and OS in pts with PD-L1 positive tumors (CPS ≥10 and ≥1) and in all pts. Secondary endpoints include ORR, DCR (CR + PR + SD ≥24 weeks), and DOR. The PFS treatment effect was assessed in subgroups descriptively using HRs and 95% CIs; although subgroup analysis by on-study chemo were pre-specified, the trial was not powered to compare efficacy among treatment groups by different chemo regimens.
**Results:** As of Dec 11 2019, median follow-up was 25.9 mo for pembro + chemo (n=566) and 26.3 mo for pbo + chemo (n=281). The HR for PFS favored pembro regardless of choice of chemo or CPS population (**Table**). Results for the key secondary endpoints of ORR, DCR, and DOR favored pembro + chemo, with the treatment effect increasing as CPS increased (**Table**).
**Conclusion:** In subgroup analysis, PFS with pembro + chemo compared to pbo + chemo in pts with metastatic TNBC was improved regardless of chemo partner. A trend toward improved efficacy with PD-L1 enrichment with pembro + chemo was observed for ORR, DCR and DOR endpoints. These data further support the potential of pembro + chemo as a first-line treatment option for metastatic TNBC.

| | **CPS ≥ 10** | | **CPS ≥ 1** | | **All pts** | |
|---|---|---|---|---|---|---|
| | **Pembro + Chemo N = 220** | **Pbo + Chemo N = 103** | **Pembro + Chemo N = 425** | **Pbo + Chemo N = 211** | **Pembro + Chemo N = 566** | **Pbo + Chemo N = 281** |
| PFS, mo median (95% CI) | 9.7 (7.6 - 11.3) | 5.6 (5.3 - 7.5) | 7.6 (6.6 - 8.0) | 5.6 (5.4 - 7.4) | 7.5 (6.3 - 7.7) | 5.6 (5.4 - 7.3) |
| HR (95% CI) | 0.65 (0.49 - 0.86) | | 0.74 (0.61 - 0.90) | | 0.82 (0.69 - 0.97) | |
| PFS by on-study chemo, (*n [%]*) mo median(95% CI) | | | | | | |
| Nab-Paclitaxel | (*63 [28.6%]*) 9.9 | (*36 [35.0%]*) 5.5 | (*130 [30.6%]*) 6.3 | (*74 [35.1%]*) 5.3 | (*173 [30.6%]*) 7.5 | (*95 [33.8%]*) 5.4 |
| HR (95% CI) | 0.57 (0.34 - 0.95) | | 0.66 (0.26 - 0.82) | | 0.69 (0.51 - 0.93) | |
| Paclitaxel | (*33 [15.0%]*) 9.6 | (*11 [10.7%]*) 3.6 | (*62 [14.6%]*) 9.4 | (*22 [10.4%]*) 3.8 | (*82 [14.5%]*) 8.0 | (*32 [11.4%]*) 3.8 |
| HR (95% CI) | 0.33 (0.14 - 0.76) | | 0.46 (0.26 - 0.82) | | 0.57 (0.35 - 0.93) | |
| Gemcitabine-Carboplatin | (*124 [56.4%]*) 8.0 | (*56 [54.4%]*) 7.2 | (*233 [54.8%]*) 7.5 | (*115 [54.5%]*) 7.5 | (*311 [54.9%]*) 7.4 | (*154 [54.8%]*) 7.4 |
| HR (95% CI) | 0.77 (0.53 - 1.11) | | 0.86 (0.66 - 1.11) | | 0.93 (0.74 - 1.16) | |
| ORR, % (95% CI) | 53.2 (46.4 - 59.9) | 39.8 (30.3 - 49.9) | 45.2 (40.4 - 50.0) | 37.9 (31.3 - 44.8) | 41.0 (36.9 - 45.2) | 35.9 (30.3 - 41.9) |
| DCR, % (95% CI) | 65.0 (58.3 - 71.3) | 54.4 (44.3 - 64.2) | 58.6 (53.7 - 63.3) | 53.6 (46.6 - 60.4) | 56.0 (51.8 - 60.1) | 51.6 (45.6 - 57.6) |
| DOR, mo, median (range) | 19.3 (1.6+ - 29.8) | 7.3 (1.5 - 32.5+) | 10.1 (1.0+ - 29.8) | 6.5 (1.5 - 32.5+) | 10.1 (1.0+ - 29.8) | 6.4 ( 1.5 - 32.5+) |
| "+" indicates there is no progressive disease by the time of last disease assessment. | | | | | | |

**Publication Number:** PD4-01

Preservation of axillary lymph nodes compared to complete dissection in T1-T2 breast cancer patients presenting 1-2 metastatic sentinel lymph nodes : A multicenter randomized clinical trial. Sinodar One.

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**Introduction:** Sentinel lymph node (SLN) staging is currently used to avoid complete axillary lymph node dissection (ALND) in breast cancer (BC) patients. The SLN is the only site of axillary metastasis (MTS) in ≤60% of cases. Recently, a randomized controlled trial (Z0011) comparing SLN biopsy (SLNB) alone with SLNB followed by ALND in patients with 1-2 SLNs+ demonstrated no significant statistical difference in relapse and overall survival rates among the two different groups. However, this study had some limitations: small tumor size (≤2cm in 70% of cases), frequent presence of only microMTS in SLN (40%), prevalent use of “whole breast” adjuvant radiotherapy (>90%). Given these considerations, the SINODA**R-**ONE study started in April 2015.**Objectives:** The aims are to assess whether ALND omission in BC patients with 1-2 SLNs+ is associated with worse survival and/or increased rate of regional/distant relapse. Thus evaluating whether SLNB is or is not inferior to ALND. Primary endpoint is overall survival (OS). Secondary endpoints are disease-free survival (DFS) referring to distant MTS and loco-regional recurrence. **Methods:** Patients receive either mastectomy or conservative surgery plus radiotherapy. They all undergo SLNB and are randomly divided into two arms of treatment: standard (SLNB plus ALND) or experimental treatment (only SLNB). According to multidisciplinary evaluation, patients may undergo additional adjuvant radiotherapy, chemo- and/or hormonal therapy , or no further therapy. Eligibility criteria: age 40-75 years; primary invasive T1-T2 tumor; axillary nodes clinically N0; no more than 2 macro-metastatic SLNs; no distant MTS; no neo-adjuvant therapy; no previous invasive BC; signed informed consent. Exclusion criteria: in situ, inflammatory, contralateral BC; micro-metastic SLNs; pregnancy or breast feeding; comorbidity impeding adjuvant therapy. All analyses are performed both on all patients according to the Intention-To-Treat principle and excluding those patients who did not receive the axillary treatment randomly assigned. Statistical analysis: OS and DFS are calculated using the Kaplan-Meier Product Limit Estimator and differences between arms are assessed with the log-rank test. **Results:** The enrollment of patients ended in April 2020 with a total of 889 cases (443: standard arm; 446: experimental arm). In June 2020, we conducted an ad interim analysis on 889 patients. We found the two groups homogeneous for epidemiologic characteristics (age and menopausal status), tumor characteristics (tumor size, pTNM, immunohistochemistry, histology, grading, vascular and lymphatic invasion), adjuvant therapies and surgery on T. In particular we have performed a 23,1% of mastectomies in the standard arm and 20,1% in the experimental arm. We found a median of 2 sentinel lymph nodes removed in both arms and 1 non-sentinel positive lymph node in the experimental arm, and only 3 micro-metastases (1 in the standard arm and 2 in the experimental arm). **Conclusion:** In sum, with a median follow-up of 30 months, there have been no axillary recurrence in both arms. In the standard arm we found 8 total events (2 deaths and 6 distant relapses) and in in the experimental arm 6 events (1 death and 5 distant relapses), with a projected 5-years cumulative incidence of 6,5% in standard arm and 4,85% in the experimental arm.

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**Publication Number:** PD12-01

# Evaluation of sleep problems and their association with febrile neutropenia, leucopenia and infections in women receiving adjuvant chemotherapy for breast cancer in the Canadian Cancer Trials Group MA.21 trial

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BackgroundInsomnia is a frequent complaint in patients with cancer. Sleep problems can affect immune functioning in healthy individuals. Our aim was to evaluate the association between sleep disturbance and the risk of febrile neutropenia, leukopenia and infections in patients treated with chemotherapy in an adjuvant setting for breast cancer.MethodologyThis is a retrospective study using the Canadian Cancer Trial Group data collected for the MA.21 trial, in which three adjuvant chemotherapy regimens (CEF, EC-T dose dense or AC-T) were compared in 2104 patients with node positive or high-risk node negative breast cancer. A total of 1731 patients had completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and 1727 patients had completed the Breast Cancer Chemotherapy Questionnaire (BCQ) quality of life questionnaires, which both include a question about sleep difficulties. The primary definition for patients with insomnia was a score of three (quite a bit) or greater at Question 11 (Have you had trouble sleeping? with answers ranging from one (not at all) to four (very much)) on the EORTC QLQ-C30 questionnaire. We compared patients classified as having “clinical insomnia” based on their response to this question with patients considered “good sleepers”. The primary endpoint was the risk of febrile neutropenia. Secondary endpoints were the risks of grade one or more leukopenia, neutropenia and infection. ResultsFebrile neutropenia was more frequent in patients with sleep problems compared with those without, with 16.3% and 12.2% of patients having at least one episode in each group respectively (p value = 0.01 in the univariate analysis (table 1)). However, after adjustment for potential confounders in the multi-variate analysis, it was not statistically significant with an odds ratio of 1.07, a 95% confidence interval of 0.76-1.50 and a p value of 0.71. Similarly, no statistically significant difference in the risk of leukopenia could be demonstrated in the multi-variate analysis for patients with sleep problems with an odds ratio of 0.92 a 95% confidence interval of 0.69-1.24 and a p value of 0.59. No significant association could be found between sleep problems and neutropenia and infections. In an unplanned exploratory analysis, chemotherapy dose reductions were significantly more frequent in patients with sleep problems with 30.6% in this group compared to 21.8% in good sleepers, with a p value <0.0001.. ConclusionWhile our univariate analysis suggested an increased risk of febrile neutropenia and leucopenia in patients with sleep problems, after adjustment for confounders, we could not show a statistically significant association in women undergoing adjuvant chemotherapy for high-risk locoregional breast cancer.

Table 1: Univariate analysis of primary and secondary outcomes in patients with sleep problems and good sleepers

| **Characteristics** | **Sleep problem= yes** | **Sleep problem = no** |
|---|---|---|
| Febrile neutropenia | | |
| No | 781 (83.7%) | 701 (87.8%) |
| Yes | 152 (16.3%) | 97 (12.2%) |
| P-value | 0.01 | |
| White blood cell count (WBC) | | |
| Grade 0 | 157 (16.8%) | 141 (17.7%) |
| Grade 1 | 135 (14.5%) | 138 (17.3%) |
| Grade 2 | 184 (19.7%) | 186 (23.3%) |
| Grade 3 | 214 (22.9%) | 173 (21.7%) |
| Grade 4 | 243 (26.1%) | 160 (20.1%) |
| P-value | 0.02 | |
| Neutropenia | | |
| Grade 0 | 778 (83.4%) | 700 (87.7%) |
| Grade 1 | 0 (0%) | 1 (0.1%) |
| Grade 2 | 2 (0.2%) | 0 (0%) |
| Grade 3 | 152 (16.3%) | 96 (12.0%) |
| Grade 4 | 1 (0.1%) | 1 (0.1%) |
| P-value | 0.014 | |
| Infection | | |
| Grade 0 | 619 (66.4%) | 564 (70.7%) |
| Grade 1 | 68 (7.3%) | 62 (7.8%) |
| Grade 2 | 158 (16.9%) | 110 (13.8%) |
| Grade 3 | 87 (9.3%) | 61 (7.6%) |
| Grade 4 | 1 (0.1%) | 1 (0.1%) |
| P-value | 0.24 | |
| Chemotherapy delay | | |
| No | 1 (0.1%) | 12 (1.5%) |
| Yes | 932 (99.9%) | 786 (98.5%) |
| P-value | 0.0008 | |
| Chemotherapy dose reduction | | |
| No | 648 (69.4%) | 624 (78.2%) |
| Yes | 285 (30.6%) | 174 (21.8%) |
| P-value | < 0.0001 | |

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# Identification of women at high risk of breast cancer and in need of supplemental screening - A cohort study

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**Background**. Mammography screening reduces breast cancer mortality, but a large proportion of breast cancers are missed and detected at later stages or develop in between screening intervals. We developed the KARMA model which identifies women who are likely to be diagnosed with breast cancer before or at the next screen.
**Materials and Methods**. The study was based on the prospective screening cohort KARMA including 70,877 participants. We identified 974 incident cancers and sampled 9,376 healthy individuals from the cohort. An image-based risk score was developed using mammographic features (density, masses, microcalcifications), their left-right asymmetries, and age. The lifestyle extended score also included menopausal status, family history of breast cancer, body-mass-index, hormone replacement therapy, and use of tobacco and alcohol. The genetic extended score also included a polygenic risk score including 313 single nucleotide polymorphisms. Relative risks were estimated using age stratified logistic regression. Tumor sub-type specific risks were estimated. Absolute risks were estimated including relative risks and national incidence rates.
**Results**. The image-based model reached an area under the curve (AUC) of 0.73 (95% CI 0.71,0.74). The lifestyle and genetic extended model AUCs were 0.74 (95% CI 0.72,0,75) and 0.77 (95% CI 0.75,0.79) respectively. There was a relative 8-fold difference in risk between the women at high and general risk. High risk women were more likely diagnosed with stage II and >= 20 mm tumors and less likely with stage I and estrogen receptor-positive tumors. The image-based model was validated in two external cohorts.
**Conclusion**. By combining three mammographic features, their left-right asymmetries, and optionally lifestyle factors, family history, and a polygenic risk score we generated a model that identifies women at high likelihood of being diagnosed with breast cancer within two years of a negative screen and in possible need of supplemental screening or preventive intervention.

**Table 1.** Discrimination performance (AUC) of the risk score in relation to the three models of the study. The 2-year risk Model 1 is compared with the two external validation datasets.

| **Model** | **AUC (95% CI)** [1] |
|---|---|
| *KARMA case-cohort (974 cancers, 9,376 healthy subjects)* | |
| 1. Model 1; mammographic density, microcalcifications, masses, age | 0.73 (0.71,0.74) |
| 2. Model 2; Model 1 + lifestyle and familial risk factors[2] | 0.74 (0.72,0.75) |
| 3. Model 3; Model 2 + PRS[3] | 0.77 (0.75,0.79) |
| *MBTST cohort (104 cancers, 9,745 healthy subjects), Model 1* | 0.71 (0.67,0.75) |
| *CSAW (613 cancers, 8,489 healthy subjects), Model 1* | 0.73 (0.71,0.76) |
| *KARMA independent test set (179 cancers, 9,491 healthy subjects), Model 1* | 0.73 (0.69, 0.77) |

Polygenic risk score included 313 SNPs.

**Table 2.** Comparison discrimination performance (AUC) of the PRS, Tyrer-Cuzick, and Gail risk scores with and without mammographic density in KARMA case-cohort.

| **Model** | **AUC (95% CI)** [1] |
|---|---|
| PRS[2] | 0.64 (0.62,0.66) |
| PRS[2] + mammographic density[3] | 0.67 (0.65,0.69) |
| Tyrer-Cuzick[4] | 0.58 (0.56,0.60) |
| Tyrer-Cuzick[4] + mammographic density[3] | 0.62 (0.60,0.64) |
| Gail[5] | 0.56 (0.54,0.58) |
| Gail[5] + mammographic density[3] | 0.61 (0.60,0.63) |

Polygenic Risk Score included 313 SNPs.Mammographic density were adjusted for age and BMI.

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Quantitative dynamic contrast-enhanced (DCE) MRI radiomic phenotypes for prediction of nodal and distal metastasis in breast cancer patients

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Background and Purpose:Image-based tumor phenotypes by using computer extraction techniques have been studied for evaluation of breast cancer invasiveness, stage, lymph node involvement, molecular subtypes and genomics. In this project we aimed to investigate ability of computer-extracted breast MR imaging radiomic phenotypes to predict nodal and distant metastasis in breast cancer patients.
MATERIALS AND METHODS:This retrospective IRB approved study included 416 biopsy proven breast cancer patients who had pretreatment DCE MRI in a single institution between 2014 and 2018. Patient's demographic, clinical data, pathology at diagnosis and surgery, nodal and distant metastasis (M1) at follow up were documented. Using QuantX imaging software, the tumor volume of interest was automatically-segmented using the multiple dynamic phases of DCE MRI. A total of 33 radiomic features describing tumor phenotype were extracted from each tumor site. A linear discriminant analysis (LDA) as a classifier with nested feature selection 10-fold cross validation was used to build the radiomic signature for prediction of nodal and distant metastasis occurrence. Receiver operating characteristic (ROC) and precision-recall analyses were used to evaluate performance, with 95% confidence intervals from 1000 bootstraps, and Kaplan-Meier was used to calculate the progression-free survival estimates and associated hazard ratio at the median cutpoint of the probability of metastasis calculated by the LDA in the 10-fold cross-validation..
RESULTS:The quantitative DCE MRI radiomic model was able to differentiate between breast cancer patients with and without distant metastatic disease at follow up with area under the ROC of 0.75 (95% CI 0.65; 0.82) and precision-recall curves 0.46 (0.33;0.69), hazard ratio at median cut point is 3.76 (2.27; 6.24), $p<0.001$. Volume, surface area, sphericity, margin, maximum uptake, and washout rate variation features played the most important role in differentiating between breast cancer patients with and without distant metastasis.
The DCE radiomic model was able predict presence of ipsilateral nodal disease (≥1 positive lymph nodes) at surgery with AUC 0.66 (95% CI: 0.60; 0.71), ≥4 positive lymph nodes at surgery with AUC 0.67 (95% CI: 0.60; 0.74), and N2/N3 disease with AUC 0.64 (95% CI: 0.56; 0.72). Effective radius was most important feature for nodal disease prediction.
CONCLUSIONS:Our results show that DCE MRI based radiomic phenotypes were able to predict nodal involvement and distant metastasis in breast cancer patients. Quantitative breast DCE MRI radiomics shows promise for noninvasive image based phenotyping for prediction of nodal and distant metastatic disease in breast cancer patients.

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# Primary analysis of OVERSTEP: A multicenter, randomized clinical trial of capecitabine or endocrine therapy as a maintenance therapy after the 1st-line chemotherapy in hormone receptor positive and HER2-negative advanced/metastatic breast cancer

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Background: Endocrine therapy(ET) and Chemotherapy(CT) are used as standard maintenance therapy for HR+ and HER2- metastatic breast cancer(MBC) in clinical practice. There was no prospective study data on which is better. In OVERSTEP, we provide some strong evidence for clinical practice. Methods: OVERSTEP(NCT02597868) is a multicenter, randomized, open-label, prospective clinical trial that enrolled 181 patients in China. patients aged 18-70 years without chemotherapy for ABC/MBC previously, histologically confirmed metastatic HR+ and HER2- breast cancer, and ECOG performance status of 0-1. These patients were received capecitabine plus another chemotherapy drug as 1$^{st}$-line salvage chemotherapy at least 4 cycles. The patients response are CR, PR and SD carried maintenance treatment next, randomly assigned (1:1) to receive either capecitabine single or endocrine therapy. Randomization was done centrally with stratification by endocrine resistance and visceral metastasis. The primary endpoint was progression-free survival(PFS) and analyses were base on all patients who received at least one dose maintenance therapy. We take superiority test in the 2 groups. Results: 136(75.14%) patients were randomized after combined chemotherapy to capecitabine single or endocrine therapy groups for maintenance treatment. 45(24.86%) patients are progress disease (PD) after combined chemotherapy. After a median follow-up of 24.3 months (IQR 20.46-37.25 ) in the endocrine maintenance therapy group and 24.1 months(IQR 20.67-36.77) in the Capecitabine maintenance therapy group ,the hazard ratio for PFS was 0.625(95%CI 0.429-0.909 P=0.013),Median PFS was 17.5 months(95%CI 11.544-23.856) in endocrine maintenance therapy group and 12,2 months(95%CI 11.170-13.230) in capecitabine maintenance therapy group. In endocrine sensitive group, the hazard ratio for PFS was 0.515(95%CI0.269-0.988 P=0.042), Median PFS was 29.3 months(95%CI 14.605-43.995) in endocrine maintenance therapy group and 14.8 months(95%CI 7.445-22.155) in capecitabine maintenance therapy group. In endocrine resistance group, the hazard ratio for PFS was 0.791(95%CI 0.499-1.253 P=0.314), Median PFS was 13.6 months(95%CI 9.111-18.089) in endocrine maintenance therapy group and 12.0 months(95%CI10.357-13.643) in capecitabine maintenance therapy group. In visceral metastasis group, the hazard ratio for PFS was 0.668(95%CI0.410-1.089 P=0.101), Median PFS was 14.3 months(95%CI 11.113-17.487) in endocrine maintenance therapy group and 11.0 months(95%CI 8.140-13.860) in capecitabine maintenance therapy group. In non-visceral metastasis group, the hazard ratio for PFS was 0.54(95%CI0.300-0.972 P=0.037), Median PFS was 25.3 months(95%CI 15.278-35.322) in endocrine maintenance therapy group and 17.0months(95%CI 10.783-23.217) in capecitabine maintenance therapy group. Conclusions: For HR+ and HER2- MBC, after 1$^{st}$-line salvage combined chemotherapy, ET maintenance has a better survival benefits than CT,especially for ET-sensitive and non-visceral involved cases. So ET maintenance is the first choice for ABC/MBC after 1$^{st}$-line combined chemotherapy.

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Radium-223 in women with HR-positive bone-metastatic breast cancer receiving endocrine therapy: International phase 2, randomized, double-blind, placebo-controlled trial

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**Background:** Approximately 65-75% of women with metastatic breast cancer (mBC) have skeletal involvement, which can result in bone pain, pathologic fractures, and spinal-cord compression (SCC), impairing quality of life and function. Radium-223 dichloride (Ra-223) is a targeted alpha-emitting radionucleotide therapy that is approved for treatment of bone metastases from castration-resistant prostate cancer, but has been little studied in mBC. **Objective:** To assess the efficacy and safety of Ra-223 in women with bone-metastatic hormone receptor (HR)-positive breast cancer receiving endocrine monotherapy. **Methods:** This international, phase 2, randomized, double-blind, placebo-controlled trial (NCT02258464) involved women ≥18 years with HER2-negative, HR-positive, bone-dominant (≥2 skeletal lesions) mBC. Women with 1-2 skeletal-related events before study entry, treated with ≥1 line of hormonal therapy in the metastatic setting and bone-supportive agents, were randomized 1:1 to receive Ra-223 55 kBq/kg or placebo intravenously every 4 weeks for up to 6 cycles, combined with local standard of practice endocrine monotherapy and bone-targeted therapy with denosumab or a bisphosphonate. The primary endpoint was symptomatic skeletal event-free survival (SSE-FS). SSE was defined as external beam radiotherapy to relieve skeletal symptoms, symptomatic pathologic fractures, SCC, cancer-related orthopedic surgery, or death from any cause. Secondary endpoints included overall survival (OS), radiologic progression-free survival (rPFS), pain measurements, and safety. **Results:** Considering the evolving treatment landscape and slow recruitment, enrollment was closed early, and patients who completed treatment were permitted to roll over early to a follow-up study. Of the planned 227 women, 99 were randomized (Ra-223 n=49, placebo n=50; median age 57 years, range 28-85 years; 89% postmenopausal). The median number of injections received was 6 (range 1-6) in both arms. Median SSE-FS was 30 months (80% confidence interval [CI] 22, 43) in the Ra-223 arm vs 18 months (80% CI 9, 28) in the placebo arm; hazard ratio 0.75 (95% CI 0.41, 1.36; P=0.334). Trends in favor of Ra-223 over placebo were found for OS and pain measurements (Table). Treatment-emergent adverse events (TEAEs) occurred in 96% of patients in the Ra-223 arm and 94% in the placebo arm; drug-related TEAEs occurred in 44% and 33% of patients, respectively, and grade 3/4 TEAEs in 31% and 39%, respectively. In the Ra-223 vs placebo arms, there were fewer serious TEAEs (6% vs 25%, respectively, most commonly bone pain), bone-associated TEAEs (21% vs 27%, respectively; fracture 4% vs 12%, respectively), and TEAEs leading to treatment discontinuation (2% vs 6%, respectively). **Conclusion:** Although the primary endpoint was not met, possibly because of the small sample size, early discontinuation of follow-up, and lower than anticipated event rates, numerical trends consistently favored Ra-223 over placebo for SSE-FS, OS, and bone pain measurements. The overall TEAE rate was similar in both arms, but fewer serious or severe TEAEs were observed with Ra-223 than placebo.

Efficacy endpoints with Ra-223 vs placebo in women with mBC on background hormone monotherapy

| | Radium-223 (n=49) | Placebo (n=50) | Difference between treatment arms |
|---|---|---|---|
| SSE-FS,* median (80% CI), months | 30.1 (21.8; 43.0) | 18.4 (9.1; 28.2) | HR 0.745 95% CI 0.409, 1.356, P=0.3339? |
| SSE, n (%) | | | |
| Overall | 13 (26.5) | 18 (36.0) | |
| External-beam radiotherapy | 13 (26.5) | 15 (30.0) | |
| Spinal-cord compression | 1 (2.0) | 1 (2.0) | |
| Symptomatic pathologic bone fracture | 5 (10.2) | 8 (16.0) | |
| Tumor-related orthopedic surgical intervention | 2 (4.1) | 4 (8.0) | |
| OS, median (80% CI), months | 43.0 (22.9; NE) | 32.4 (23.7; NE) | HR 0.888 95% CI 0.458, 1.724, P=0.7259? |
| rPFS, median (80% CI), months | 8.1 (5.7; 10.6) | 5.8 (5.1; 7.9) | HR 1.02395% CI 0.640, 1.637, P=0.9227? |
| Time to opiate use for cancer pain, median (80% CI), months | 21.3 (8.3; NE) | 20.2 (8.8; NE) | HR 0.932 95% CI 0.374, 2.323, P=0.8785? |
| Time to pain progression, median (80% CI), months | 14.8 (5.9; 21.3) | 8.8 (3.7; 14.3) | HR 0.824 95% CI 0.452, 1.502, P=0.5240? |
| Pain improvement rate, % (n/N evaluable)? | 37.5 (12/32) | 25.7 (9/35) | P=0.345? |
| Time to cytotoxic chemotherapy, median (80% CI), months | 16.0 (14.1; 22.4) | 17.3 (10.9; 27.6) | HR 0.968 95% CI 0.535, 1.750, P=0.9128? |

*Primary endpoint. ?Two-sided P-value, log-rank test, stratified by geographic region, prior lines of hormone therapy in the metastatic setting, and prior skeletal-related events). ?Cochran-Mantel-Haenszel test (same strata). ?Confirmed pain improvement was defined as a 2-point decrease in worst pain score from baseline over two consecutive assessment periods conducted at least 4 weeks apart, without an increase in pain management in patients with a worst pain score ≥2 at baseline. CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; rPFS, radiologic progression-free survival; SSE, symptomatic skeletal events, SSE-FS, symptomatic skeletal event-free survival.

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# Novel approach to HER2 quantification: Digital pathology coupled with AI-based image and data analysis delivers objective and quantitative HER2 expression analysis for enrichment of responders to trastuzumab deruxtecan (T-DXd; DS-8201), specifically in HER2-low patients

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**Background**
T-DXd (Enhertu®) is an FDA-approved antibody-drug conjugate (ADC) targeting HER2. T-DXd has shown anti-tumor activity, not only in patients with HER2-overexpressing (IHC3+/2+ ISH+) breast cancer (BC) but also in patients with BC with low HER2 expression (IHC1+/2+ ISH−). Current HER2 protein expression assessment is based on manual pathologist scoring that classifies tumors by the percentage of tumor cells with highest intensity and completeness of staining. A critical need exists for more objective and quantitative methods to assess HER2 expression, specifically to better identify patients with low-level expression if T-DXd proves to be efficacious in this patient population.
**Methods**
We used deep learning (DL)-based image analysis (IA) to generate a novel HER2 **Q**uantitative **C**ontinuous **S**core (QCS). Data analytic techniques determined optimal HER2 QCS for the J101 trial (NCT02564900) of 151 patients with varying HER2 expression levels (1+, 2+, 3+). HER2 QCS consists of DL models to detect membrane, cytoplasm, and nuclei of all tumor cells. QCS was extensively trained using pathologists' annotations, and the performance was validated on unseen data to ensure its generalization and robustness. QCS was blindly applied to J101 data. The optical density (OD; level of brown stain intensity) was computed on detected membrane to derive features that could be linked to survival prediction. QCS features were selected to maximize ORR in positive group, minimize ORR in negative group maintaining while high prevalence in the positive group.
**Results**
Analytical validation showed high correlation between QCS from automatically detected membranes and QCS from those annotated by pathologists (R=0.993). This is in the same range as correlation between three pathologists (R=0.995). HER2 QCS was largely consistent with pathologist HER2 scoring as well but showed broad quantitative overlap between IHC and ISH categories. HER2 QCS showed a direct linear relationship between ORR and increased HER2 expression across the entire assay range. In the HER2-low population (n = 65), for whom HER2-targeting therapies are not currently approved, 42% of patients responded to T-DXd, with a median PFS (mPFS) of 11 mo. Using HER2 QCS, we were able to further stratify this population into a subgroup of QCS-high patients (above a staining intensity cut-off determined by IA), with response and mPFS increased to 53% (95% CI: 36%-68%) and 14.5 mo (95% CI: 10.9 mo-NR) respectively, while the QCS-low group only showed ORR of 24% (95% CI: 9%-45%) and mPFS of 8.6 mo (95% CI: 4.2 mo-NR). Generally, best-performing QCS cutoffs were driven by most tumor cells expressing a minimal amount of HER2, in contrast to current clinical guidelines that are driven by a minority of cells expressing higher levels of HER2. We also examined spatial heterogeneity by characterizing cells as either bearing membrane stain above a determined OD threshold (positive cell) or lying within certain distances from a positive cell. We observed similar efficacy with best performing-cutoffs, again, being found when a minimal level of HER2 expression (OD) was examined.
**Conclusions**
Taken together, these data establish a first proof-of-concept demonstrating that use of HER2 QCS can potentially enhance prediction of patient outcome with T-DXd by increasing sensitivity and specificity of response, especially in the HER2-low population. The ability to identify patients in the HER2-low group who could benefit from T-DXd is critical for its use in a patient population with a high unmet need that would otherwise not be treated with anti-HER2 therapy. Further clinical verification and validation is ongoing.

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# Intra-epithelial tumor immune landscapes are associated with clinical outcomes in early-stage triple-negative breast cancer

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Introduction: Stromal tumor-infiltrating lymphocytes (sTILs) have established prognostic and predictive significance in triple-negative breast cancer (TNBC). However, the roles of other immune cells in TNBC are less well-established. We performed high-plex quantitative spatial profiling in a cohort of early-stage TNBC to 1) apply spatial context to tumoral immune landscapes and 2) identify immune proteins associated with clinical outcomes, independently of TILs and other established prognostic clinicopathologic variables, in patients (pts) treated with or without adjuvant chemotherapy (CTX). Methods: The Mayo TNBC cohort comprises pts with centrally-verified, CTX-naive tumors resected from 1985-2012. Using a cohort-based TMA, with Nanostring GeoMX DSP, we quantitated 58 proteins within spatially-distinct intra-epithelial, cytokeratin-positive tumor segments and adjacent cytokeratin-negative/nuclei-positive stromal segments. Differentially-expressed (DE) proteins were identified using a negative binomial generalized linear model (SNR>2, $p< 0.05$) and a target DE protein set was dichotomized ($80^{th}$ percentile). After adjusting for prognostic clinicopathologic variables, proteins associated with recurrence-free survival (RFS, defined as time from surgery to either local, regional, and distant recurrence, or death by any cause) were identified by performing variable selection using the Akaike Information Criterion (AIC) obtained from fitting all possible Cox proportional hazards regression models (performed separately for intra-epithelial/stromal segments, and in groups +/- adjuvant CTX. Results: From the TNBC TMA, DSP data (N=250 tumors) included 169 pts who received adjuvant CTX+ and 81 who did not (CTX-). Overall, 85/250 developed recurrent disease. In the CTX+ group, intra-epithelial tumor segments from pts without recurrent disease were enriched in 10 immune proteins, including CD8, markers involved in antigen presentation/dendritic cells (CD11c, CD40, HLA-DR) or NK cells (CD56) (FC: 1.4-2.1, $p<0.05$); CD14 was increased in stroma (FC: 1.5, $p<0.05$). In contrast, in the CTX- group, both the intra-epithelial tumor and stromal segments from pts without recurrences were enriched in immune proteins (N= 12 and 15 respectively; FC 1.6-5.5, $p< 0.05$) most markedly CD40, IDO1 and HLA-DR (FC: 3.2-5.5, $p< 0.05$). Overall, CD3, CD4, CD27, CD44, and ICOS among others were enriched only in the CTX- group; CD14 and CD56 were enriched only in the CTX+ group. Based on these spatial data, biologic function and DSP data from another set of TNBC (FinXX trial), CD11c, CD14, CD27, CD40, CD56, and IDO1 were selected for RFS analysis. After applying our model selection criterion and adjusting for pt age at surgery, tumor size, lymph node status, and sTILs, intra-epithelial CD56 was independently associated with improved RFS in the CTX+ group (HR: 0.31[0.12, 0.81]). In the CTX- group, intra-epithelial CD11c was independently associated with improved RFS (0.10 [0.01, 0.81]). Conclusion: In this early-stage TNBC cohort, spatially-distinct tumor immune landscapes were associated with RFS but differed according to receipt of CTX after surgical resection. In the patients who received CTX, the intra-epithelial compartment, rather than stromal compartment, was immune-enriched in pts without recurrences. Among a targeted protein set, intra-epithelial CD56 remained associated with improved outcomes, independent of sTILs and other clinicopathologic features. In the CTX- group, spatial landscapes were more balanced, and intra-epithelial CD11c was independently associated with improved outcomes. These data provide insight into the spatial context of intrinsic immune landscapes in TNBC, and identify candidate prognostic immune biomarkers which may inform therapeutic strategies.

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# Consumer and patient reactions to trials of chemotherapy reductions reveal an urgent need to name and explain the concept

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**Introduction**: A growing trend in cancer research is the study of de-escalation of treatment, particularly chemotherapy. The hope is that eliminating or reducing drug(s) from treatment regimens will reduce toxicity burden and increase quality of life without increasing risk of recurrence and death. Large well-designed clinical trials are needed to ensure this hope is a reality. One such trial is EA1181 CompassHER2 pCR, which has an accrual goal of 1,250 patients.

**Methods**: This qualitative study included: (A) 2 focus groups with patients diagnosed with HER2+ breast cancer 3-5 years ago, for their ability to draw on their experience and react to the trial and (B) 3 focus groups with consumers who have never had a cancer diagnosis, for their ability to provide the "cancer-naïve" perspective that may more closely match that of newly diagnosed patients (the EA1181 population). One of the consumer groups was composed of Black women and moderated by a Black facilitator to allow issues to surface that may be specific to this group. Patients were identified via Living Beyond Breast Cancer; consumers were identified via a nationwide market research panel. Groups took place online in April and May 2020, after the COVID pandemic had begun. After a brief introduction to the trial, questions focused on: Reactions and questions, motivations, concerns, and descriptive language.

**Results**: A total of 30 women (11 patients and 19 consumers) participated, representing a mix of age groups, educational attainment, and racial and ethnic social identities.

The trial description raised many questions in participants' minds. Some of the more frequent responses from both patients and consumers related to the rationale for reducing treatment and the side effects and benefits of each drug. Consumers demonstrated confusion between what is to be tested in the trial versus what is part of the neoadjuvant process. Patients questioned the timeline and length of each step.

Motivations for participation centered on avoiding some chemotherapy and the associated side effects, costs, and recovery time. Some discussed taking only what is needed.

Concerns were significant and centered on: (A) Fear and the feeling that it is best to take everything, (B) Possible lengthened duration of treatment since chemotherapy may be needed after surgery (versus the certainly of having all chemo prior to surgery). The duration issue generated strongly negative reactions among patients who felt they would prefer chemo and its side effects all at once.

Some motivations and barriers also seemed tied to the likelihood of not needing post-surgical chemo, with participants expecting thresholds (unaided) of 50% to 80% of the perceived desirable outcome.

Language around the concept is a critical issue. Participants expressed many ideas related to possible milder treatment that is modified. The word, de-escalation, garnered very negative reactions including many comparisons to military action. Toxicity is also a term that was less familiar to consumers and disliked by many as it elicits additional fear; "side effects" seems more familiar and palatable.

**Conclusion**: Communication about trials with reduced chemotherapy will need to be effective to lead to successful accrual. Providing tools to oncologists and patients to enhance two-way communication may be necessary to ensure concepts are understood. Since de-escalation is already becoming a term commonly used by researchers, replacing it with a more effective descriptor that is clear and connects to the benefits appears time-critical. Quantifying reactions to language options and other qualitative findings via a survey with a larger sample of consumers and patients is advised. Including patient voices in trial design, as well as consumers particularly for trials for the newly-diagnosed, sheds light on communication needs.

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Plk1 expression & efficacy of palbociclib in advanced hormonal receptor-positive breast cancer patients from PEARL study (GEICAM 2012-03)

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**Background:** CDK 4/6 inhibitors (CDK 4/6i) with endocrine therapy (ET) combination therapy have improved outcomes in patients (pts) with hormonal receptor positive (HR+)/human epidermal growth factor receptor negative (HER2-) advanced breast cancer (ABC). However, most pts eventually develop resistance to these drugs, and one third never respond. Aside from HR positivity, predictive markers of clinical benefit from CDK 4/6i remains elusive. We aimed to identify biomarkers of response to palbociclib (PAL) and analyze potential therapeutic targets to reverse resistance. **Methods**: PEARL trial is a multicenter phase 3 study that assigned 601 postmenopausal HR+/HER2- ABC pts, whose disease progressed on aromatase inhibitors (AIs), to receive PAL + ET vs capecitabine (CAPE). We performed a differential gene expression analysis in pre-treatment tumors in extreme responders to PAL using the HTG EdgeSeq Oncology Biomarker Panel (HTG Molecular Diagnostics, Inc.), containing 2534 cancer related genes. Samples were subset in 2 categories: refractory (progressive disease as best response) vs sensitive (progression-free survival (PFS) within the upper quartile). Cox regression and Significance Analysis of Microarrays (SAM) analysis adjusting for multiple comparisons were performed. **Results:** We analyzed 455 (75.7%) pts with pre-treatment tumors available [from them, PAL + ET arm: 229 (50.3%) pts; CAPE arm: 226 (49.7%) pts]. Fifty genes (false discovery rate (FDR)<0.05) were differentially expressed in pts sensitive vs refractory to PAL (E2F target genes, epithelial-to-mesenchymal transition (EMT) and cell cycle genes, mainly). Unsupervised hierarchical clustering of pts based on the expression of these genes revealed two clusters. Cluster 1 is composed mostly of resistant tumors, highly proliferative (Ki67≥20%: 70%) with a great proportion of luminal B (59%) and non-luminal tumors (19%). Cluster 2 is composed of sensitive, low proliferative (Ki67<20%: 58%), mostly luminal A tumors (75%). There was no difference in ESR1 mutations distribution between the two clusters (Table 1). Forty genes were up-regulated and associated with resistance, including CCNE1 and PLK1 (Polo Like Kinase 1). In the whole cohort, pts with high levels (> median) of PLK1 (PLK1-high) treated with PAL, had a worse PFS in a multivariate model (5.7 months (m) vs 9.3 m of median PFS in PLK1-High vs -Low; HR=1.64, 95% CI (1.25-2.34), p=0.0008; adjusted model for confounders: age, site of disease, sites of metastasis, prior chemotherapy and Ki67). There were no differences in population treated with CAPE (9.9 m vs 9.4 m, PLK1-High vs -Low; HR=0.82, 95% CI (0.56-1.21), p=0.3189). In the METABRIC cohort, PLK1-High was associated with worse overall survival in HR+/HER2- BC but not in triple negative nor in HER2+ tumors. Among HR+/HER2- tumors, PLK1 expression was higher in luminal B and HER2-enriched intrinsic subtypes. We interrogated DepMap database and found that in BC cells lines there was an inverse correlation between PLK1 expression and effect on cell viability of CDK4 CRISPR knock-out (Pearson correlation r:0.54, p=0.009), but not of CDK6 knock-out. Also, HR+/HER2-/High Ki67 BC cell lines (HCC1428, EFM19 and MCF7) showed resistance to PAL on cell proliferation assays but sensitivity to the PLK1 inhibitor BI-2536. **Conclusion:** High expression of PLK1 is associated with intrinsic resistance to PAL and ET, this might be overcome with PLK1 inhibition.**Table 1**

| **PATIENT CHARACTERISTICS** | | | |
|---|---|---|---|
| | **Cluster 1** | **Cluster 2** | **ALL** |
| | **n=57** | **n=47** | **n=104** |
| Responders | | | |
| Sensitive | 42 (73.68%) | 14 (29.79%) | 56 (53.85%) |
| Refractory | 15 (26.32%) | 33 (70.21%) | 48 (46.15%) |
| ESR1 | | | |
| Mutated | 9 (15.79%) | 13 (27.66%) | 22 (21.15%) |
| Wild type | 45 (78.95%) | 34 (72.34%) | 79 (75.96%) |
| Unknown | 3 (5.26%) | 0 (0%) | 3 (2.88%) |
| PriorQT | | | |
| N | 42 (73.68%) | 31 (65.96%) | 73 (70.19%) |
| Y | 15 (26.32%) | 16 (34.04%) | 31 (29.81%) |
| Subtype | | | |
| LumA | 43 (75.44%) | 10 (21.28%) | 53 (50.96%) |
| LumB | 14 (24.56%) | 28 (59.57%) | 42 (40.38%) |
| Non Luminal | 0 (0%) | 9 (19.15%) | 9 (8.65%) |
| Metastasis | | | |
| One | 21 (36.84%) | 15 (31.91%) | 36 (34.62%) |
| Multiple | 36 (63.16%) | 32 (68.09%) | 68 (65.38%) |
| KI67 20% | | | |
| KI67<20 | 33 (57.89%) | 7 (14.89%) | 40 (38.46%) |
| KI67≥20 | 16 (28.07%) | 33 (70.21%) | 49 (47.12%) |
| Unknown | 8 (14.04%) | 7 (14.89%) | 15 (14.42%) |
| Objective Response | | | |

| | | | |
|---|---|---|---|
| Complete | 1 (1.75%) | 0 (0%) | 1 (0.96%) |
| Partial | 16 (28.07%) | 6 (12.77%) | 22 (21.15%) |
| Progressive | 15 (26.32%) | 33 (70.21%) | 48 (46.15%) |
| Stable | 25 (43.86%) | 8 (17.02%) | 33 (31.73%) |

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# Open-label, randomized, phase 2 study of sapanisertib (TAK-228/MLN0128) in combination with fulvestrant in postmenopausal women with estrogen receptor-positive (ER+)/human epidermal growth factor receptor-2-negative (HER2-) advanced or metastatic breast cancer (MBC) that previously progressed during or after aromatase inhibitor therapy (NCT02756364)

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**Background:** Sapanisertib (S) is an investigational, oral, and highly selective adenosine triphosphate (ATP)-competitive inhibitor of target of rapamycin complex 1/2 (TORC1/2). Simultaneous inhibition of ER and phosphoinositide 3kinase (PI3K)/serine/threonine-specific protein kinase (AKT)/mammalian target of rapamycin (mTOR) pathway with S may restore sensitivity to endocrine therapies in patients (pts) with breast cancer, who have progressed during or after aromatase inhibitor (AI) therapy. Here we report data from a phase 2 study of continuous once-daily or once-weekly S + fulvestrant (F) compared with single-agent F in pts with breast cancer. **Methods:** Postmenopausal women with ER+ and HER2- advanced or metastatic breast cancer following progression during/after AI therapy were randomized 1:1:1 to receive F (500 mg intramuscularly on day 1 of a 28-day cycle) alone (Arm A) or in combination with oral S either daily (4 mg; Arm B) or weekly (30 mg; Arm C) until progressive disease (PD), unacceptable toxicity, or consent withdrawal. Pts were stratified according to presence/absence of visceral metastases, previous sensitivity to hormonal therapy, and previous exposure to cyclin-dependent kinase (CDK) 4/6 inhibitors. Pts on Arm A could receive S at PD. Key exclusion criteria were: prior therapy with mTOR inhibitors, PI3K inhibitors, or F; >1 prior line of chemotherapy for MBC; recurrent disease or PD on >2 endocrine therapies for MBC. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR; any duration and at 24 weeks), overall survival (OS), and safety. **Results:** Between Aug 2016 and May 2018, 141 pts were randomized (Arm A: 46; Arm B: 47; Arm C: 48). One patient in Arm C was not treated. Median age was 58 years (range 33-84). Stratification was well balanced across arms; overall, 65% had visceral metastases, 84% had prior sensitivity to hormonal therapy, and 34% had received prior CDK 4/6 inhibitors. Pts received a median of 4 cycles (range 1-40) of F on Arm A, 5 cycles (range 1-33) of daily S + F on Arm B, and 4 cycles (range 1-39) of weekly S + F on Arm C. The last follow-up visit was in Nov 2019. The main reasons for treatment discontinuation included PD (76%, 60%, 53%; Arm A, B, and C, respectively) and adverse events (AEs; 4%, 32%, 36%; Arm A, B, and C, respectively). Of the pts in Arm A with confirmed PD, 18 crossed over to Arm B and C (9 each); crossover was analyzed separately. Efficacy data are shown in the table; median PFS was 3.5, 7.2, and 5.6 months in Arm A, B, and C, respectively. OS data were immature at the primary data cut-off. Three pts died during the study (2 and 1 in Arm A and B, respectively); all deaths were attributed to underlying disease. Most common any-grade AEs were: asthenia (24%), hyperglycemia, fatigue, and headache (22% each) in Arm A; hyperglycemia (57%) and nausea (49%) in Arm B; nausea (87%) and vomiting (70%) in Arm C. **Conclusion**: Daily or weekly treatment with S + F demonstrated modest clinical benefit in ER+/HER2- advanced or MBC pts who progressed during/after AI compared with single-agent F. The S + F combinations had increased toxicity leading to more treatment discontinuations compared with single-agent F.

**Table: PFS and response data**

| | Arm A Single-agent F (n = 46) | Arm B S (QD) + F (n = 47) | Arm C S (QW) + F (n = 48) |
|---|---|---|---|
| Median PFS (95% CI), months | 3.5 (1.9-5.6) | 7.2 (3.9-10.6) | 5.6 (4.1-9.0) |
| HR (95% CI) | | 0.77 (0.47-1.26) | 0.88 (0.53-1.45) |
| ORR*, n/N (%) | 5/46 (10.9) | 10/47 (21.3)? | 6/47 (12.8) |
| CBR*, n/N (%) | 28/46 (60.9) | 35/47 (74.5) | 31/47 (66.0) |
| CBR≥6 months*, n/N (%) | 15/46 (32.6) | 23/47 (48.9) | 12/47 (25.5) |

*Safety population ?Including 2 complete responses

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# Site of recurrence after neoadjuvant therapy: A multi-center pooled analysis

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**Background:** Achieving a pathologic complete response (pCR) has been shown on the patient level to predict excellent long-term event-free survival outcomes. Residual cancer burden (RCB) quantifies the extent of residual disease for patients who did not achieve pCR. We have previously observed in the I-SPY 2 TRIAL that while metastatic events outside the central nervous system (CNS) were dramatically reduced in the setting of pCR, the incidence of CNS metastasis remained similar across RCB classes, raising the possibility that these CNS events may be independent of response in the breast. In this study, we evaluate the type and sites of recurrences by RCB in a large pooled dataset, which allows for analysis within subtype, to validate these findings. **Methods:** 5161 patients pooled across 12 institutions/trials with available RCB and event-free survival (EFS) data were included in this analysis. EFS was calculated as the interval between treatment initiation, and locoregional recurrence, distant recurrence or death from any cause; patients without event are censored at time of last follow-up. The median follow-up is 4.6 years. We summarized the EFS event type, further sub-dividing the distant recurrence events (DR) by their site of relapse (CNS-only, CNS and other sites, Non-CNS). We used a competing risk (Fine-Gray) model to assess which of these site-specific relapses differ between RCB classes and estimated the cumulative incidence of CNS-only and non-CNS events at 5 years. Analyses were performed across the entire study population and within HR/HER2 defined subtypes. **Results:** Among the 5161 subjects, there were 1164 EFS events, including 92 (7.9%) local recurrences (without distant recurrence and/or death) and 1072 distant recurrence-free survival (DRFS) events. Among the DRFS events, 158 patients died without a distant recurrence. 914 experienced distant recurrences, including 90 (9.8%) with CNS-only, 145 (15.9%) with CNS and other sites, 664 (72.6%) with non-CNS distant recurrence; 15 (1.6%) patients had missing recurrence site information. Table 1 summarizes the cumulative incidence of CNS-only and non-CNS recurrence at 5 years and the proportion of CNS-only recurrences among DR events by RCB class overall and within each HR/HER2 subtypes. The incidence of CNS-only recurrences was low and similar across RCB classes. In contrast, the incidence of non-CNS recurrences increases with increasing RCB. As a result, CNS-only recurrences are proportionally higher within the RCB-0 and RCB-I than in the RCB-II and RCB-III groups, largely because of the low DR event rate and relative low frequency of non-CNS recurrence events within the RCB-0 and RCB-I classes. Overall, 27% of the recurrences in the setting of pCR (RCB-0) are due to CNS-only recurrences.**Conclusions:** Consistent with previous studies, our large pooled analysis confirmed that CNS-only recurrences are uncommon but appear similar across RCB groups, independent of response, suggesting that the CNS is a treatment sanctuary site. In contrast, non-CNS recurrence rates increase as RCB increases. These findings suggest that inclusion of CNS-only recurrences as an outcome event may impact the association between neoadjuvant therapy response and long-term outcomes in the context of current therapies. Novel therapies that cross the blood brain barrier will be needed to impact CNS recurrence rates.

Table 1: Cumulative Incidence of CNS Only and non-CNS Distant Recurrences at 5 years and proportion of CNS-only events among DR events

| | RCB Class | 0 | I | II | III | p |
|---|---|---|---|---|---|---|
| Overall (5161) | N | 1676 | 662 | 2017 | 806 | |
| | Cum. Inc. CNS Only | 2% | 2% | 2% | 1% | 0.627 |
| | Cum. Inc. Non-CNS | 3% | 6% | 16% | 27% | <0.001 |
| | # CNS-Only / # DR events (%) | 26/96 (27%) | 14/74 (19%) | 39/443 (9%) | 11/301 (4%) | |
| HR-HER2- (1774) | N | 770 | 212 | 590 | 202 | |
| | Cum. Inc. CNS Only | 2% | 3% | 2% | 4% | 0.298 |
| | Cum. Inc. Non-CNS | 4% | 11% | 19% | 42% | <0.001 |
| | # CNS-Only / # DR events (%) | 13/50 (26%) | 6/32 (19%) | 13/148 (9%) | 8/111 (7%) | |
| HR-HER2+ (572) | N | 376 | 67 | 100 | 29 | |
| | Cum. Inc. CNS Only | 1% | 5% | 5% | 0% | 0.022 |
| | Cum. Inc. Non-CNS | 2% | 5% | 18% | 38% | <0.001 |
| | # CNS-Only / # DR events (%) | 4/17 (24%) | 3/10 (30%) | 6/31 (19%) | 0/13 (0%) | |
| HR+HER2+ (858) | N | 313 | 172 | 291 | 82 | |
| | Cum. Inc. CNS Only | 1% | 1% | 2% | 0% | 0.37 |
| | Cum. Inc. Non-CNS | 2% | 3% | 15% | 26% | <0.001 |
| | # CNS-Only / # DR events (%) | 3/10 (30%) | 2/16 (12%) | 7/68 (10%) | 0/29 (0%) | |
| HR+HER2- (1957) | N | 217 | 211 | 1036 | 493 | |
| | Cum. Inc. CNS Only | 3% | 2% | 1% | 0.2% | 0.087 |
| | Cum. Inc. Non-CNS | 5% | 4% | 13% | 20% | <0.001 |
| | # CNS-Only / # DR events (%) | 6/19 (32%) | 3/16 (19%) | 13/196 (7%) | 3/148 (2%) | |

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# Biomarkers predicting response to durvalumab combined with olaparib in the neoadjuvant I-SPY 2 TRIAL for high-risk breast cancer

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**Background:** Preclinical studies suggest synergy between PARP inhibitors and immune checkpoint inhibitors. In the I-SPY 2 TRIAL, the anti-PDL1 therapeutic antibody durvalumab combined with the PARP inhibitor olaparib showed increased efficacy relative to control in both the HR+/HER2- and TN subtypes. Pre-specified biomarker analysis was performed to test 7 immune genes/signatures previously associated with response to pembrolizumab [Pembro] and/or durvalumab and a DNA Repair Deficiency (DRD) signature previously associated with response to veliparib/carboplatin, as specific predictors of response to durvalumab/olaparib [Durva]. We also assessed MammaPrint (MP) High1/(ultra)High2 risk class (MP1/2), a prognostic signature used in the trial's adaptive randomization engine, and performed exploratory analysis on additional signatures.
**Methods:** 105 patients (Durva: 71, controls: 34) had Agilent 44K gene expression from FFPE pre-treatment biopsies and pCR data; and 370 (Durva: 71, controls: 299) had MP1/2 and pCR data. We evaluated 13 genes/signatures (10 immune, 1 DRD, 1 ER, 1 proliferation) and MP1/2 as biomarkers of Durva response, using logistic modeling to assess performance. A biomarker is considered a specific predictor of Durva response if it associates with response in the Durva arm, and if the biomarker x treatment interaction is significant (likelihood ratio test, $p<0.05$). pCR rates within MP1/2 classes are estimated using Bayesian logistic modeling. Analysis is also performed adjusting for HR status as a covariate, and numbers permitting, within receptor subsets. Our statistics are descriptive rather than inferential and do not adjust for multiplicities.
**Results:** 8/10 immune biomarkers, including the genes PD1 and PDL1, and B-cell, dendritic cell and mast cell (but not T-cell or CD68) signatures associate with response to Durva in the population as a whole and in a model adjusting for HR status. As seen in previous immunotherapy trials, higher levels generally associate with pCR, with the exception of the mast cell signature, where high levels associate with non-response as was also shown for Pembro (I-SPY 2). In addition, high levels of the DRD (PARPi7) and proliferation signatures associate with response, as do low levels of ER signaling (ESR1/PGR average). Many of these biomarkers also associate with response in the control arm, and for no immune biomarker is the treatment interaction significant, suggesting a lack of predictive specificity. In subset analysis, 13/14 biomarkers (all but CD68) predict Durva response in the HR+/HER2- subset, with the strongest association to pCR being a low level of ESR1/PGR ($p=2E-08$). In our Bayesian analysis, the difference in estimated pCR rates between arms are primarily observed in the MP2 subtype, particularly in the HR+/HER2- MP2 patients (estimated pCR rate of 64% in Durv vs 22% in Ctr). In the TN subset, only 3/14 biomarkers associate with response: the STAT1 and TAM/TcCassII-ratio signatures that also associate with durvalumab response in a prior study (NCT02489448) and, interestingly, the proliferation signature. Notably, the dendritic, T-cell and tumor inflammatory signatures (TIS) predicting TN response to Pembro (I-SPY2, GeparSixto) do not associate with Durva response in TNBC, suggesting differences in the biology underlying response to PD1 and PDL1 inhibitors.
**Conclusion:** Multiple immune, DRD, proliferation, and ER signatures associate with response to durvalumab/olaparib therapy, but many lack predictive specificity. MP2 class and/or low ESR1/PGR are the strongest predictors of pCR in the HR+/HER2- subset; whereas for TNs, cytokine- and monocyte-dominated immune signatures like STAT1 [PMID: 19272155] and TAM/TcClassII ratio [PMID: 24205370] are most predictive of response. These results require validation.

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Patient perception of breast and gynecologic cancer care during the SARS-CoV-2 (COVID-19) pandemic in NYC: A single center survey-based study

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**Background:** The 2019 novel coronavirus has become a world-wide pandemic which has disproportionately affected patients undergoing treatment for cancer. Within the field of medical oncology, dramatic changes in practice patterns occurred rapidly to accommodate transition of resources, while maintaining safety of oncology patients. At our large cancer treatment center in NYC, there have been significant changes in the delivery of surgical and medical treatments, with a shift towards neo-adjuvant therapy, oral chemotherapy administration, extended ovarian suppression, as well as closure or delay of many clinical trials. This study aims to determine the impact of the COVID-19 pandemic on the perceived oncology related care of patients with breast/gynecologic cancers as measured by survey results, as well as the impact on quality of life (QOL) and overall health (OH). **Methods:** A 34-question survey was administered to all patients receiving care at our outpatient center between March 1, 2020 and June 30, 2020. Of the 622 patients who received the survey via RedCap online or physical copy in clinic, 211 (34%) completed the survey. Survey questions were answered on a 5-point Likert scale and 7-point EORTC *QLQ-C30* QOL scale. There is no existing COVID specific questionnaire, therefore we designed several original questions. Difference in mean QOL scores prior to the pandemic and at the end of the response period were evaluated using a paired t-test. **Results:** Of the 184 patients who responded to the question about their diagnostic history, 54 (30%) of patients had a history of DCIS (ductal carcinoma in situ)/ADH (atypical ductal hyperplasia)/LCIS (lobular carcinoma in situ), 94 (51%) had a history of invasive breast cancer, 6 (3%) had a gynecologic malignancy and 30 (16%) responded “other.” Due to the COVID pandemic, 121 patients (58%) reported that they had a medical oncology visit cancelled, delayed or changed from in-person to video telehealth. Of the 156 respondents that had endocrine therapy or chemotherapy scheduled, 26 (17%) reported a cancellation or delay of their medical treatment. As a result of the pandemic, 186 (91%), 110 (57%) and 119 (60%) of patients reported new or increased levels of anxiety, depression and mood swings, respectively. A minority of patients (n=39, 19%) felt that the COVID pandemic negatively impacted their cancer care, and a majority (n=151, 73%) felt that the changes in delivering cancer care during the pandemic were in their best interest (somewhat/strongly agree). Overall, QOL was reported with a mean (SD) of 5.5 (1.3) out of 7 (1=very poor, 7-excellent) prior to the pandemic, and 5.1 (1.4) out of 7 by the end of the pandemic period (March 1 through June 30, 2020); $p<0.0001$. Fifty-three (26%) of patients reported having excellent (7) QOL prior to pandemic which decreased to 32 (16%) after the pandemic period; $p<0.0001$. Overall health was reported with a mean (SD) of 5.3 (1.3) out of 7 prior to the pandemic, and 5.1 (1.3) out of 7 by the end of the response period; $p=0.0368$. **Conclusions:** The COVID-19 pandemic required major changes in the care of patients with breast and gynecologic cancer in order to balance continued oncologic care with safety of COVID exposure. In our study population, 17% of patients at our center reported a delay or cancellation in their medical treatment and 58% reported a change to their medical oncology visits. Despite this, only 19% of all patients felt that the changes in care delivery as a result of the COVID-19 pandemic negatively impacted their cancer care, and the large majority (73%) felt that the changes were made in their best interest. The QOL for our patients was significantly affected by the pandemic, with increases in anxiety, depression and mood swings, and a numeric decrease in QOL and OH.

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Gut pathogen, *Bacteroides fragilis* promotes breast cancer liver and lung metastasis

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**Background:** The last decade established significant contributions of microbiome to many organ specific cancers. Existence of distinct breast microbiota has been recently established but their biological impact in breast cancer progression remains elusive. A few recent studies suggested the existence of distinct breast microbiota and a shift in microbial community composition in diseased breast compared to normal breast however, their functional impact and underlying mechanisms are unknown. Present study was designed to examine the contribution of pro-carcinogenic bacteria in breast cancer initiation, progression and metastasis. Utilizing extensive data mining and metagenomic analyses, we discovered the presence of toxin producing enterotoxigenic *Bacteroides fragilis* (ETBF) in malignant breast. ETBF is a pro-carcinogenic bacteria known for its potential to initiate and/or promote colon cancer and its pathogenicity has been attributed to its unique toxin *B. fragilis* toxin (BFT)'.
**Results:** Using mammary intraductal model we discovered that ETBF can successfully colonize the breast confirmed by qPCR and Fluorescent *in situ* hybridization where it induces local inflammation, fibrosis and hyperproliferation of breast epithelial cells. Mice bearing gut ETBF infection exhibit significant circulating BFT confirmed by qPCR and ELISA and distinct morphological alterations in mammary gland as observed from whole breast mounting and histological evaluation. Gut colonization with ETBF rapidly induces hyperplasia in mammary glands with systemic and local breast inflammation validated by flow cytometry, immunohistochemistry and cytokine profiling. While no changes are observed in cell growth and clonogenicity upon BFT treatment, significant increase in migration and invasion potential and decreased adhesion of MCF10A and MCF7 cells are observed. BFT leads to prominent cytoskeletal reorganization, and increase in migration, invasion and stemness potential of breast cancer cells. Our results indicate that breast cancer cells exposed to BFT ensue to exhibit increase tumor growth, form multifocal tumors and show a striking increase in tumor-initiating cells upon *in vivo* limiting dilution in immunocompromised mice exhibiting retention of 'BFT memory' from the initial exposure. Mechanistically, RNA-sequencing shows enrichment of βcatenin and Notch pathway in secondary tumors derived from BFT-exposed breast cancer cells. Inhibitors of βcatenin and Notch axis abrogates BFT-induced migration and invasion potential indicating the functional importance of this axis. Intriguingly, gut colonization with ETBF at a physiologically relevant level strongly induces growth and metastatic progression of 4T1 tumor cells implanted in mammary ducts monitored by whole animal bioluminescent imaging. *In vivo* and *ex vivo* analyses of tumors and distant organs reveal a significant induction of lung and liver metastasis of breast cancer by ETBF while gut colonization with non-toxigenic *Bacteroides fragilis* (NTBF) does not exhibit any tumor-augmenting impact. We mechanistically evaluate the oncogenic impact of alpha bug ETBF on breast cancer progression and its role in promoting liver and lung metastasis using multiple mice models and multiple techniques including multi-color flow cytometry, immunohistochemistry, quantitative PCR, multiplexed ELISA, *ex vivo* functional assays and western blotting.
**Conclusion**: Collectively, these findings present the first evidence to show that gut colonization with *Bacteroides fragilis* rapidly induces inflammation, fibrosis and hyperplasia in the breast. In syngeneic breast cancer model, gut colonization with ETBF aggravates breast cancer progression and induces enhanced lung and liver metastasis *via* systemic immune modulation, cytokine synthesis and activation of pro-oncogenic pathways.

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# Highly multiplexed tissue-based cyclic immunofluorescence (t-CyCIF) for precision oncology identifies novel patterns of HER2 heterogeneity in breast cancer

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**Background**
Immunohistochemical (IHC) evaluation has shown that human epidermal growth factor receptor 2 (HER2) may not be expressed homogeneously among all cancer cells within a given tumor. The clinical significance of intratumoral HER2 heterogeneity is unclear. Exploration of tumor heterogeneity is facilitated by tissue imaging technologies such as t-CyCIF, a highly multiplexed immunofluorescence microscopy technique that permits visualization of up to 60 antigens and analysis on a single cell level from formalin-fixed, paraffin-embedded tissue. To utilize t-CyCIF for the evaluation of breast tumors, this study was undertaken to: 1) validate antibodies to be used against the clinically relevant markers HER2, estrogen receptor (ER) and progesterone receptor (PR), and 2) use these antibodies along with other validated antibodies to define the tumor microenvironment (TME) to interrogate breast tumors at a single cell level.

**Methods**
T-CyCIF is an iterative whole-slide imaging process, in which successive four-channel images, each involving different antibodies, are collected from the same sample and then merged to generate a high-dimensional representation used for visualization and analysis. In phase one of this study, 948 tissue cores (representing 295 patients in triplicate) were used to validate HER2, ER, and PR antibodies against a single antibody commonly used in clinical practice as a reference. Analyses were performed at the level of tissue cores, cells and pixels. Inter-assay analyses were performed comparing: t-CyCIF *vs.* IHC, the latter assessed by digital pathology and two pathologists; and also, t-CyCIF *vs.* fluorescence *in situ* hybridization (FISH) for HER2. In the second phase, following selection of validated HER2, ER and PR antibodies, expression of CD45, CD68, PD-L1, p53, Ki67, pRB and the androgen receptor (AR) were evaluated at a single cell level in 312 $HER2^{+}$ invasive breast cancer samples, representing 104 patients, to better understand the TME, cancer cell heterogeneity and the cell identities/states present in breast carcinomas.

**Results**
In the first phase of the study, 13 different ER, PR or HER2 antibodies were analyzed. The pixel-to-pixel evaluation, which evaluates concordance in staining, resulted in r scores of 0.86 (ER; Pearson correlation), 0.93 (PR) and 0.94 (HER2) and correlation scores in single-cell comparisons ranged from 0.76 to 0.81. Correlation scores on the tissue core level were high in the inter-assay analyses, i.e. t-CyCIF *vs.* IHC (e.g. r scores up to 0.87 and 0.91 for ER and HER2, respectively, on t-CyCIF *vs.* Aperio; and 0.85 to 0.94 by pathology review) and t-CyCIF *vs.* HER2 FISH (r scores up to 0.71). This resulted in validated fluorophore-conjugated antibody panels for use in t-CyCIF that correspond well to established standards. In the second phase, single cell analysis of HER2+ breast cancer was performed. Cancer cells were defined as keratin positive and using t-Distributed Stochastic Neighbor Embedding (t-SNE) seven cancer cell clusters were identified including two $HER2^{hi}$ clusters differing in ER, p53, AR and PD-L1 expression, two $HER2^{lo}$ clusters differing in PR, Ki67, pRB, p53 and AR and three $HER2^{neg}$ clusters differing in PR, Ki67, ER, PD-L1 and AR. Heterogeneity scores were calculated based on diversity among clusters.

**Conclusion**
This study is the first to evaluate the performance of breast cancer-specific antibodies in a highly multiplexed imaging platform such as t-CyCIF. Using the validated antibody panel, we uncovered patterns of expression of markers relevant to breast cancer biology that correlate with HER2 high, low and negative states. Ongoing studies are looking at correlations between HER2 heterogeneity, responses to therapy and clinical outcomes.

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# Prognostic relevance of the HER2 status of circulating tumor cells in metastatic breast cancer patients screened for participation in the DETECT study program

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**Background**
Circulating tumor cells (CTCs) have been reported to predict clinical outcome in metastatic breast cancer (MBC). Biology of CTCs may differ from the primary tumor and HER2-positive CTCs are found in some patients with HER2-negative disease. In this analysis, we evaluated the clinical relevance of the HER2 status of CTCs in patients screened for participation in the DETECT trials, the largest study program for CTC-based therapy interventions in MBC.
**Methods**
Patients with HER2-negative MBC were screened for CTCs using CellSearch. CTCs were labeled with an anti-HER2 antibody and classified according to staining intensity (negative, weak, moderate, or strong staining). Patients with HER2-positive CTCs were invited to participate in the randomized phase III DETECT III trial, which evaluated treatment with physicians' choice therapy with and without lapatinib. Patients with HER2-negative CTCs could participate in the DETECT IVa/b trials which investigated serial blood measurements during in-label systemic therapy. Patients who participated in the screening but were not enrolled in the DETECT III or DETECT IV trials were treated at discretion of their physician and followed up for progression and death.
**Results**
Screening blood samples were analyzed in 1933 patients with HER2-negative MBC. Out of these, 102 were enrolled in the DETECT III and 213 in the DETECT IVa/b trials, respectively. 1217 out of the 1933 screened patients (63.0%) had ≥ 1 CTC per 7.5 ml blood. ≥ 5 CTCs were detected in 735 patients (38.0%; range 1 – 35,078 CTCs, median 8 CTCs). Patients with ER-positive tumors were more likely to be CTC-positive than patients with ER-negative disease (≥ 1 CTC in 64.7% vs. 57.1% patients, respectively, $p = 0.011$; ≥ 5 CTCs in 40.8% vs. 29.5%, $p < 0.001$). CTC status was also associated with ECOG performance status (≥ 1 CTC in 63.2% of patients with ECOG 0 vs. 69.0% with ECOG 1-3, $p = 0.020$; ≥ 5 CTCs in 36.3% vs. 47.2%, $p < 0.001$). HER2 status of CTCs was assessed in 1159 CTC-positive patients. At least one CTC with strong HER2 staining was found in 174 (15.0%) patients. The proportion of CTCs with strong HER2 staining among all CTCs of an individual patient ranged between 0.06% to 100% (mean: 15.8%). Patients with ER- and PR-positive tumors were more likely to harbor ≥ 1 CTC with strong HER2 staining. For survival analysis, 52 patients receiving anti-HER2-therapy with lapatinib in the interventional arm of the DETECT III trial were excluded. CTC status was significantly associated with OS (median OS in patients with ≥ 1 CTC: 15.5 [95%-CI: 14.2-16.8] months vs. 37.2 [32.7-41.7] months in CTC-negative patients, $p < 0.001$, HR 2.359; median OS in ≥ 5 CTCs vs. < 5 CTCs: 12.0 [10.0-14.0] vs. 28.6 [25.5-31.6] months, $p < 0.001$, HR 2.204). Detection of ≥ 1 CTC with strong HER2 staining was associated with shorter OS (9.7 [7.1-12.3] vs. 16.5 [14.9-18.1] months in patients with CTCs with negative-to-moderate HER2 staining only, $p = 0.013$). In the multivariate analysis, only age, ER status, PR status, ECOG performance status, therapy line, and CTC status independently predicted OS.
**Conclusion**
To our knowledge, this is the largest analysis to date regarding the clinical relevance of HER2 status of CTCs in MBC. We confirm the high prognostic value of CTC detection in patients with HER2-negative disease. Presence of ≥ 1 CTC with strong HER2 staining was significantly associated with shorter OS in univariate analysis. However, the CTC-HER2 status did not correlate with survival in multivariate analysis.
* VM and MBP contributed equally to this work

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# The influence of pathogenic variants in breast cancer predisposition genes on secondary breast cancer events in a prospectively collected cohort of breast cancer patients

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Background: About 10-20% of breast cancers (BC) are hereditary. Patients (pts) with BC and pathogenic variants (PVs) in the BRCA1 or BRCA2 gene are at increased risk of contralateral breast cancer (CBC). However, risks of CBC and recurrent BC associated with PVs in other established BC predisposition genes (e.g. *PALB2, CHEK2, ATM*) are less well established. We performed research genetic testing of over 4000 pts with BC treated at Mayo Clinic. Because most pts were unaware of their mutation status prior to selection of therapy, this cohort provides a unique opportunity to evaluate the natural history of BC recurrence after treatment of the index BC in pts with a deleterious mutation in predisposition genes. Methods: Women diagnosed and treated for BC at Mayo Clinic between 2001-2016 were enrolled in an IRB-approved research cohort. Pts were not selected for age of diagnosis or family history. Coding regions and consensus splice sites of established BC predisposition genes were subjected to amplicon-based deep sequencing using the QIAseq method in germline DNA extracted from peripheral blood or buccal samples. PVs in the genes were identified using GATK haplotype caller and Vardict. Patient, tumor, oncologic management and follow up data were reviewed. Herein we report on the differences in the incidence of local recurrence and CBC, among carriers and non- carriers and by predisposition gene using the cumulative incidence estimator and Fine and Gray regression to account for competing risks. Results: Of 4272 women with BC (median age 57, range 21-94), a PV in a BC predisposition gene was identified in 287 (6.7%). The most common PVs were seen in *CHEK2* (67, 1.6%), *BRCA1* (62, 1.5%), *BRCA2* (60, 1.4%), *ATM* (47, 1.1%); 8 (0.2%) patients had more than one PV. Pts with any PVs presented at younger age (median 51 vs 58 years, p<0.001), were more likely to have stage IV disease (4.5% vs 2.3%, p=0.02), estrogen receptor (ER) negative BC (19.5% vs 13.5%, p=0.005), and bilateral cancer (8.8% vs 4.3%, p<0.001). ER- BC proportion varied by gene - 38.9% in pts with PVs associated with ER- BC (BRCA1, BARD1, BRIP1, RAD51C, RAD51D) and 11.9% in those with PVs associated with ER+ BC (BRCA2, ATM, CDH1, CHEK2), p<0.001. NCCN criteria for genetic testing were assessed for 3763, with 69.9% of those with PVs qualifying for testing compared to 46.3% of those without PVs (p<0.001). Among 3973 pts (249 with PVs, 3724 without) with unilateral stage 0-III cancer, 168 pts developed local recurrence, 131 pts developed CBC and 248 pts developed distant disease with median 5 years of follow-up. Patients with any PV had higher rates of local recurrence after breast conserving surgery (HR 2.3, 95% CI: 1.2-4.2, p=0.01) but overall did not have significantly higher risk of CBC if contralateral prophylactic mastectomy was not performed (HR 1.7, 95% CI: 0.9-3.2, p=0.11). Specifically, pts with PVs in genes other than *BRCA1* or *BRCA2* did not have a higher risk of CBC compared to pts with no PV (HR 1.0, 95% CI: 0.4-2.7, p=0.96); the comparison of CBC risk in *BRCA1* or *BRCA2* versus those with no PV was HR 2.9 (95% CI: 1.3-6.5, p=0.01), while *BRCA1* or *BRCA2* compared to those with other PVs was HR 2.7 (95% CI: 0.8-9.3, p=0.13). In pts with *CHEK2* PVs, the probability of CBC at 10-years follow-up was 5.4%, which was similar to pts without a mutation (5.3%), p=0.47. Conclusion: While PVs in known BC predisposition genes increase risk of BC development, risk of CBC in carriers of PVs in non-BRCA predisposition genes with BC are not as high as seen with BRCA1 or 2 PV carriers. This information regarding future BC will be helpful in personalizing decisions on the extent of surgery in carriers of PVs in BC predisposition genes.

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Spatially defined immune-related proteins and outcome in triple negative breast cancer in the FinXX trial and Mayo Clinic cohort

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**Background:** Growing data established the pivotal role of preexisting immune response in triple negative breast cancer (TNBC). Conventionally, preexisting immune response can be evaluated by quantifying tumor infiltrating lymphocytes mainly in the stroma or gene expression analysis from the whole tumor section. Due to technical challenges with these conventional methods, limited data regarding specific subtypes and spatial distribution of these immune infiltrates are currently available. **Methods:** NanoString IO360 gene expression analysis and Digital Spatial Profiling (DSP) were used. DSP was used to quantify 29 immune-related proteins in stromal and tumor-enriched segments from 44 TNBC samples from the FinXX trial (NCT00114816) and 335 samples from the Mayo Clinic (MC) cohort of centrally reviewed TNBC (Leon-Ferre BCRT 2018). In FinXX trial, 22 patients with recurrence and 22 patients without recurrence were included. In MC cohort, 217/335 patients received adjuvant chemotherapy while 118 patients had surgery only without adjuvant chemotherapy. Regions were segmented based on pancytokeratin staining. The general linear model was used for statistical analysis of differential expression with recurrence free survival (RFS) as a categorical variable (recur yes or no). Kaplan-Meier (KM) estimates and Cox regression models were also used for analysis. **Results:** In the FinXX trial, there were 12 out of 29 proteins in tumor epithelial segments (intraepithelial) which were significantly expressed at higher levels among patients who were free of recurrence. These proteins include Beta-2 microglobulin, CD11c, CD20, CD40, CD56, CD8, Granzyme B, HLA-DR, ICOS, PD-L1, PD-L2, and TGFB1. In contrast, merely 5 out of 29 proteins in stromal segments were significantly differentially expressed in these 2 groups of patients. Granzyme B, IDO1, PD-L1, and PD-L2 in stroma were significantly higher and SMA was significantly lower in patients without recurrence. Using Cox regression models, intraepithelial CD56, CD40, and HLA-DR were significantly associated with outcome. When comparing between highest and lowest intraepithelial protein expression by tertile, intraepithelial CD56 (HR 0.12, 95%CI 0.03-0.39, $p < 0.001$), CD40 (HR 0.13, 95%CI 0.04-0.46, $p = 0.002$), and HLA-DR (HR 0.24, 95%CI 0.06-0.89, $p = 0.032$) were significantly associated with improved outcome. However, expression of these same proteins in stroma was not associated with outcome. Using KM estimates, intraepithelial CD56 ($p < 0.0001$), CD40 ($p = 0.0006$), and HLA-DR ($p = 0.013$) were also significantly associated with improved outcome. Nonetheless, RNA expression of these proteins by IO360 from whole tumor sections were not significantly associated with outcome (CD56 $p = 0.27$, CD40 $p = 0.21$, HLA-DR $p = 0.48$). Similar findings with DSP were observed in MC TNBC cohort. Comparing between the highest and lowest quartiles, there were significantly fewer patients who developed recurrence with high protein expression of intraepithelial CD56 ($p < 0.001$), CD40 ($p = 0.002$), and HLA-DR ($p = 0.006$). **Conclusions:** Using an in-depth analysis with spatially defined context, we identify that there were numerically more intraepithelial immune-related proteins associated with outcome compared to proteins in stroma. Specifically, intraepithelial CD56, CD40, and HLA-DR were significantly associated with improved outcome in both FinXX and MC TNBC cohorts. However, neither expression of these proteins in stroma nor RNA expression from whole tumor were associated with outcome. Our study highlights the impact of spatial biology and the importance of evaluating each potential biomarker in a spatially defined manner. **Support:** W81XWH-15-1-0292, BCRF 19-161, P50CA116201-9, P50CA015083

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# The relationship of established breast cancer risk factors with breast cancer subtypes

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**Background**: Molecular characterization of breast tumors has revealed four subtypes which differ in expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Breast cancer subtypes have different prognosis and unique risk factors. Breast cancer risk assessment models mainly reflect risk of ER/PR+ HER2- tumors, the most common subtype, and may not reflect risk of other subtypes. The study objective was to compare associations of established breast cancer risk factors across invasive breast cancer subtypes.
**Methods**: The study population included women aged 40-84 years who had a screening mammogram at Massachusetts General Hospital, Newton Wellesley Hospital, or the University of Pennsylvania from 2006-2015. Patients completed a risk factor questionnaire and additional risk factors were ascertained from clinical records. Women with prior breast cancer, breast implants, or *BRCA1/2* mutations were excluded. Women diagnosed with breast cancer within 6 months were excluded to remove those with cancer at the time of risk assessment. Tumor characteristics were obtained from linkage with hospital and state cancer registries. For invasive tumors, subtype was defined based on immunohistochemistry as ER and/or PR+ HER2-, ER and/or PR+HER2+, ER and PR- HER2+, or ER and PR and HER2- (triple negative breast cancer, TNBC). Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for breast cancer using time from mammogram to cancer diagnosis or censoring. Separate Cox models were fit for each subtype, and patients who developed DCIS or another subtype, died, or were alive and cancer free on December 31, 2017 were censored. Age, biopsy history, atypical hyperplasia, age at menarche, age at first live birth, family history, race, BMI, and breast density at the time of screening were included in the models.
**Results:** The study population (N=197,836) had a mean age of 54 years and 74% of patients were white, 15% were Black, and 11% were other races. During a mean follow-up of 6.3 years, 4,510 (2.3%) women developed breast cancer. Of these cancers, 1068 (24%) were DCIS. Of the invasive cancers, 2675 (77%) were ER/PR+HER2-, 290 (8%) were ER/PR+HER2+, 108 (3%) were ER/PR-HER2+, 264 (8%) were TNBC and 105 (3%) had missing subtype. For ER/PR+HER2- cancers, all risk factors were consistent with the literature and statistically significant. Breast density was associated with increased risk of all four subtypes compared to women with less dense breasts. Atypical hyperplasia was strongly associated with HER2+ cancers (HR=2.97 CI 1.63-5.40 p<0.01), less strongly associated with ER/PR+HER2- cancers, and not significantly associated with TNBC. Black women had higher risk of TNBC than white women (HR=2.61 CI 1.91-3.57 p<0.01).
**Conclusion** Our results highlight both similarities and heterogeneity in risk factors across breast cancer subtypes. Prior diagnosis of atypical hyperplasia was more strongly associated with HER2+ compared to HER2- tumors. While it is well known that Black women have higher risk of TNBC, it is striking that the more than two-and-a-half-fold increased risk persisted even with comprehensive adjustment for breast cancer risk factors in a screened population. These results suggest that additional factors, such as genetics, biomarkers, and environmental exposures should be included in risk assessment to better capture risk of less common breast cancer subtypes such as TNBC.

Risk factors for breast cancer subtypes among 197,836 women undergoing screening mammography*

| | **ER/PR+ HER2- N=2674** | | **ER/PR+ HER2+ N=290** | | **ER/PR-HER2+ N=108** | | **ER/PR/HER2- N=264** | |
|---|---|---|---|---|---|---|---|---|
| | **HR,95% CI** | **p** | **HR,95% CI** | **p** | **HR,95% CI** | **p** | **HR,95% CI** | **p** |
| Black vs. white unadjusted | 0.67,0.58-0.77 | <0.01 | 0.73,0.48-1.09 | 0.12 | 0.91,0.49-1.68 | 0.77 | 2.61,1.96-3.46 | <0.01 |
| Black vs. white multivariate* | 0.72,0.63-0.83 | <0.01 | 0.75,0.49-1.15 | 0.19 | 1.23,0.65-2.33 | 0.53 | 2.61,1.91-3.57 | <0.01 |
| Atypical Hyperplasia* | 1.38,1.02-1.87 | 0.04 | 2.77,1.42-5.42 | <0.01 | 3.89,1.03-14.7 | 0.04 | 0.43,0.06-3.14 | 0.40 |
| 1 FDR** vs. none | 1.46,1.32-1.63 | <0.01 | 1.16,0.82-1.65 | 0.39 | 1.93,1.18-3.16 | 0.01 | 1.11,0.75-1.63 | 0.60 |
| 2 FDR** vs. none | 2.12,1.67-2.71 | <0.01 | 1.17,0.44-3.15 | 0.75 | 1.90,0.47-7.76 | 0.37 | 2.81,1.44-5.49 | <0.01 |
| BMI ≥25 vs. <25 kg/m2* | 1.37,1.25-1.50 | <0.01 | 1.35,1.04-1.75 | 0.03 | 1.07,0.71-1.64 | 0.74 | 1.29,0.97-1.73 | 0.08 |
| Dense vs. non-dense breasts | 1.55,1.42-1.69 | <0.01 | 1.75,1.34-2.29 | <0.01 | 1.97,1.25-3.10 | <0.01 | 1.65,1.26-2.17 | <0.01 |

*Adjusted for all factors in the table and additionally age, biopsy, age at menarche, age at first live birth

**FDR= first degree relative with breast cancer

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Global myocardial perfusion is reduced in premenopausal breast cancer patients treated with ovarian function suppression and aromatase inhibitor therapy: An adenosine stress T1 map CMR study

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**Introduction:** Premenopausal women with high-risk hormone receptor-positive (HR+) breast cancer (BC) undergo abrupt menopause induction with aromatase inhibitor (AI) anti-estrogen therapy and ovarian function suppression (OFS). This treatment improves recurrence-free survival but may increase cardiovascular (CV) risk associated with early hypoestrogenemia as observed in women with non-cancerous reasons for early loss of ovarian function. We sought to identify if OFS+AI therapy is associated with myocardial perfusion changes, a subclinical marker of coronary heart disease. **Methods:** We evaluated women with paired adenosine cardiovascular magnetic resonance imaging scans at 3-to 6-month intervals using cines and T1 maps in standard short-axis planes. As increased blood flow from vasodilation increases adenosine stress parametric T1 values of the myocardial tissue, the myocardial perfusion reactivity was calculated from the percent increase of stress versus native (pre-stress) T1 maps. Double-blinded post-processing of images was performed in CircleCVI software. Statistical analyses were performed in MATLAB ($p<0.05$ defined as statistically significant) using paired t-tests for within-group comparisons and two-sample t-tests for between-group comparisons. **Results:** Twenty-one premenopausal women (16 Caucasian, 5 African American; median age 44.7 years) were accrued in 16 months - 14 with HR+ BC within 3 years of initiating OFS+AI (median 8 months) and 7 with triple negative BC within 3 years of chemotherapy (median 10 months) for comparators. Global myocardial perfusion reactivity to adenosine stress declined in HR+ women on OFS+AI therapy during the 3-6 month study interval (-1.3%; 95%CI: -3.4-0.7%) which was significantly different ($p=0.02$) from changes observed in comparators who had an improvement in perfusion during the interval (3.2%; 95%CI: -1.2-7.6%) (Table). Left ventricular (LV) function remained unchanged during the 3-6 month interval for all groups ($p>0.05$). The cardiovascular stress tests identified two HR+ women (14%) with abnormal results during stress imaging who were sent for further cardiovascular evaluations.**Conclusions:** Women with HR+ BC treated with OFS+AI exhibited a decline in global microcirculatory perfusion during an adenosine cardiac stress test with normal LV functional parameters. Alternatively, triple negative BC patients trended to have an improvement in LV function during the interval with non-significant improvement in myocardial perfusion. This study demonstrates a decline in myocardial perfusion in premenopausal women on OFS+AI therapy, suggesting subclinical coronary artery effects due to early hypoestrogenemia. Future work should confirm these results, identify women at higher risk, and test strategies to mitigate cardiotoxicity in premenopausal women with HR+ BC.

| CMR Measure | **Hormone Receptor-Positive Breast Cancer(n=14)** | **Triple Negative Breast Cancer(n=7)** | **p-value for difference in change by group** | | | | |
|---|---|---|---|---|---|---|---|
| | **Baseline** | **Follow-up** | **p-value** | **Baseline** | **Follow-up** | **p-value** | |
| LV Ejection Fraction, % | **56** (51, 61) | **56** (51, 62) | 0.82 | **55** (50, 60) | **60** (55, 65) | 0.06 | 0.12 |
| $EDV_{index}$, mL/m$^2$ | **70.6** (63.7, 77.5) | **69.9** (63.5, 76.3) | 0.73 | **65.2** (58.0, 72.3) | **66.8** (51.4, 82.1) | 0.74 | 0.60 |
| $ESV_{index}$, mL/m$^2$ | **31.3** (26.2, 36.5) | **30.4** (26.2, 34.5) | 0.37 | **29.4** (23.8, 35.0) | **27.1** (19.4, 34.8) | 0.36 | 0.55 |
| $SV_{index}$, mL/m$^2$ | **39.3** (34.3, 44.2) | **39.5** (33.9, 45.1) | 0.90 | **35.8** (32.3, 39.3) | **39.7** (31.2, 48.2) | 0.23 | 0.29 |
| Myocardial mass index, g/m$^2$ | **48.1** (42.7, 53.6) | **44.6** (40.0, 49.3) | 0.08 | **43.5** (40.2, 46.8) | **41.0** (33.3, 48.7) | 0.42 | 0.77 |
| Global myocardial perfusion reactivity, % | **2.8** (1.1, 4.4) | **1.4** (-0.4, 3.3) | 0.19 | **1.4** (-0.9, 3.7) | **4.6** (0.9, 8.4) | 0.13 | **0.02** |
| Basal SAX myocardial perfusion reactivity, % | **2.2** (0.7, 3.7) | **1.4** (0.3, 2.5) | 0.26 | **1.8** (0.2, 3.4) | **2.1** (-1.7, 5.9) | 0.85 | 0.46 |
| Mid SAX myocardial perfusion reactivity, % | **2.4** (-.3, 5.2) | **0.5** (-1.5, 2.7) | 0.22 | **1.2** (-1.9, 4.2) | **3.3** (-0.9, 7.6) | 0.36 | 0.12 |
| Apical SAX myocardial perfusion reactivity, % | **3.4** (1.2, 5.7) | **2.1** (-1.4, 5.7) | 0.49 | **0.8** (-2.6, 4.1) | **8.8** (3.7, 13.9) | <0.05 | **<0.01** |
| LV = left ventricular, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, SAX = short-axis slice; volumetric and mass measures indexed to body surface area. Data are presented as **mean** (95% Confidence Interval). | | | | | | | |

**Table**: Cardiovascular magnetic resonance (CMR) study measures for HR+ BC patients on OFS+ AI therapy and triple negative BC patients

**Publication Number:** GS4-02

E2112: Randomized phase 3 trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. A trial of the ECOG-ACRIN cancer research group

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Background: Endocrine therapy resistance in advanced breast cancer remains a significant clinical problem that may be overcome with use of histone deacetylase (HDAC) inhibitors such as entinostat. The ENCORE 301 randomized phase II study reported an improvement in progression-free (PFS) and overall survival (OS) with the addition of entinostat to the steroidal aromatase inhibitor (AI) exemestane in patients with advanced hormone receptor (HR)-positive, HER2-negative breast cancer. Protein lysine acetylation in peripheral blood mononuclear cells (PBMCs) was associated with prolonged PFS in the entinostat arm.
Methods: E2112 is a multicenter randomized double-blind, placebo-controlled phase III study that enrolled men or women with advanced HR-positive, HER2-negative breast cancer whose disease had progressed on a non-steroidal AI in the adjuvant or metastatic setting (NCT02115282). Study participants were also required to have an ECOG performance status 0-1 with measurable or non-measurable (limited to 20% of the study population) disease. One prior chemotherapy for metastatic disease and prior treatment with fulvestrant and a CDK4/6 inhibitor was permitted but not required. Participants received exemestane 25mg po daily and entinostat (EE)/placebo (EP) 5mg po every week. Primary endpoints were PFS (central review) and OS. One-sided type 1 error 0.025 was split between two hypothesis tests: 0.001 for PFS test and 0.024 for OS. PFS tested in the first 360 pts, 88.5% power to detect 42% reduction in the hazard of PFS failure (median PFS, 4.1 to 7.1 months); OS tested in all 600 pts, 80% power to detect 25% reduction in the hazard of death (median OS, 22 to 29.3 months). Secondary endpoints included **s**afety, objective response rate (ORR), and changes in protein lysine acetylation status in PBMCs (CD3+ T cells, CD14+ monocytes, CD19+ B cells, pan-leukocyte marker CD45+ cells, CD56+ NK cells) between C1D1 and C1D15 (integrated biomarker).
Results: A total of 608 participants were randomized between March 2014 and October 2018 (305 EE, 303 EP), 98% enrolled in USA. Characteristics were well balanced between the arms. Median age was 63 years (range, 29-91), 99% female, 95% postmenopausal, 80% white and 15% black. A majority (84%) had disease resistant to AI in the metastatic setting at study entry, 78% had measurable disease and 60% visceral disease. Prior treatments included chemotherapy (60%), fulvestrant (30%), CDK4/6 inhibitor (35%), everolimus (3%). Median prior lines of chemotherapy was 1 (range, 0-4) and endocrine therapy was 2 (range, 1-7); in adjuvant/metastatic setting. Grade 3/4 adverse events in EE arm included neutrophil count decreased (20%), hypophosphatemia (14%), anemia (8%), white blood cell decreased (6%), fatigue (4%), diarrhea (4%), and platelet count decreased (3%). At final analysis, median PFS was 3.3 months (EE) versus 3.1 months (EP) (HR=0.87, 95% CI: 0.67, 1.13, p=0.30). Median OS was 23.4 months (EE) versus 21.7 months (EP) (HR=0.99, 95% CI: 0.82, 1.21, p=0.94). ORR was 4.6% (EE) and 4.3% (EP). The median fold change in lysine acetylation in PBMCs was approximately 1.5 in EE arm, and 1 in EP arm. Participants on EE had significantly higher increase in lysine acetylation by C1D15 than patients on EP (397 paired samples available for analysis, p<0.001 for all). Additional biomarker analyses will be presented at time of meeting.
Conclusion: The combination of exemestane and entinostat did not improve survival in AI resistant advanced HR-positive, HER2-negative breast cancer. Pharmacodynamic analysis confirmed target inhibition in entinostat-treated patients.

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# A good prognosis of endocrine-dependent tumors among residual invasive cancer after anti-HER2 therapy: CALGB 40601 (Alliance) and validation studies

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**Background**: Patients with HER2+ breast cancer who have residual disease after neoadjuvant anti-HER2 plus chemotherapy have a high risk of recurrence and benefit from adjuvant trastuzumab emtansine (T-DM1). We hypothesize that endocrine-responsive residual tumors after neoadjuvant treatments may have good outcomes among patients receiving only adjuvant endocrine therapy plus trastuzumab. Using paired pre- and post-treatment samples from CALGB 40601 and other neoadjuvant cohorts that did not include adjuvant T-DM1, we investigated survival by pretreatment and residual disease *ESR1* and *PgR* gene expression in CALGB 40601, and by estrogen receptor (ER) and progesterone receptor (PR) immunohistochemistry (IHC) in the other cohorts. We considered endocrine-responsive tumors those with ER and/or PR expression by gene expression or IHC.
**Methods:** CALGB 40601 is a randomized neoadjuvant trial of single vs. dual HER2-targeting (trastuzumab and/or lapatinib added to paclitaxel). We only included those patients who had not suffered from disease progression or death during their preoperative treatments. In total, 77 patients with paired pretreatment and residual disease tumors were profiled by mRNA sequencing and studied. Cutoffs for *ESR1* and *PgR* mRNA expression mimicking clinical positivity were obtained using 265 pretreatment CALGB 40601 tumors (and 1,045 TCGA samples for *ESR1)*. We also examined ER and PR IHC in paired tumors from 202 patients treated at 4 different collaborating institutions; all had residual disease after neoadjuvant HER2 targeting plus chemotherapy. We considered ER- or PR-positive as ≥10% positively staining cells. The primary endpoint was EFS, defined as the time from randomization to event in CALGB 40601 and from the first systemic therapy to event in the 4-institution validation cohort.
**Results**: In 77 patients from CALGB 40601 with paired (pretreatment/residual disease) specimens, 38 (49.3%) had *ESR1*+/*ESR1*+ tumors. The EFS was superior in the *ESR1*+/*ESR1*+ (n=38) group than in the remaining others (the log-rank test, *p*=0.011). The 5- and 7-year EFS rates for the *ESR1*+/*ESR1*+ (n=38) were 92.1% and 89.2%, whereas the rates were uniformly < 70% in the others. In particular, the 5-year EFS rate among 11 patients with *ESR1*+/*ESR1*- tumors was 61.4%. This remained significant in multivariable analysis with clinical stage and treatment arm; the hazard ratio (HR) for EFS in *ESR1+/ESR1*+ versus all others was 0.29 (95% CI, 0.09-0.90). In *ESR1*+/*ESR1*+ tumors, 5-year EFS rates were high for those whose residual disease and also being *PgR*+ (n=32) or PAM50 LumA or Normal-like (n=34) (93.8% and 97.1%, respectively). In the institutional validation cohort, pretreatment /residual disease ER(+)/ER(+) tumors (n=113) had superior 3-year EFS versus all others (*p*=0.010). At a median follow-up of 35.9 months, the 3-year EFS rates for ER(+)/ER(+) and all other groups were 96.6% and 82.6%, respectively. This remained strongly significant in multivariable analysis with clinical stage; the HR for EFS in ER(+)/ER(+) versus all other groups was 0.28 (95% CI, 0.09-0.88). Among 46 who also had PR+ in the residual disease, the 3-year EFS was 100.0%.
**Conclusions**: HER2+ patients with ER+ pretreatment and ER+ residual disease after neoadjuvant chemotherapy + HER2-targeting have a very good survival outcome despite not receiving additional anti-HER2 targeting with T-DM1. This may provide a simple mechanism to better tailor therapy within residual disease patients using serial ER measurements.

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# Sentinel node biopsy should not be routine in older patients with ER positive breast cancer

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*Background:*Based on randomized controlled trials demonstrating no survival benefit of axillary dissection in elderly breast cancer patients, the SSO/Choosing Wisely campaign recommended against the routine use of sentinel lymph node biopsy (SLNB) in clinically node negative patients aged ≥70 with estrogen receptor (ER) positive breast cancer in 2016. SLNB is still performed in >80% of such patients and we have previously shown that at our institution, SLNB positivity influences adjuvant therapy decisions in this population. In this study, we sought to validate the association of SLNB positivity and adjuvant treatment in a larger population-based cohort, and to evaluate the impact of this finding on oncologic outcomes.
*Methods:*The Breast Cancer Outcome Unit (BCOU) prospectively collects demographic, pathologic, treatment and outcomes data on all patients referred to BC Cancer with breast cancer in British Columbia, Canada. Female patients aged ≥70 with newly diagnosed estrogen receptor-positive invasive breast cancer who underwent SLNB from 2010-2016 were included. Patients with HER2-positive disease or those treated with neoadjuvant therapy were excluded. Multivariable analysis was used to assess the effect of SLNB positivity on adjuvant treatment. Overall survival (OS) and breast cancer specific survival (BCSS) were assessed using Kaplan-Meier analysis and Cox regression was used to assess contribution of SLNB positivity and adjuvant treatment. A nomogram was created to model the effect of nodal positivity and adjuvant treatment on BCSS.
*Results:*We identified 2580 patients who met study criteria with a median age of 75 and a median tumor size of 15 mm. SLNB was positive in 23%. Sixty-seven percent of patients had breast conserving surgery (BCS) and 62% of patients had RT (BCS 79%, mastectomy 25%). As systemic therapy 5% of patients had chemotherapy (CT) and 78% of patients had hormone therapy (HT). Use of adjuvant therapies was associated with SLNB positivity: Systemic therapy (HR = 2.4, 95% CI: 1.84-3.14, p <0.0001), RT (HR = 4.94, 95% CI: 3.91-6.25, p <0.0001) and nodal RT (HR = 61.4, 95% CI: 26.6-141.7, p <0.0001). The 5-year OS was 86% and BCSS was 96% with a median follow-up of 4.33 years (95% CI 4.21-4.47 years). There was improved BCSS with receipt of HT (HR 0.51 95% CI 0.301-0.875, p=0.0142) and worse BCSS with grade 3 vs grade 1 disease (HR 4.09, 95% CI 2.06-8.10, p<0.0001). Age, tumor size, status of SLNB and use of RT were not significant prognostic variables. Patients with a positive SLNB who did not receive any adjuvant therapy had lower BCSS (HR 3.22 95% CI 1.235-8.418, p=0.0168) than those with a negative SLNB. However, amongst those who received any combination of CT, HT and RT, there was no significant difference in BCSS regardless of nodal status. A nomogram was developed incorporating tumor size, grade, SLNB status and adjuvant treatment. Using the nomogram, patients aged 75-79 with T1, grade 1-2 tumors, with or without positive SLNB and treated with or without adjuvant therapy had 5-year BCSS ≥95%. The nomogram also indicated that 5-year BCSS was similar for patients with positive and negative SLNB for all combinations of tumor features when patients received HT.
*Conclusions:*In this modern, population-based cohort of patients over 70 with ER-positive breast cancer, 5-year BCSS was excellent at 96%. Although the use of adjuvant treatment was associated with a positive SLNB, BCSS was not changed based on nodal status when patients received HT. Our results support the Choosing Wisely recommendations; SLNB can be safely omitted in elderly patients willing to take HT, and we advocate that SLNB can be omitted in low-risk patients aged ≥75 even in the absence of planned HT.

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Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancerand with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B

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**Background:** About one third of patients with hormone-receptor-positive (HR+), HER2- primary breast cancer with residual invasive disease after neoadjuvant chemotherapy will relapse despite adjuvant endocrine therapy. The risk of relapse can be assessed more accurately using the CPS-EG scoring system (Mittendorf et al. JCO 2011). Therapeutic inhibition of cyclin-dependent kinase 4 and 6 (CDK 4/6) by palbociclib combined with endocrine therapy demonstrated highly relevant efficacy in metastatic breast cancer. Thus, we hypothesize that palbociclib may also be active in these high-risk patients with primary breast cancer. **Methods:** PENELOPE-B (NCT01864746) is a double-blind, placebo-controlled, phase III study in women with centrally confirmed HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+). After completion of neoadjuvant chemotherapy and locoregional therapy, patients were randomized (1:1) to receive 13 cycles of palbociclib 125mg daily or placebo on days 1-21 in a 28d cycle in addition to standard endocrine therapy. Randomization was stratified by lymph node status (at surgery), age, Ki-67, global region, and CPS-EG score. Primary endpoint is invasive disease-free survival (iDFS). Final analysis was planned after 290 iDFS events with efficacy boundary $p<0.0463$ due to 2 interim analyses. Main secondary endpoints include iDFS excluding second primary invasive non-breast cancers, overall survival, and safety. **Results:** A total of 1250 patients were randomized between 2/2014 and 12/2017. Median age was 49.7 years [range 19-79]; 96.8% had residual disease in the breast, 94.6% were ypN+; G3 was reported in 47.4%, Ki-67 >15% in 27.7 %; 54.7% of patients had risk status CPS-EG score ≥3. 1118 patients (89%) completed at least 7 cycles of therapy. 50.1% of patients received aromatase inhibitor (AI), 49.8% tamoxifen, 6.6% AI + gonadotropin-releasing hormone (GnRH) and 9.7% tamoxifen + GnRH. Most common related serious adverse events (SAEs) were infections and vascular disorders. 8 fatal SAEs were reported. **Conclusions:** PENELOPE-B evaluates the effect of palbociclib for 1 year compared to placebo in addition to endocrine therapy in high-risk primary breast cancer patients. The database was locked with 308 events on September 25th 2020. After breaking the blind for analysis, top line results will be available as of mid October 2020. Results of the final iDFS analysis will be presented at the meeting.

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# Moving in the fast lane: Test design and validation to produce up-to-date hereditary breast and gynecologic cancer tests

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Introduction

Germline genetic testing is increasingly relevant to breast and gynecologic (GYN) cancer clinicians for monitoring and managing high-risk patients. In particular, multi-gene panels (MGPs) can identify unsuspected cancer syndromes and variants that may become clinically significant. Effective MGPs must be comprehensive and up-to-date. For the current study, we used a probe panel designed for targeted enrichment of 4,500 genes associated with various inherited diseases to develop and validate a 66-gene comprehensive hereditary cancer panel, including subsets of genes associated with breast and GYN cancers.

Materials and Methods

Genomic DNA was extracted and taken through next generation sequencing (NGS) library preparation to be sequenced on an Illumina NovaSeq instrument. Targeted capture-based enrichment with a long-range PCR (LR-PCR) component was used to interrogate all protein-coding exons, intron-exon splice sites (+/-10bp), as well as clinically relevant deep intronic, 5'UTR, and 3'UTR regions for single nucleotide variants (SNVs) and insertions/deletions (indels) of all genes of interest. Copy number variations (CNVs) were also interrogated for all applicable regions. Data analysis was performed using a proprietary in-house bioinformatics variant analysis pipeline.

For validation, samples from the Coriell Repository and more than 100 unique de-identified genomic DNA specimens from whole blood and saliva were analyzed for 17,911 variants in 508 genes. Variants were previously identified by orthogonal methods (in-house Sanger sequencing, CLIA validated NGS assays, and microarray). The well-characterized Genome in a Bottle (GIAB) NA12878 and Ashkenazim Trio samples (NA24149, NA24385, and NA24143) were also included. The analytic sensitivity (Positive Percent Agreement, %PPA) and specificity (Technical Positive Predictive Value, %TPPV and Negative Percent Agreement, %NPA) were determined for each variant type (SNV, indel, and CNV).

The 66-gene hereditary cancer panel includes genes that confer ≥2-fold increased risk or 5% lifetime risk for developing cancer (*APC*, *ATM*, *AXIN2*, *BAP1*, *BARD1*, *BLM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN1B*, *CDKN2A (p16, p14)*, *CHEK2*, *DICER1*, *EGFR*, *EPCAM*, *FANCA*, *FANCC*, *FANCM*, *FH*, *FLCN*, *GALNT12*, *GREM1*, *HOXB13*, *MAX*, *MEN1*, *MET*, *MITF*, *MLH1*, *MRE11 (MRE11A)*, *MSH2*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *NTHL1*, *PALB2*, *PMS2*, *POLD1*, *POLE*, *POT1*, *PTCH1*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RECQL*, *RET*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SMARCA4*, *SMAD4*, *STK11*, *SUFU*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *XRCC2*). Of these, 30 genes increase the lifetime risk of breast and/or GYN cancers and are also distributed among smaller phenotype-specific panels.

Results

The analytical sensitivity (%PPA) for SNVs and indels was 100.0% and 97.8% for CNVs. The overall specificity for SNVs, indels, and CNVs was >99.0%. The %TPPV for SNVs, Indels, and CNVs was 100.0%, 99.3%, and 100.0%, respectively. The %NPA for SNVs, Indels, and CNVs was 100.0%. The %PPA, %TPPV, and %NPA for LR-PCR was 100.0%.

Conclusion

Validation of the 66-gene hereditary cancer panel demonstrated high analytical sensitivity and specificity. As additional gene-cancer associations are established, using an already designed and developed comprehensive 4,500 gene panel will expedite the process of updating panel tests to include relevant candidate genes, allowing clinicians and patients to benefit from up-to-date and comprehensive testing.

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# Adaptlate -a randomized, controlled, open-label, phase-iii trial on adjuvant dynamic marker - adjusted personalized therapy comparing abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy in (clinical or genomic) high risk, hr+/her2- early breast cancer

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Goals: The WSG ADAPT trial program is one of the first new generation trials addressing the issue of individualization of (neo)-adjuvant decision-making in early breast cancer (EBC) in a subtype-specific manner. The first WSG ADAPT umbrella trial (NCT01779206) aimed to establish early predictive molecular surrogate markers for response after a short 3-week induction treatment and to omit chemotherapy in a large cohort of early high risk HR+/HER2- patients. The aim of the ADAPTlate phase-III-trial is to improve adjuvant therapy for patients at high risk for late disease recurrence, who have completed definite locoregional therapy (with or without neoadjuvant or adjuvant chemotherapy) and are under adjuvant endocrine treatment. This high-risk population does not derive optimal benefit from standard ET, often develops secondary resistance against ET and consequently late recurrences. With ADAPTlate, it is planned to evaluate whether patients with high-risk EBC derive additional benefit from adding abemaciclib to ET even 2-6 year after their initial diagnosis. Abemaciclib has been shown to improve outcome in metastatic breast cancer and recently, even in early breast cancer when given as part of primary therapy. Methods: WSG-ADAPTcycle is a prospective, multi-center, interventional, two-arm, non-blinded, randomized, controlled adjuvant phase III trial (NCT not yet assigned). It investigates whether patients with HR+/HER2- EBC identified as high-risk during screening (based on clinical or genomic risk) derive additional benefit from 2 years of the CDK4/6 inhibitor abemaciclib combined with ET compared to ET alone. Starting Q3 2020 (enrollment 36 months, 50 sites), 1250 patients will be screened and 903 randomized in a ratio 3:2 (602 to abemaciclib + ET; 301 to standard ET). Pre-/postmenopausal patients with histologically confirmed invasive HR+/HER2- EBC and 2-6 years after primary diagnosis, with either known high clinical risk (c/pN 2-3 OR high CTS score in pN 0-1 OR non-pCR after neoadjuvant chemotherapy in cN 1 or G3 tumors OR G3 and Ki-67 ≥ 40% in pN 0-1) or known high genomic risk (Oncotype Dx® / RS >25 in c/pN 0, RS >18 in c/pN 1 OR high risk Prosigna®, EPclin® or Mammaprint® in pN 0-1) or intermediate clinical, but unknown genomic risk (luminal B-like (G3 or Ki-67 ≥20%) in c/pN 0-1 AND Oncotype DX® in screening either RS >25 in c/pN 0 or RS >18 in c/p N1) will be eligible. Treatment duration is 2 years for the interventional abemaciclib + ET (premenopausal: AI+GnRH) arm, followed by at least 3-6 years ET alone. Patients in control arm will receive 5-8-years ET at investigator´s choice. ePROs are collected using CANKADO. Primary objective is to demonstrate superiority of invasive disease-free survival (iDFS) of abemaciclib + ET vs. standard ET. Secondary objectives include overall survival (OS), distant disease-free survival (dDFS), occurrence of CNS metastases, quality of life (EORTC QLQ-C30, QLQ-BR23, EQ-5D-5L) and translational research. Translational analyses: Exploratory tissue biomarker research will be conducted to assess alterations in molecular markers (e.g., ESR1, PIK3CA, CCND1, CDKN2A, RB1). In addition, ctDNA/ctRNA from optional blood samples will be assessed for mutations and gene expression relevant for HR+/HER2- EBC using the most appropriate technology at the time of testing. Conclusions: ADAPTlate seeks to evaluate whether enhancing ET with a CDK 4/6 inhibitor is superior to ET alone in patients with clinical or genomic high risk EBC even 2-6 years after their initial diagnosis. Translational research aims at assessing potential mechanisms of resistance to endocrine and/or CDK4/6 targeted therapy.

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# A phase I/Ib study evaluating GDC-0077 + palbociclib (palbo) + fulvestrant in patients (pts) with *PIK3CA*-mutant (mut), hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC)

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**Background**
GDC-0077 is a PI3Kα-selective inhibitor and mutant PI3Kα degrader that demonstrates antitumor activity in *PIK3CA*mut BC xenograft models. A phase I/Ib study of GDC-0077 alone and combined with endocrine therapy ± the CDK4/6 inhibitor (i) palbo is ongoing (NCT03006172). Data from GDC-0077 + palbo + fulvestrant in pts with *PIK3CA*mut, HR+/HER2- mBC are presented herein.

**Methods**
Safety (NCI-CTCAE v4), pharmacokinetics (PK), and preliminary antitumor activity (clinical benefit rate [CBR]: RECIST v1.1 stable disease for ≥ 24 weeks, partial response [PR], or complete response) of 9 mg oral once daily GDC-0077 + 125 mg palbo 21/28 days + 500 mg intramuscular fulvestrant on day 1 (and day 15 of cycle 1) of 28-day cycles were assessed in Arms E and F, until intolerable toxicity or disease progression. In Arm F, pts were obese and/or pre-diabetic (body mass index ≥ 30 kg/m$^2$ and/or HbA1c ≥ 5.7%) and also received metformin up to 2000 mg daily starting at 500 mg in cycle 1 day 1, prior to initiating GDC-0077 at cycle 1 day 15 instead of day 1 as in Arm E. Additional key eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, no prior PI3Ki therapy, no prior CDK4/6i, and ≤ 1 prior chemotherapy for Arm E (no restrictions on prior CDK4/6i or chemotherapy for Arm F). *PIK3CA*mut allele frequency was assessed in circulating tumor (ct) DNA from serial plasma collections.

**Results**
At clinical cutoff (03/20/2020), 28 pts were enrolled (13 in Arm E and 15 in Arm F). Median age was 55 years in Arm E and 65 years in Arm F. ECOG PS was 0 in 8 pts (62%) in Arm E and in 7 pts (47%) in Arm F. Three (23%) and 12 (80%) pts in Arm E and F, respectively, had received ≥ 2 prior lines of therapy for mBC. One pt (8%) in Arm E and 10 pts (67%) in Arm F received prior fulvestrant. Nine pts (60%) received prior CDK4/6i (all Arm F). Median GDC-0077 treatment duration was 7.8 months (range 0.1-13.9) in Arm E and 6.5 months (1.2-11.2) in Arm F. GDC-0077 cumulative dose intensity was 98% in Arm E and 88% in Arm F. Thirteen pts (46%) discontinued treatment: 11, due to radiographic disease progression (3 in Arm E, 8 in Arm F); 1, due to an adverse event (AE; treatment-related grade 2 panniculitis in Arm F); and 1 pt withdrew (Arm F). The most common treatment-related AEs (≥ 4 pts) were stomatitis (grouped term; 92%), neutropenia (85%), diarrhea and hyperglycemia (62% each), fatigue (38%), alopecia, nausea, and thrombocytopenia (31% each) in Arm E; and hyperglycemia (67%), diarrhea and neutropenia (53% each), nausea (47%), stomatitis (grouped term; 47%), anemia, decreased appetite, and blurred vision (27% each) in Arm F. Grade ≥ 3 treatment-related AEs (≥ 2 pts) were neutropenia (62%) and hyperglycemia (23%) in Arm E; and hyperglycemia and neutropenia (47% each), and anemia (13%) in Arm F. AEs led to GDC-0077 dose reduction in 2 pts (15%) in Arm E and 4 pts (27%) in Arm F. The PK of GDC-0077 in combination with palbo + fulvestrant was similar to single agent GDC-0077. Overall, 7/25 pts (28%) with measurable disease had a PR (5/10 [50%] pts in Arm E; 2/15 [13%] pts in Arm F, both received prior fulvestrant), of whom 6 pts (24%; 4 in Arm E; 2 in Arm F) had a confirmed PR. CBR was 61% (17/28 pts: 8 in Arm E; 9 in Arm F). *PIK3CA*mut allele frequency by ctDNA analysis decreased during treatment in most pts.

**Conclusion**
This study demonstrated a manageable safety profile when combining GDC-0077 at its single agent recommended phase II dose of 9 mg with palbo + fulvestrant at standard doses, similar PK to GDC-0077 alone, preliminary anti-tumor activity, and modulation of *PIK3CA*mut allele frequency in ctDNA. In obese and/or pre-diabetic patients enrolled to Arm F, hyperglycemia was frequent despite initiating metformin prior to GDC-0077. A phase III study of GDC-0077 + palbo + fulvestrant is enrolling currently (NCT04191499).

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# Racial disparities persist despite with uptake of digital breast tomosynthesis (DBT) for breast cancer screening

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Background: Breast cancer screening with digital breast tomosynthesis (DBT) has been shown to improve recall rates and detection of invasive cancer compared to 2D full field digital mammography (FFDM). The Federal Drug Administration (FDA) approved the use of DBT in 2011, and the Centers for Medicare and Medicaid Services (CMS) approved coverage in 2015. We report a single institution's longitudinal experience of the utilization and effectiveness of DBT for breast cancer screening over time with a focus on racial differences.
Materials and Methods: The analytic population (n = 140,346) included females >18 years who underwent one or more breast cancer screening examinations performed at Johns Hopkins (a tertiary care institution) and affiliated sites between 4/1/2013 and 3/30/2020. Females were categorized as having only FFDM for screening (n = 43,323) or including DBT views (n = 97,023). Recall rate and cancer detection rate were compared between the two groups overall and stratified by race using the Chi-squared test and Fishers Exact test. Univariate and multivariate logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) of having a DBT screening mammogram compared to an FFDM mammogram adjusted for year, race, and an interaction term between year and race.
Results: The mean age was 58.9 +/- 10.8 years for the FFDM group and 60.3 +/- 11.1 years for the DBT group. A larger percentage of White patients (62% FFDM vs 71.1% DBT) than Black patients (30.4% FFDM vs 22.6% DBT) or Asian patients (3.8% FFDM vs 3.0% DBT) were in the DBT group (p<0.001).
During the study period, there was rapid increased in utilization of DBT. In year 1 (4/1/2013-3/30/2014), 2791/14841 (18.8%) of patients had a screening mammogram with DBT. By year 3, during which CMS approved coverage of DBT, this increased to 15069/21304 (70.7%). By year 6, 18759/20929 (90.0%) included DBT views.
All women irrespective of race had similar increases in utilization rates\ of DBT during the study period (effect modifier term OR 0.99, 95% CI 0.98-1.00). However, Black women and Asian women were significantly less likely to have a screening study with DBT compared to White women (Black women: OR 0.51, 95% CI 0.48-0.70; Asian women: OR 0.59, 95% CI 0.57-0.80).
Overall the DBT group had lower recall rate compared to the FFDM group (9.1% versus 11.2%, p<0.001). This was observed for White women (8.6% vs 10.7, p<0.001), Black women: 10.4% vs 11.9% p=0.001) but not Asian women (11.5% vs 11.6%, p=0.97). The DBT group also had higher cancer detection rate overall compared to the FFDM group (6.0 vs 4.1, p<0.001). This was observed for White women (7.3 vs 4.5, p<0.0001); Black women (7.1 vs 4.3, p=0.001), and Asian women (10.4 vs 2.6, p=0.01).
Conclusions: We observed racial differences in the utilization of DBT for screening mammography, which could have significant clinical implications given the improved recall rate and cancer detection of DBT over the study period. Longer follow up is needed to understand the impact of these racial differences. Studies are also needed to understand and address existing obstacles such as socioeconomic level, insurance status, and education to reduce the disparity preventing all patients equitable access to DBT.

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# Randomized trial of 12 months of omega-3 fatty acids vs placebo during a weight loss intervention in post-menopausal women at increased risk for breast cancer

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**Objectives**: The primary objective was to determine tolerability of ω-3 fatty acids (2150 mg of eicosapentaenoic acid (EPA) and 1050 docosahexaenoic acid (DHA) ethyl esters) vs placebo in women in undergoing a behavioral weight loss intervention (6 months loss and 6 months maintenance). Secondary objectives were to explore potential differences in modulation of blood and benign breast tissue risk biomarkers, satiety and quality of life indices, and weight loss. **Results:** 46 peri and postmenopausal women were randomized and 42 completed the 6 months of the weight loss intervention and were biomarker evaluable (22 placebo and 20 ω-3 FA). Median baseline BMI in the 42 evaluable women was 31 kg/m$^2$ with a median 6-month relative weight loss of 11% and relative fat mass loss of 20% (DXA). Median 12-month relative mass loss was 10% in the 35 women completing 12 months of the intervention. ω-3 fatty acids increased the ratio of (EPA+DHA): arachidonic acid 2.6-fold (median, range 1.8 - 3.8) vs no change for placebo. There was no difference by randomization group in relative weight or fat mass loss at 6 or 12 months, grade 2 and 3 adverse events, early discontinuation, satiety or other quality of life measures. More serum biomarkers exhibited significant within-group improvement at 6 and 12 months for evaluable women randomized to ω-3 FA than to placebo. At 6 months, significant change ($P<0.05$) was observed for adiponectin, leptin, adiponectin:leptin ratio, insulin, lipocalin-2, resistin, PAI-1, HGF, CRP, SHBG, and bioavailable testosterone in women randomized to ω-3 FA but only for leptin, adiponectin: leptin ratio and SHBG in those randomized to placebo. At 6 months, the 21 women who lost >10% weight (median 15%) showed significant within-group improvement in adiponectin, leptin, adiponectin:leptin ratio, insulin, lipocalin-2, resistin, PAI-1, HGF, CRP, SHBG, bioavailable estradiol and bioavailable testosterone. For women with <10% weight loss (median 6%) there was significant within-group improvement only for leptin, the adiponectin: leptin ratio, and SHBG. Little change was observed for inflammatory cytokines IL-6, TNF-alpha, MCP-1 or FABP4, or FGF-21 with ω-3 FA or >10% weight loss. Given the dramatic effect of weight loss on biomarkers, we examined within-group and between-group change from baseline to 6 and 12 months for the four subgroups (10-11 women in each) defined by ω-3 FA or placebo and < or > 10% weight loss at 6 months. The subgroup of >10% loss + ω-3 FA had the greatest within-group change in the proportion of significantly modulated biomarkers at 6 months. >10% loss + ω-3 FA was the only subgroup with a significant within-group increase in adiponectin at both 6 and 12 months and achievement of a beneficial ratio of adiponectin (ug/ml) to leptin (ng/ml) of > 1.0 in 100% of participants. There was a significant between-group effect for adiponectin for >10% loss + ω-3 FA vs each of the other groups. Biomarkers were assessed in tissue acquired by random periareolar fine needle aspiration (RPFNA). There were no significant differences in change in cytomorphology or Ki-67 between women randomized to ω-3 FA or placebo but there were significant within-group increases in benign breast adiponectin (pg/ug protein) at 12 months ($p=0.014$) for women randomized to ω-3 FA. **Conclusions:** EPA + DHA ethyl esters (3150 mg/day), added to a behavioral weight loss program in overweight women at increased risk for breast cancer, is well-tolerated and may further improve risk biomarker modulation. The increase in adiponectin when ω-3 FA is added to weight loss is of particular interest given that adiponectin opposes the oncogenic effect of leptin and is associated with improved insulin sensitivity and reduced mTOR signaling. Further study is warranted with enough subjects to detect between-group differences.

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# Dcis as a risk lesion for invasive breast cancer and death from other cancers

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Introduction: Ductal carcinoma in situ (DCIS) is considered a non-obligatory precursor of invasive breast cancer. Using a prospective cohort study of screen detected non-invasive neoplasia from a national breast screening program, this analysis examined subsequent DCIS or invasive cancers and death due to other cancers or other causes. Methods: Prospective data on 9191 screen detected non-invasive breast neoplasia with a median 9.2 years follow up was matched to a subsequent diagnosis of invasive breast cancer or death from another primary, non-breast cancer at any site or other cause of death, cross validating data from the National Cancer Registry, Hospital Episode Statistics and mortality data.
Results: Following a diagnosis of screen detected DCIS, in 9191 women, for those undergoing breast conservation surgery (BCS), 413 women developed ipsilateral invasive breast cancer, at a proportion of 5/1000 per annum consistent over a decade and more. By contrast DCIS re-occurances in the same, conserved, breast (in 222 women) occurred at a similar rate for the first 5 years then the rate halved beyond 5 years. Contralateral breast cancer (DCIS or invasive) occurred in 431 women over the same time period. Mortality occurred in 1062/9191 (11.6%) women, attributed to breast cancer in 130/1062 (12.2%) and due to cancer at other sites in 397/1062 (37.4%). Death from other, non-breast, cancers was predominantly from primaries of the lung (98 women), ovary (43), pancreas (37) and colon (23) and rarely associated with a confounding diagnosis of invasive breast cancer (present in only 8% of those patients). Non-cancer mortality was identified in 496/1062 (46.7%) women, most commonly attributed to cardiovascular disease (in 188 women) or disease of the respiratory system (in 93). Conclusion: Screen detected DCIS is a marker for subsequent invasive breast cancer, but mortality from other, non-breast, cancers following treatment for DCIS is three times more likely than death due to breast cancer, suggesting DCIS is a more general marker for subsequent cancers than hitherto recognized. Awareness of, and potentially screening for, other cancers should be considered in women treated for DCIS.

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# Assessment of early ctDNA dynamics to predict efficacy of targeted therapies in metastatic breast cancer: Results from plasmaMATCH trial

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**Background:** Early changes in circulating tumour DNA (ctDNA) levels may identify which patients respond to therapy earlier than imaging, with ctDNA levels falling rapidly in patients who respond to therapy. The plasmaMATCH trial assessed the utility of ctDNA testing with an error-corrected 73-gene targeted panel (Guardant360, Guardant Health) to allocate patients to four mutation matched therapy cohorts. *ESR1*-extended fulvestrant (A), *HER2*-neratinib +/- fulvestrant (B), *AKT1*-capivasertib + fulvestrant (C), *AKT* basket-capivasertib (D). Here, we report paired baseline and early on treatment ctDNA analysis from plasmaMATCH, to establish the optimal criteria for predicting progression free survival (PFS). **Methods:** In plasmaMATCH treatment cohorts, plasma samples were collected for ctDNA analysis pre-treatment at cycle 1-day 1 (C1D1) and cycle 2-day 1 (C2D1) timepoints, and sequenced with the Guardant 360 assay. Patients were included if they had a minimum of 14 days of treatment in the first cycle. Multiple different methods were investigated to integrate variant allele fractions (VAF) of mutations identified at each timepoint to estimate the level of ctDNA, including maximum VAF, mean VAF and weighted mean VAF, and weighted mean VAF of clonal mutations at C1D1. Variants with a VAF <0.3%, set as the limit of detection, in C1D1 were excluded. Genes frequently mutated in CHIP were excluded (*GNAS*, *JAK2*, *IDH1*, *IDH2* and *ATM)* from the weighted mean VAF of clonal mutations method. The circulating DNA ratio (CDR) was calculated as the ratio of C2D1 level relative to C1D1 level. The optimal cut-point for predicting PFS was assessed by fitting a range of cutpoints for each VAF integration method, identifying the cut-point with the highest Harrell's C-index. **Results:** A total of 142 patients were enrolled into plasmaMATCH cohorts A-D, 79 patients had samples sent for paired C1D1-C2D1 plasma ctDNA sequencing, 1 failed sequencing and 1 insufficient treatment, and 77 (54%) patients had assessable C1D1-C2D1 plasma ctDNA sequencing results (45 cohort A, 12 cohort B, 12 cohort C, 8 cohort D). A weighted mean of clonal mutations in C1D1 ctDNA sequencing was the optimal method for integrating VAF, with peak C-Index 0.67. At the optimal C-index cutoff of 0.132, median PFS with high ctDNA CDR was 2.4 months (95% CI 2.0-3.7) and with suppressed ctDNA CDR was 9.9 months (95% CI 7.0-13.7) (HR 4.3, 95% CI 2.4-7.6, p<0.0001). Early changes in ctDNA level were also predictive in cohorts A extended dose fulvestrant alone (HR 5.8, 95% CI 2.2-16, p=0.0001) and cohorts B-D of targeted therapy (HR 3.8, 95% CI 1.7-8.6, p=0.00063). In analysis that was not pre-planned, patients with undetectable ctDNA at C2D1 had a particularly good outcome (p<0.0001, table 1). **Conclusions:** We identify an optimal methodology for assessing early dynamic changes in ctDNA that predicts treatment efficacy in patients with metastatic breast cancer. This methodology will require validation in independent data-sets, and if validated would allow trials of adapting therapy on the basis of early ctDNA dynamics.

Table 1

| **ctDNA dynamics category** | **Median PFS months (95%CI)** | **6-month PFS** | **ORR** |
|---|---|---|---|
| **Undetectable (N=11)** CDR=0 | 18.2 (10.2-NA) | 91% | 9/11 (82%) |
| **Suppressed (N=14)** CDR <0.132 and >0 | 5.4 (4.6-NA) | 48% | 6/14 (43%) |
| **High (N=52)** CDR >=0.132 | 2.4 (2.0-3.7) | 8% | 4/52 (8%) |

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Permanent marker free surface-guided breast radiotherapy: Implementing a new technique

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**Background:**It is standard practice in our centre for patients to be given permanent skin marks during breast radiotherapy planning, for use as reliable landmarks in daily reproduction of their positioning for treatment. However, these permanent marks (tattoos) may have a significant psychological impact on patients (1). In recent years, there have been technological advances in surface-guided radiotherapy techniques (SGRT) which may provide improved set-up accuracy compared to permanent markers.**Aims:**1. To evaluate if surface-guided set-up is as good, if not better, than set-up with permanent markers alone.2. To safely implement a permanent marker (PM) free, surface-guided set-up technique.**Methods:**A pilot study was conducted with tangents-only breast patients treated in free breathing (FB). All treatments were delivered on Varian TrueBeam linear accelerators, with patients immobilised on a couch indexed breast board. The study group (n=20) were set up using PMs with adjustments guided by the AlignRT® SGRT system to optimise patient positioning. Imaging (MV tangent images) was performed as per standard protocol on fractions 1-3, 8 and 12. Additional imaging was performed if indicated. The translational and rotational displacements calculated by the TrueBeam verification system for this group were compared to average displacements calculated for patients set up using PMs alone (the control group, n=20). Encouraged by the results of the pilot study, the centre moved to safely roll-out the PM-free technique to include additional applications. The step-wise approach taken will be described.**Results:**The mean displacements calculated from the verification imaging are shown in Table 1 below:

| **Displacement** | **20 patients PM only (106 #s)** | **20 patients PM + SGRT (114 #s)** | **Statistical significance** |
|---|---|---|---|
| Lateral (mm) | 2.27 | 1.56 | yes |
| Vertical (mm) | 2.69 | 2 | yes |
| Longitudinal (mm) | 1.44 | 1.53 | no |
| Total translation/Vector (mm) | 4.1 | 3.21 | yes |
| Pitch ($^0$) | 0.61 | 0.42 | yes |
| Yaw ($^0$) | 0.67 | 0.53 | yes |

SGRT set-up demonstrated statistically-significant improvements compared to PM set-up alone with respect to lateral, vertical and total translational displacements. Longitudinal displacements
favoured PM set-up alone but this did not reach statistical significance. Rotational displacements favoured SGRT set-up and the results reached statistical significance.Given the improved set-up accuracy with SGRT, and the wish to reduce the psychological morbidity of radiotherapy for our breast cancer patients, the centre moved to safely implement a PM free SGRT technique along agreed timelines as shown in Table 2:

| Development stage | Detail | Date |
|---|---|---|
| Set up tangents only FB patients using PM + SGRT | Patients set up using PM + SGRT – pilot study showed comparable or better than PM alone (see Table 1) | Oct 2018 |
| Breast Working Party decision to use PM + SGRT for all set-ups | To build on SGRT experience from pilot study to include all breast set-ups (nodal regions & Deep Inspiration Breath Hold, DIBH) | Sept 2019 |
| Site visit to Birmingham, UK | Radiographer-led visit to observe PM free breast technique | Oct 2019 |
| Report to Breast Working Party about PM + SGRT guided set up | Report showed improved consistency using SGRT and reduction in displacements for all set-ups | Nov 2019 |
| Site Visit to Inverness, UK | Multi-disciplinary team (ClinOnc/Rad/Dosimetry) attended Inverness to review PM free CT, Planning &Treatment | March 2020 |
| Need to Improve Social distancing from COVID19 | Increased use of SGRT to maintain social distancing in RT treatment room at outbreak of pandemic | March 2020 |
| Removal of breast borders | To simplify set up process | May 2020 |
| Use treatment capture images to resolve set up issues + use SGRT for electron sets with PMs | Staff will have time to practice SGRT set up without using PMs before the PM-free technique is implemented | 26th May 2020 |
| New CT protocol for DIBH | This allows fusion of scans so that patients can be set up in FB and monitored during treatment in DIBH | 8th June 2020 |
| 1st PM free Tangent only FB patient treated | Mean translational displacements (mm) 0.05 Vert/0 Long/0.04 LatMean rotational displacements (o) Pitch 1.3/Roll 0/Yaw 0.9 | 17th June 2020 |

**Conclusions:**Our pilot study demonstrated that surface-guided radiotherapy (SGRT) set-up is as good, if not better, than set-up with permanent markers (PM) alone in tangent-only free-breathing patients. Subsequent further analysis showed improved consistency of set-up guided by PM plus SGRT for all breast set-ups (to include nodal regions and DIBH). We have described our step-wise approach to setting up PM free radiotherapy delivery for breast cancer patients, which has additional advantages in maintaining social distancing in the COVID19 era.**Refs1. Psychosocial impacts of radiation tattooing for breast cancer: a critical review. B Clow et al.**

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# Digital MammaPrint and BluePrint using machine learning and whole slide imaging

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**Background:** The rise of whole slide imaging systems has enabled pathologists to remotely view cases in high resolution to diagnose cancer, and efficiently archive images . The advent of machine learning techniques and their application in digital pathology have facilitated the identification of histological patterns for effective diagnosis of disease. Deep learning-based solutions have been developed to detect and recognize cancer types, and automatically grade and stage tumors through evaluation of pathological features and patterns. However, no image-based solutions have been able to replicate a multivariate test, such as a risk -of recurrence assay for early stage breast cancer. Traditionally, subtle differences in gene expression have been measured by microarray or NGS, however these changes may also be recognized phenotypically from hematoxylin and eosin stained (H&E) slides by digital biomarkers developed using novel machine learning techniques. The large repository of images with MammaPrint and BluePrint results may enable us to develop digital MammaPrint and digital BluePrint biomarkers that predict the risk of distant recurrences and the molecular subtypes of a tumor sample using only H&E stained digitized tumor slides. **Methods:** Using over70,000 H&E images of early stage breast cancer patients in combination with machine learning techniques, digital versions of MammaPrint and BluePrint were developed. In total 20,000 images were used for feasibility and algorithm optimization, another 50,000 images were used for further finetuning. MammaPrint indices and BluePrint scores and categorical results were used to train the system. After the algorithms were optimized, they were locked and validated in an independent set of 5000 H&E stained images. The MammaPrint and BluePrint predictions were compared to the original MammaPrint and BluePrint results obtained from the microarray assay. The finalized and locked algorithms were further validated for precision and reproducibility in a large data set of xx Images and processed multiple times. Multicenter clinical validation was performed in H&E stained images of multiple series with long term follow up (tbd), totaling ##k images. In this ##K cohort of patients, #% were HR+/HER2-, #% were clinically HER2+ and x% were triple negative. **Results:** Using an independent dataset of 5000 samples, we compared the MammaPrint and BluePrint predictions obtained from the H&E slides to the traditional versions of MammaPrint and BluePrint based on a microarray. The binary performance of the digital MammaPrint had a concordance of xx% (with an AUC of xx%),%NPA and %PPA when compared to the traditional MammaPrint high-low classification. For digital BluePrint, the system had a concordance of xx% and a classification accuracy of xx%. The analytical performance showed a precision and reproducibility of xx% In a multicenter clinical validation the DRFI was xx% in dMP low risk and yy% in dMP high risk groups. The xxx dataset the performance was *similar* to the microarray and better than compared to clinical parameters. *Analyses will be available by the Placeholder Abstract deadline.* **Conclusions:** The combination of machine learning and digital pathology has enabled development of rapid and highly accurate *in silico* versions of MammaPrint and BluePrint. Implementation of digital H&E based risk of recurrence and molecular subtyping could enable preservation of valuable diagnostic tissue, faster turnaround time for test results, and a more cost effective approach to treatment planning tools, especially in countries that do not allow send out of human tissue and this adoption of risk scoring is low. *Final conclusions tbd*

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# Patient-reported outcomes (PROs) from the Ph 3 IMpassion031 trial of neoadjuvant (NA) atezolizumab + chemo in early triple-negative breast cancer (eTNBC)

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**Background:** In IMpassion031 (NCT03197935), patients (pts) (N = 333) with invasive stage II or III eTNBC who received NA treatment (tx) with atezolizumab (A) + *nab*-paclitaxel (nP) followed by doxorubicin + cyclophosphamide (AC; A-chemo) had significantly improved pathologic complete response (pCR, primary endpoint) regardless of PD-L1 status vs placebo (P) with nP and AC (P-chemo). Balancing efficacy and toxicity is key in this potentially curable eTNBC setting. PROs were collected to comprehensively assess tx burden from the pts' perspective, inform clinical benefit and decision-making and address the lack of pt-reported data in this setting. **Methods:** Pts received double-blind A 840 mg or P every 2 weeks (q2w) with nP 125 mg/m$^2$ once weekly for 12 wk followed by A 840 mg or P q2w with AC q2w for 4 doses. After surgery and pathological evaluation, pts in the A-chemo arm received open-label A 1200 mg every 3 weeks for 11 doses. The P-chemo arm was observed. To capture pts' experience of tx-related symptoms, associated bother, and impact on day-to-day functioning and health-related quality of life (HRQoL), pts completed the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and single-item GP5 from the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire at baseline (BL) and day (D)1 of each cycle (C) of NA and adjuvant (adj) tx, at end of tx and in follow-up every 3 mo (year 1), every 6 mo (years 2-3), then annually. Mean and mean change from BL scores (≥ 10-point change considered clinically meaningful) by C and between tx arms in the QLQ-C30 function (role and physical) and global health status/QoL scales were predefined secondary endpoints. Mean and mean change from BL scores in tx-related symptoms, as well as an assessment of tx side-effect bother, were exploratory endpoints. **Results:** QLQ-C30 completion rates (ITT) in both arms were 100% at BL and > 90% in the NA phase and > 89% in the adj phase through C16. GP5 completion rates in both arms were > 98% at BL (C2D1) and > 88% in the NA and adj phases. BL mean [95% CI] values were high for physical function (A-chemo, 91 [89-93]; P-chemo, 90 [88-92]), role function (A-chemo, 89 [86-93]; P-chemo, 89 [86-92]), and HRQoL (A-chemo, 79 [76-82]; P-chemo, 76 [73-79]). Physical and role function, and HRQoL mean values were similar between arms across on-tx assessments to C16 and through follow up. Mean change from BL values for physical and role function, and HRQoL were similar between arms and of the same magnitude. In both arms mean physical function had a clinically meaningful decline during the NA period from C3 to C5, rebounding in the adj period, and stabilizing starting C7. In both arms mean role function had a clinically meaningful decline in the NA period from C2 (A-chemo) or C3 (P-chemo) to C5, rebounding in the adj period, and stabilizing at C9 in the P-chemo arm only. In both arms mean HRQoL had a clinically meaningful decline in the NA period from C3 to C5, rebounding in the adj period and stabilizing from C6. Tx symptoms of fatigue, diarrhea, nausea, and vomiting in the NA period worsened through C5 in both arms with trends in mean and mean change from BL values similar to the functional and HRQoL data. In the adj period, mean symptom scores in both arms through C16 were similar to BL except for fatigue. 65% (A-chemo) and 66% (P-chemo) of pts reported their level of bother with tx side effects to be "somewhat" or "quite a bit" by C5. During the adj period, no added side-effect bother was experienced by pts receiving A compared with the P-chemo arm under observation, with a similar % of pts in each arm reporting being bothered "somewhat," "quite a bit," or "very much" by C16. **Conclusions:** Adding A to nP-AC improved pCR without added tx burden to pts. These results address the paucity of PRO data informing clinical benefit and decision-making in this potentially curable setting.

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# The immune microenvironment of liver metastasis as a guide for immunotherapeutic potential in breast cancer

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**Background**: The benefits of immune check point inhibition (ICI) are primarily seen in immunogenic cancer types. Unfortunately, most breast cancers are non-immunogenic, and therefore new approaches that target tumor immunogenicity are key to increasing the efficacy of ICI. Even within a single breast cancer subtype, patients with liver metastases are less responsive to ICI as compared to other metastatic sites. Therefore, the objective of this analysis is to investigate differences in prognostic and predictive ICI related biomarkers such as PD-L1 expression, tumor mutation burden (TMB), and immune-cell populations between primary tumors, liver metastases (LM) and non-liver metastatic (NLM) sites from breast cancer patients. Our goal is to provide an in-depth analysis of current and potential markers of immunogenicity within LM and NLM.

**Methods**: Unpaired samples taken from primary and recurrent breast (BT), liver metastases (LM) and non-liver metastases (NLM) (all identified as breast cancer) were compared using Fisher-exact or $Chi^2$ and corrected for multiple comparison. Tumors were classified as hormone receptor positive (HR+), HER2+ or triple negative breast cancer (TNBC). Breast cancer samples were tested using NextGen DNA sequencing (NextSeq, 592 gene panel) and whole transcriptome RNA sequencing (NovaSeq). PDL1 was scored on immune cells using VENTANA PD-L1 (SP142) assay. TMB was measured by counting somatic non- synonymous missense mutations on the 592 gene panel and ≥ 10 mutations/Megabase (mut/Mb) was considered high. MCP counter was used to evaluate relative cell abundance (in arbitrary units) in TME using transcriptome data.

**Results**: Biopsies from 3166 tumors were queried, 1268 of which were from BT, 495 from LM, and 1403 from NLM, all are unpaired. All histologic subtypes are represented. $HR^+$ breast cancer was the most prevalent among LM. Both metastatic groups (LM and NLM) were significantly more likely to have a high TMB as compared to BT (24.8 & 24.8 vs. 16.6%, $p<0.0001$). PD-L1 expression in immune cells however, was significantly decreased in LM as compared to BT (12 vs. 34%, $p<0.0001$) and NLM (12 vs. 28%, $p<0.0001$), a trend largely driven by $HER2^+$ and TNBC subtypes. Comparison of immune cells within tumor biopsies of LM vs. BT demonstrated significantly fewer cytotoxic CD8+ T cells (1.38 vs. 0.69, $p<0.001$), B cells (234 vs. 98, $p<0.001$), and myeloid dendritic cells (DCs) (1.5 vs. 1.02, $p<0.001$). These observations were most predominant in TNBC and $HR^+$ breast cancers. $HR^+$ LM also had fewer natural killer cells (0.85 vs. 0.03, $p<0.005$). Cytotoxic T cells and DCs were not significantly altered in $HER2^+$ LM. All immune cell types, except for the monocytic lineage, were significantly ($p<0.001$) higher within NLM as compared to LM. Investigation of molecular alterations revealed significant differences in LM vs. NLM vs. BT, e.g, LM from all subtypes were enriched for copy number alterations in genes such as CCND1 and FGF19/14, FGFR1. Significant ($p<0.001$) enrichment of mutations in ESR1 (2.8 vs. 27.1%), HER2 (1.9 vs.6.1%), and GATA3 (7.8 vs> 12.9%), were observed in LM vs. BT.

**Conclusions**: In this patient cohort, immune cells within the TME of LM were less abundant and suggest the liver is a less immunogenic niche. However, LM had increased TMB as compared to breast tumors, suggesting that immunosuppressive cells (i.e. Tregs and MDSCs) or cytokines, may be preventing cytotoxic immune cell infiltration into the TME. Moreover, immune cell populations within LM had decreased PD-L1 expression when compared to breast tumors, suggesting another mechanism that could explain the lack of response to ICI in such patients. Further characterization of the genetic and molecular alterations of breast cancer LM and NLM will help identify additional biomarkers of response and determine their role in defining tumor immune response to ICI.

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Safety and efficacy of an alternative schedule of palbociclib (PAL) in hormone receptor positive (HR+), HER2 negative (HER2-) metastatic breast cancer (MBC) and the utility of serum thymidine kinase 1 (sTK1) activity in predicting PAL response

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**Background:** The approved 3 weeks (wks) on/1 wk off schedule of PAL results in grade (G)3+ neutropenia (ANC) up to 66%. We hypothesized that an alternative schedule (Alt Dose Pal), 5 on/2 off every 7 days, reduces the rate of G3+ ANC, allowing continued weekly dosing. In addition, based on our previous study supporting sTK1, an E2F-dependent enzyme critical for DNA synthesis, as a pharmacodynamic indicator of CDK4/6 inhibition, we hypothesized that Alt Dose Pal inhibits sTK1 and sTK1 dynamics predicts PAL response. **Methods:** A single arm phase II trial was conducted in HR+ HER2- MBC, ≤1 prior endocrine therapy (ET) for MBC (NCT03007979). Pts received PAL 125 mg daily, 5 on/2 off weekly, plus letrozole (LET) or fulvestrant (FUL) per physician choice, on a 28-day cycle (C). Goserelin was added if premenopausal. Complete blood count and chemistry panel were done at baseline (BL), C1&2D15, and D1 of C2+. The primary objective was to determine the rate of G3+ ANC in C1 D1-D29. Secondary objectives were to assess the rate of all cycle G3+ ANC, PAL dose reduction/discontinuation, adverse events (AE) per CTCAE v5, progression free survival (PFS), objective response rate (ORR: CR+PR (complete and partial responses)) and clinical benefit rate (CBR: no progression (PD) in 24 wks) by RECIST 1.1. The sample size of 47 provides 90% power, 1-sample binomial exact test, 5% alpha, to test the 1-sided null hypothesis of G3+ ANC rate >62% vs the alternative of <40%. Serial sTK1 was analyzed at BL, C1D15, C2D1, every 3 cycles with tumor imaging, and at PD, using the DiviTum™ assay. **Results:** From July 2017 to Feb 2020, 54 pts were enrolled. 3 pts went off in C1, unrelated to study, leaving 51 pts (38 LET, 13 FUL), median age of 62 (range 34-87) years, 8 (16%) premenopausal, 26 (51%) with visceral mets. 22 (43%) and 29 (57%) had adjuvant chemo or ET, respectively. 4 (8%) had 1 prior ET for MBC. 22 (43%) had primary or secondary ET resistance defined by ESMO. 17 (33%) had de novo MBC. The median follow up was 12 months (mo). Treatment is ongoing for 23 (45%) pts. Among 47 evaluable pts, 10 (21.3%, 95% CI: 11.2%-36.1%) had G3 ANC in C1 D1-29, with no G4 AE. 22 of 54 (40.7%; 95% CI: 27.9%-54.9%) had G3 (n=21) or G4 (n=1) ANC in all cycles. 37 pts in C1 and 32 pts in all cycles, were without G3+ ANC, exceeding the predefined boundary for better tolerability. PAL was dose reduced in 11 (20.3%) pts and discontinued in 3 (4.8%) due to AE. Table 1 lists treatment related AEs of >10% or G3+. The ORR was 50% (2 CR, 13 PR, 95% CI: 33.15%-66.85%) in 30 pts with measurable disease (n=29) or non-measurable but CR (n=1). The CBR was 81.63% (95% CI: 67.5%-90.76%) in 40 (2CR, 13 PR, 25 SD ≥24 wks) of 49 evaluable pts. The median PFS (mPFS) was 24.3 mo (95% CI 15~not reached (NR)) overall. The mPFS was 33.5 mo (95% CI 17.3~NR) and 12 mo (95% CI: 10.4~NR), in ET sensitive and resistant population, respectively. sTK1 was significantly reduced, 80% down to undetectable, as early as C1D15 (p=7.77E-07). BL sTK1 levels correlated with PD vs non-PD (p=0.003) as best response and negatively correlated with PFS (p=0.002). sTK1 rose significantly at PD (p=0.0003). A median lead time of 80.6 (IQ range 6.8-189.2) days was observed for rising TK before RECIST PD. **Conclusion:** The Alt Dose Pal trial met its primary endpoint with reduced G3+ ANC. The efficacy data is comparable to prior reports. sTK1 shows promise for PAL response prediction and monitoring. **Table 1 AE**

| **AE** | G1 | G2 | G3 | G4 | Total |
|---|---|---|---|---|---|
| **C1 D1-29 (n=47)** | | | | | |
| Leukopenia | 13 (27.6%) | 22 (46.8%) | 7 (14.9%) | 0 | 42 (89%) |
| Neutropenia | 6 (12.8%) | 18 (38.3%) | 10 (21.3%) | 0 | 34 (72%) |
| Anemia | 18 (38.3%) | 5 (10.6%) | 0 | 0 | 23 (49%) |
| Lymphopenia | 6 (12.8%) | 8 (17%) | 2 (4.3%) | 0 | 16 (34%) |
| Fatigue | 13 (27.7%) | 0 | 0 | 0 | 13 (28%) |
| Hot flashes | 7 (14.9%) | 0 | 0 | 0 | 7 (15%) |
| Nausea | 6 (12.8%) | 1 (2.1%) | 0 | 0 | 7 (15%) |
| Thrombocytopenia | 5 (10.6%) | 1 (2.1%) | 0 | 0 | 6 (13%) |
| Alopecia | 5 (10.6%) | 0 | 0 | 0 | 5 (11%) |
| Dizziness | 1 (2.1%) | 0 | 1 (2.1%) | 0 | 2 (4%) |
| **All cycles (n=54)** | | | | | |
| Leukopenia | 10 (18.5%) | 22 (40.7%) | 21 (38.9%) | 0 | 53 (98%) |
| Neutropenia | 4 (7.4%) | 21 (38.9%) | 21 (38.9%) | 1 (1.9%) | 47 (87%) |
| Anemia | 29 (53.7%) | 12 (22.2%) | 3 (5.6%) | 0 | 44 (82%) |
| Lymphopenia | 8 (14.8%) | 16 (29.6%) | 10 (18.5%) | 0 | 34 (63%) |
| Fatigue | 19 (35.2%) | 4 (7.4%) | 0 | 0 | 23 (43%) |
| Nausea | 19 (35.2%) | 3 (5.6%) | 0 | 0 | 22 (41%) |
| Alopecia | 18 (33.3%) | 0 | 0 | 0 | 18 (33%) |
| Thrombocytopenia | 15 (27.8%) | 0 | 1 (1.9%) * | 0 | 16 (30%) |
| ALT elevated | 3 (5.6%) | 0 | 2 (3.7%) | 0 | 5 (9%) |
| AST elevated | 4 (7.4%) | 0 | 1 (1.9%) | 0 | 5 (9%) |
| *pt died from subdural hematoma (G5) | | | | | |

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# Kinome profiling of ER+ breast cancer PDXs identifies PKMYT1 as a marker of hormone independent growth and poor outcome

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**Background:** Endocrine therapy resistance is common and is a leading cause of breast cancer-related death. Thus, the search for therapeutic targets based on mechanistic insights into endocrine therapy resistance continues. Kinases are important drug targets and regulators in cells, many of which are involved in tumorigenesis and the development of treatment resistance. Mass spectrometry-based kinome analysis has been impeded by the low abundance of individual kinases. Here we utilized kinase inhibitor-conjugated beads to enrich and thereby sensitively profile the kinome of estrogen receptor-positive (ER+) breast cancer patient-derived xenograft (PDX) tumors under estradiol-deprivation treatment.
**Experimental design and methods**: We harvested tumor samples from 20 breast PDX lines with various degrees of estradiol (E2) dependence in ovariectomized SCID-beige mice with and without E2 supplementation (n=3 per PDX line per arm). The kinases in the tumor lysates were enriched using kinase inhibitor pulldown (KIP) beads and the tightly bound kinases were quantified by mass spectrometry. To identify candidates, we selected for kinases that were highly E2-regulated in the E2-dependent PDX lines but constitutively expressed in E2-independent PDX lines. Survival analysis of candidate kinases in patients with ER+ breast cancer was performed using the METABRIC dataset.
**Results:** Each PDX line had a unique yet reproducible kinome. To seek kinases with consistent relationships with estrogen dependence, we sought kinases that were statistically differentially expressed in tumors between E2 supplied and deprived conditions. Noticeably, membrane-associated tyrosine-and threonine-specific cdc2-inhibitory kinase (PKMYT1), a WEE family kinase known to have estrogen response elements (EREs) in its regulatory region, was significantly decreased after E2 deprivation in E2-dependent PDXs (log2 fold change = -7.86, $p<0.001$) but was constitutive in E2-independent PDXs. High *PKMYT1* mRNA expression was associated with poor prognosis in the ER+ samples in METABRIC (hazard ratio=2.2, $p<0.001$). In contrast, the more studied member of the WEE family, WEE1, lacks an estrogen response element (ERE) and is not E2-regulated from the kinome profiling result. *WEE1* mRNA expression level is not associated with the outcome of patients with ER+ breast cancer, suggesting that PKMYT1 has evolved a specific role in the cell cycle of ER+ tumors.
**Conclusion:** Here, we analyzed the kinomes of 20 ER+ breast cancer PDX tumors with or without E2 by mass spectrometry. We discovered that PKMYT1 is a marker of hormone independent growth and poor outcome. Ongoing experiments that study the effects of PKMYT1 inhibition in both ER-dependent and independent circumstances will be presented.

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Influence of a breast cancer polygenic risk score on adherence to preventive endocrine therapy in high risk women at 1 and 2 year follow-up: The genetic risk estimate (GENRE) trial

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**Background**: Preventive endocrine therapy (ET) has been proven extensively to decrease breast cancer (BC) risk by 50-65%. Despite this significant reduction, a small proportion of high risk women take ET, due to attitudes toward medications, inaccurate risk perception and drug side-effects. The addition of a polygenic risk score (PRS), comprised of 77 BC genetic susceptibility loci (Single Nucleotide Polymorphisms (SNP)), to the standard risk calculator estimates, can be used to improve BC risk estimation. We previously reported on the influence of the PRS-adjusted BC risk estimates on the intent to use ET (Abstract, SABCS, 2019). Here we report on the influence of PRS-adjusted BC risk estimates on ET adherence at 1 and 2 year follow –up. We also report on ET side effects over this same time period.
**Methods**: Women older than age 35 were eligible if they were deemed at high risk for BC by either a 5 year Gail Model risk of ≥3% or 10 year Tyrer-Cuzick risk (IBIS) of ≥5%. We excluded women with a personal history of BC or hereditary BC syndromes. At baseline, participants were counseled on their BC risk using standard risk calculators: Gail and IBIS risk scores (5 yr, 10 yr, & lifetime) and ET options were discussed, including benefits and risks. Blood samples were obtained and genotyped for 77 SNPs, and an updated BC -PRS risk report was shared with study participants that reflected the IBIS and Gail risk predictions for 5 yr, 10 yr, & lifetime BC risk with and without the PRS. A baseline self-reported questionnaire assessed understanding of BC risk and decision to take ET. Follow-up questionnaires at 1 and 2 years assessed self-reported ET adherence and ET side effects (vasomotor symptoms, vaginal symptoms, sexual dysfunction, weight gain, GI symptoms, headaches, breast sensitivity, mood changes, and joint pain). Adherence to ET at 1 and 2 year follow-up was stratified by three categories of lifetime PRS-BC risk: 0-20%; 20-40%; 40-100%.
**Results**: 151 women at Mayo Clinic Rochester and CancerCare Manitoba were enrolled in the study from 2016 to 2017. Of the 149 participants with evaluable data at 1 and 2 year follow-up, 57 (38%) started on ET therapy, all within 1 year of the baseline visit; 43 (29%) were taking ET at 1 year and 33 (22%) were taking ET at 2 year follow-up, representing a discontinuation rate of 26% at 1 year and 42% at 2 year follow-up.
Adherence to ET use at 1 year and 2 year follow-ups correlated significantly with the category of PRS-BC risk estimation: at 1 year follow up, 17% of those in the lowest PRS-IBIS risk category , 23% in the middle risk category and 50% of those in the highest risk category were taking ET (p=0.001). At 2 year follow up, 12% of those in the lowest PRS-IBIS risk category, 18% in the middle risk category and 38% of those in the highest risk category were taking ET (p=0.008).
At 1 year follow up, participants taking ET reported significantly more bothersome symptoms of vaginal itching (p=0.010), weight gain (p=0.015) and joint pain (p=0.044), compared with those not on ET. There was a trend towards increased irritability and mood swings on those taking ET (p=0.059). At year 2 there was no significant difference in side effects between those taking and not taking ET.
**Conclusion:** Adherence to ET in a population of women at high risk for BC decreased overtime and strongly correlated with the level of risk, with 38% of those at highest risk of breast cancer taking ET at 2 year follow up. Side effects of vaginal itching, weight gain and body aches were more common on those taking ET versus not taking ET at the 1 year follow-up, but did not differ at 2 year follow-up, possibly due to the fact that those with the most bothersome symptoms have discontinued ET by the 2 year follow up.

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# Radiologic review to refine selection of candidates for de-escalation of neoadjuvant therapy

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**Purpose**In the on-going I-SPY2 TRIAL, participants receive 12 cycles of weekly paclitaxel with or without addition of experimental agents for 12 weeks (first regimen), followed by 4 cycles of anthracycline-cyclophosphamide (AC, second regimen) prior to surgery. A de-escalation strategy currently being introduced in I-SPY2 will give patients the option to skip AC if it is highly likely that they have achieved early pathologic complete response (pCR) at the inter-regimen time point (12 weeks). To guide selection of candidates for this option, a prediction model combining subtype-specific MRI predictive probabilities with mid-treatment percutaneous core biopsy pathology has been developed. The combined model predicts a patient as early pCR if the MRI model based on a quantitative measure of functional tumor volume predicts a high likelihood of pCR, and pathology determines that there are no invasive cancer cells detected in the mid-treatment core biopsy. This study was performed to develop radiologic criteria for post-selection review to further reduce the possibility for incorrect de-escalation recommendation.

**Methods**A review of 87 I-SPY2 patients with serial MRI and inter-regimen core biopsy identified 25 patients where both the subtype specific MRI model and at least 2 of 11 I-SPY2 pathologists predicted early pCR. One radiologist retrospectively reviewed MRIs at pre-treatment and inter-regimen for the 25 patients in a blinded fashion, and labeled the presence of residual disease on MRI at inter-regimen as follows: rank 0, no residual disease; rank 1, possible residual disease; rank 2, obvious residual disease.To evaluate the accuracy of selecting candidates for de-escalation of neoadjuvant therapy (i.e. predicting patients with early pCR at inter-regimen), surgical pathology of pCR after the completion of NAC (both first and second regimens) was defined as a surrogate “truth” in this study. Positive predictive value (PPV) and sensitivity for the combined MRI-pathology model were computed for all pathologist pairs. After adding qualitative radiologic review, patients labeled as rank 2 were excluded from the candidates with predicted early pCR by the combined MRI-pathology model. PPV and sensitivity before and after radiologic review were compared.

**Results**The 25 patients included 21 patients that ultimately achieved pCR, and 4 patients that did not. Radiologic review of the inter-regimen MRI for these patients classified their MRIs as 20% (5/25) rank 0 (no residual disease), 36% (9/25) rank 1 (possible residual disease), and 44% (11/25) rank 2 (obvious residual disease). Most (3/4) non-pCR patients were classified rank 2, however one (1/4) was assessed rank 0. Eight of the 21 pCR patients (38%) were classified as having obvious residual disease on inter-regimen MRI. Without radiologic review, the combined MRI-pathology model predicted pCR with a mean PPV of 92% (range 83-100%) and a mean sensitivity of 91% (range 76-100%). When patients labeled as rank 2 by radiologic review were excluded from candidates with predicted early pCR, PPV increased to 99% (range 93-100%) at the expense of lower sensitivity of 59% (range 52-62%).

**Conclusion**

In this study, elimination of rank 2 lesions resulted in substantial improvement in PPV (92% to 99%) with a consequent reduction in sensitivity from 91% to 59%. Notably, none of the rank 1 lesions, where diagnostic interpretation was less certain, were found to be non-pCR at surgery. High PPV is essential to ensure high accuracy and safety in directing early pCR patients to therapy de-escalation. These findings will be further validated in continuing studies and radiologic re-review will be included in the de-escalation strategy for omission of AC in the I-SPY2 TRIAL.

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Molecular alterations in the androgen receptor and associated clinical outcomes in hormone receptor-positive/HER2- metastatic breast cancer

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Background: Although the androgen receptor (AR) is frequently co-expressed with ER and PR in hormone receptor-positive (HR+)/HER2- breast cancer, the biological significance of detectable AR alterations ($AR^{alt}$) in metastatic disease (MBC) remains poorly understood. The primary objective of this study was to evaluate the association of $AR^{alt}$ status with clinical outcomes among women with HR+/HER2- MBC.
Methods: Retrospective review was performed on patients with HR+/HER2- MBC treated at an academic institution, for whom genotyping information was available. $AR^{alt}$ status was determined using Guardant360, a 73-gene next-generation sequencing assay that detects both AR mutations and amplifications in circulating tumor DNA. Women with positive or unknown HER2 status and triple-negative breast cancer were excluded from analysis, as were cases of male breast cancer. Time-to-progression on the therapy initiated immediately following Guardant testing was compared based on $AR^{alt}$ status, excluding patients treated with androgen-directed therapies given potential for confounding. Cumulative incidence plots were generated and analyzed by Gray's test, and propensity score-adjusted competing risk models were generated with the probability of treatment as a function of age at metastatic diagnosis, presence of visceral metastasis, presence of *de novo* metastases, as well as number of prior therapies. Additional analysis was performed to assess progression stratified by treatment type (endocrine or non-endocrine based).
Results: Among women with HR+/HER2- MBC (n=222), 16 patients (7%) had detectable $AR^{alt}$ (12 point mutations, 4 amplifications). No baseline differences were observed between women with $AR^{alt}$ and those without AR alterations ($AR^{wt}$), with respect to age at primary or metastatic diagnosis, menopause status, time to onset of metastasis or *de novo* metastatic disease, presence of visceral metastases, or number of endocrine/chemotherapies received prior to Guardant testing. $AR^{alt}$ tumors had a higher frequency of detected mutations (14% vs. 5%, p<0.01), and frequently co-altered genes included *TP53*, *PIK3CA*, *ERBB2*, *SMAD4*, and *NF1*. Genes with a tendency towards co-alteration in $AR^{alt}$ but not in $AR^{wt}$ included *MAP2K2*, *ARAF1*, *MAPK1*, *SMAD4*, *MYC*, *ROS1*, *TERT*, and *NRAS*. In a multivariable model adjusting for age, *de novo* metastases, visceral metastases, and number of prior therapies, $AR^{alt}$ status was associated with a higher rate of progression (HR 2.5; 95% CI 1.2-5.0, p=0.01), particularly among patients treated with endocrine-based therapies following Guardant testing (HR 4.2, 95% CI 2.4-7.2, p<0.0005) but was not statistically different in women treated with non-endocrine based therapies (HR 1.6; 95% CI 0.5-4.9, p=0.4).
Conclusions: $AR^{alt}$ tumors demonstrate a higher rate of progression on endocrine-based therapy as compared to $AR^{wt}$ tumors, highlighting a potential role of AR in mediating resistance to endocrine therapy in HR+/HER2- disease. Further translational investigations are warranted to determine whether $AR^{alt}$/HR+/HER2- disease represents a unique biological subtype that predominantly relies on AR signaling and may thus benefit from blockade with AR antagonists.

Table 1. Multivariable competing risks model for endocrine progression.

| Covariate | PFS | | |
|---|---|---|---|
| | Multivariable | | |
| | HR | 95% CI | P-value |
| **Positive $AR^{alt}$ status** | **4.17** | **2.43-7.17** | **<0.01** |
| Age at metastatic dx | 1.00 | 0.97-1.02 | 0.89 |
| De novo metastases | | | |
| Yes | 1.77 | 0.96-3.26 | 0.07 |
| No | [ref] | | |
| Visceral metastases | | | |
| Yes | 1.25 | 0.72-2.16 | 0.43 |
| No | [ref] | | |
| No. of prior therapies | 1.06 | 0.93-1.21 | 0.98 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PD3-02

# Final analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of first-line pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer

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**Background** The role of bidirectional cross talk between the HER2 and estrogen receptors in resistance to anti-HER2 and endocrine therapy has been studied extensively (Kaufman et al. J Clin Oncol 2009; Arpino et al. J Natl Cancer Inst 2007). The CLEOPATRA study showed that first-line pertuzumab (P) + trastuzumab (H) + docetaxel (T) improved progression-free survival (PFS) and overall survival (OS) significantly compared with placebo + H + T in patients (pts) with HER2-positive metastatic BC (MBC) (Baselga et al. N Engl J Med 2012; Swain et al. Lancet Oncol 2013; N Engl J Med 2015; N Engl J Med 2020). PERTAIN (NCT01491737) was the first randomized phase II trial to assess the addition of P to H + an aromatase inhibitor (AI) ± induction chemotherapy for the first-line treatment of pts with HER2-positive and hormone receptor-positive MBC or locally advanced BC (LABC). PERTAIN met its primary PFS endpoint at 31 months' median follow-up, with a potentially enhanced effect in some groups, such as pts who did not receive induction chemotherapy (Rimawi et al. J Clin Oncol 2018). We present the final analysis at more than 6 years' median follow-up, including updated PFS, mature OS (secondary endpoint), and updated safety. **Methods** Pts were randomized 1:1 to P + H + AI (Arm A) or H + AI (Arm B). P was given as an 840 mg intravenous (IV) loading dose followed by 420 mg every 3 weeks (q3w); H IV, at 8 mg/kg followed by 6 mg/kg q3w; anastrozole, at 1 mg daily; or letrozole, at 2.5 mg daily. Induction IV chemotherapy with T q3w or weekly paclitaxel could be given for 18-24 weeks at the investigator's discretion before the start of endocrine therapy. Treatment was given until disease progression or unacceptable toxicity. Pts were stratified by induction chemotherapy (yes/no) and time since adjuvant hormone therapy (<12 months, ≥12 months, no adjuvant hormone therapy). Time-to-event endpoints were analyzed using Kaplan-Meier methods. **Results** Pts were randomized across 71 sites and 8 countries between Feb 2012 and Oct 2014. Intent-to-treat populations were 129 pts per arm; safety populations, 127 and 124 in Arms A and B, respectively; induction chemotherapy was received by 75 and 71 pts, respectively. Baseline demographics and disease characteristics were generally balanced between arms. Efficacy results are shown in the table. One hundred twenty-two pts per arm reported adverse events (AEs) at any grade (96.1% in Arm A; 98.4% in Arm B); 72 (56.7%) and 51 pts (41.1%) had grade ≥3 AEs, the most common grade ≥3 AEs (≥5.0%; Arm A vs. Arm B) being hypertension (11.8% vs. 10.5%), diarrhea (9.4% vs. 2.4%), and neutropenia (3.1% vs. 7.3%).

| | **Arm A** | **Arm B** |
|---|---|---|
| Median PFS, mo HR (95% CI) | | |
| ITT | 21 | 16 |
| | 0.7 (0.5-0.9) p=0.006 | |
| With induction | 17 | 17 |
| | 0.7 (0.5-1.0) p=0.08 | |
| No induction | 27 | 12 |
| | 0.7 (0.4-1.0) p=0.07 | |
| Median OS, mo HR (95% CI) | | |
| ITT | 60 | 57 |
| | 1.1 (0.7-1.5) p=0.8 | |
| With induction | 59 | 66 |
| | 1.2 (0.7-1.9) p=0.5 | |
| No induction | 65 | 54 |
| | 0.9 (0.5-1.6) p=0.7 | |
| CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months. | | |

**Conclusions** With a median follow-up of more than 6 years at final analysis, the PFS benefit of adding P to H + an AI was maintained. OS was similar between arms. A potentially enhanced treatment effect was observed by addition of P to H + an AI in pts who did not receive induction chemotherapy after randomization. There were no new safety concerns at final analysis. Overall, PERTAIN provides additional evidence on the role of P + H in the first-line treatment of HER2-positive MBC/LABC and suggests that some pts benefit from P + H + AI without induction chemotherapy.

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# A randomised phase IB/IIA study of CApecitabine plus Radium-223 in breast cancer patients with BONe metastases (CARBON) - Safety and preliminary efficacy findings

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Background: Bone metastases (BMs) occur in approximately 70% of patients (pts) with metastatic breast cancer (MBC). Despite significant advances in the management of BMs with bone-targeted agents and the associated reduction in skeletal-related events, there remains an unmet need for further treatment options to improve median overall survival beyond 2-3 years. Radium-223 [R] dichloride is an alpha-emitting radiopharmaceutical that is avidly taken up, like calcium, into the bone where it emits high-energy, short-range alpha-particles resulting in a targeted anti-tumour effect on BMs. Combining R with current systemic therapy could potentially enhance efficacy in MBC with BMs. Methods: CARBON is a UK, open-label, multi-centre phase IB/IIA study evaluating the combination of capecitabine [C] (1000mg/m$^2$ bd days 4-17, 12x21 day cycles) with R 55kBq/kg day 1 given on a 6-weekly schedule in pts with BMs from MBC (+/- other sites of disease) with ≥2 bone lesions on radionuclide bone scan and/or ≥1 lesion confirmed on plain radiographs, CT or MRI. Other eligibility criteria included ECOG PS 0-2, ≤ 2 lines of chemotherapy for MBC and current use of a bisphosphonate / denosumab for ≥6 weeks. To establish the feasibility and safety of C+R the phase IB opened in August 2016 registering 6 pts; the primary endpoint was dose-limiting toxicities (DLTs), defined as ≥grade 3 gastrointestinal toxicity lasting >48 hours or ≥grade 4 haematological toxicity lasting >7 days. Subsequently, between April 2017 and March 2019 28 pts were randomised (2:1) to C+R vs C in phase IIa to further characterise the safety profile, with frequency of CTC grade 3-4 toxicities and diarrhoea as primary endpoints. Preliminary evaluation of efficacy through assessment of bone turnover marker changes from baseline to end of cycle 5 and time to progression in bone and overall was made. Results: Baseline clinico-pathologic characteristics and prior treatments were well balanced between the arms; 13 C+R and 9 C pts had visceral metastases. There were 0 DLTs in the 6 phase IB pts, therefore the same C+R dose and schedule was studied in phase IIA. 2 pts randomised to C+R received C alone and are included in the C arm. The safety population consists of 34 pts (23 C+R, 11 C). Median number of cycles received was 8.5 (range 3-12) in C+R arm and 12 (range 1-12) in C arm. 38/307 (12%) treatment cycles were delayed (25 [13%] C+R arm, 13 [12%] C arm). 11 (48%) C+R and 6 (55%) C pts had a permanent C dose reduction. 94/95 (99%) prescribed R cycles were administered. 9 (39%) C+R and 9 (82%) C pts completed all 12 cycles. Other reasons for discontinuation were: progressive disease in 12 (52%) C+R and 0 in C pts; toxicity in 1 (4%) C+R and 1 (9%) C pt; clinician decision in 1 (9%) C pt; progressive disease and toxicity in 1 (4%) C+R pt. Only 25/575 (4%) reported AEs were grade 3-4 (n=21 in 11 [48%] C+R pts, n=4 in 4 [36%] C pts) with 0 episodes of grade 3-4 diarrhoea. Table 1 shows maximum grades of diarrhoea and haematological AEs experienced by arm. 18 SAEs occurred (n=11 in 8 C+R pts, n=7 in 2 C pts). 8 (44%) SAEs were grade 3 (C+R: 6, C: 2); none were related to diarrhoea. There were 0 SUSARs. Conclusion: In the first completed trial evaluating R with chemotherapy in MBC pts, the combination of C+R is safe and well-tolerated. Preliminary efficacy analyses including bone markers are ongoing and will be presented at the meeting. The creation of the data was supported in part by Bayer Plc and Yorkshire Cancer Research.

Table 1: Maximum CTCAE grade (G) experienced - diarrhoea and haematological AEs.

| | | | **C+R (n=23)** | | | | | **C (n=11)** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Not experienced** | **G1** | **G2** | **G3** | **G4** | **Not experienced** | **G1** | **G2** | **G3** | **G4** |
| **Diarrhoea** | 7 (30%) | 14 (61%) | 2 (9%) | 0 | 0 | 6 (55%) | 4 (36%) | 1 (9%) | 0 | 0 |
| **Neutropenia** | 18 (78%) | 0 | 2 (9%) | 3 (13%) | 0 | 10 (91%) | 0 | 1 (9%) | 0 | 0 |
| **Thrombocytopenia** | 21 (91%) | 1 (4%) | 1 (4%) | 0 | 0 | 9 (82%) | 1 (9%) | 1 (9%) | 0 | 0 |
| **Anaemia** | 21 (91%) | 2 (9%) | 0 | 0 | 0 | 8 (73%) | 1 (9%) | 2 (18%) | 0 | 0 |

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Estrogen-induced cell cycle arrest as an unexpected outcome of aromatase inhibitor-resistance: Insights from single-cell trajectory analysis of a patient-derived xenograft model

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**Background:** Estrogen such as estradiol (E2) is known to promote $ER^+$ breast cancer. However, several clinical trials reported the unexpected therapeutic benefit of E2 for aromatase inhibitor (AI)-resistant cases of $ER^+$ postmenopausal breast cancer. The objective of this study is to uncover the mechanisms of E2-induced tumor regression, leading to an unconventional treatment of AI resistance. **Methods:** An E2-suppressive patient-derived xenograft model (named GS3) was established from an AI resistant $ER^+/PR^-/HER2^-$ brain metastatic breast cancer. Placebo or E2 pellets were implanted in mice carrying GS3 for evaluating the effects of E2. Immunohistochemistry (IHC) and RNA sequencing of GS3 were conducted to decipher molecular changes after E2 treatments. Since the cancer tissue has a heterogeneous structure, the single-cell analysis was further performed to examine gene expression profiles in individual cells. In addition, *in vitro* cell proliferation analysis was carried out using organoids from GS3. **Results:** E2 inhibited the growth of GS3 both *in vivo* and *in vitro*. ERα and ERβ genes in GS3 are wild-type and not amplified. ERα is involved because E2-mediated inhibition of GS3-organoids can be reversed by the co-treatment of ERα antagonist, not by ERβ antagonist. IHC showed that ER, Ki-67 and CEA expressions decreased and PR expression appeared after E2 treatment. Gene set enrichment analysis (GSEA) using RNAseq results showed that the E2 response gene sets were significantly up-regulated after E2 treatment. However, the cell cycle gene sets and the TNFA/NFKB gene set were down-regulated. GS3 gained an E2 independence after three cycles of intermittent E2 treatment (E2 pellet on/off every 4 weeks; Int-E2). Interestingly, the cell cycle and TNFA/NFKB gene sets were up-regulated after Int-E2 treatment. Single-cell RNAseq analysis revealed that cells from one-week E2-treated and Placebo-treated GS3 were placed in different clusters based on principle component analysis of Highly Variable Genes. Although E2 response genes were up-regulated, the percent of $ESR1^+$ cells decreased after E2 treatment (41.3% vs. 31.5%). The number of cells arrested at the G1 phase increased (+12.5%) after E2 treatment. GSEA using genes expressed in only $ESR1^+$ cells showed that the TNFA/NFKB gene set was significantly down-regulated after E2 treatment. Meanwhile, GSEA using genes expressed in only $ESR1^-$ cells showed that cell cycle gene sets were significantly down-regulated. Single-cell trajectory analysis disclosed three major branches; 1) common E2 and placebo, 2) E2, and 3) placebo. In the E2 only branch, the cell cycle arrested at the G1 phase, the E2 response gene sets were up-regulated, and the NFKB gene set was down-regulated in $ESR1^+$ cells. Significantly, E2 response gene sets were also up-regulated and cell cycle genes were down-regulated even in $ESR1^-$ cells. In the placebo branch, E2 response gene sets were not up-regulated and cell cycle genes were not down regulated. A group of $MKI67^+$ cells (at G2M phase), including some $ESR1^+$ cells, were present in both E2-treated and placebo-treated tumors. **Conclusions:** E2-induced suppression is an unexpected outcome of AI resistance. In these cases, elimination of estrogen by AI results in maintaining tumor growth. Analysis of GS3 PDX has revealed that estrogen can induce cell cycle arrest and the expression of estrogen-regulated genes. Our results also suggest the cross-talk between $ESR1^+$ and $ESR1^-$ cells as well as potential roles of the TNFA/NFKB pathway. Our findings point out the need of markers for such patients who can benefit from E2 treatment after AI resistance, and measurements of ER and PR expression are not sufficient. An intermittent treatment strategy does not sustain the effect of estrogen-mediated suppression.

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# Chronic interpersonal stress predicts depressive outcomes in the first year of invasive breast cancer: Moderation by the serotonin-transporter polymorphism

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**Background:** Depression in cancer patients predicts lower survival, and early identification of individuals at highest risk for depression is needed. In the general population, depression is higher in contexts of both childhood adversity and chronic interpersonal stress, but their collective influence on depressive outcomes in the first year after breast cancer diagnosis is unknown. Genetic polymorphisms related to socioemotional functioning (e.g., the serotonin transporter) may moderate the associations among childhood adversity, chronic interpersonal stress, and depressive outcomes, specifying which women are most at risk.
**Methods:** 460 women with invasive breast cancer were assessed for depressive symptoms and major depressive episodes (MDEs) seven times across one year. Associations between depressive symptoms and childhood adversity, chronic interpersonal stress, and the 5-HTTLPR polymorphism were examined. We used multilevel modeling for predicting longitudinal depressive symptoms, logistic regression for predicting any MDEs over the year, and multinomial logistic regression for predicting odds of belonging to Low/Recovery/High depressive symptom trajectory classes (Stanton et al., 2015). Models controlled for known sociodemographic and clinical confounding variables such as age, ethnicity, SES, cancer stage, treatments received, medical comorbidities, history of depression, and neuroticism.
**Results:** Higher chronic interpersonal stress predicted greater depressive symptoms at study entry (b=4.56, 95% CI [2.60,6.52]), greater odds for belonging to a High vs. Low depressive trajectory class (OR=3.16, [1.53, 6.51]), and greater odds of having an MDE (OR=2.28, [1.10, 4.73]). 5-HTTLPR moderated the influence of chronic interpersonal stress on depressive symptoms over time (b=0.24, [0.06,0.41]), with no decline in symptoms for SS genotype women under high chronic interpersonal stress vs. significant improvement in symptoms despite high chronic interpersonal stress for LL/LS genotype women. There were no significant effects of childhood adversity on depressive outcomes considered.
**Conclusion:** Women with greater chronic interpersonal stress are at risk for high, unremitting depressive symptom trajectories and MDEs in the first year after invasive breast cancer diagnosis. Unchanged depressive symptoms across the year were most pronounced for women bearing the SS allele of the 5-HTTLPR polymorphism. Women with high chronic interpersonal stress and the SS genotype may benefit from early intervention to prevent depression after breast cancer diagnosis.

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**Publication Number:** GS2-02

# 12 year results of anastrozole versus tamoxifen for the prevention of breast cancer in postmenopausal women with locally excised ductal carcinoma in-situ

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**Background:** Two large clinical trials have reported divergent results in their initial analysis of the benefit of aromatase inhibitors compared to tamoxifen in women with ductal carcinoma in situ (DCIS) (IBIS-II and NSABP B-35). Here, we report blinded 12-year median follow-up efficacy and adverse event data for the IBIS-II trial, which compared anastrozole to tamoxifen in women with hormone receptor positive DCIS and focus on the post-treatment follow-up period.**Methods**: A multi-centre randomised trial of 1mg/day anastrozole (N=1471) vs. 20mg/day tamoxifen (N=1509) for five years was conducted in postmenopausal women with locally excised DCIS diagnosed between 2003 and 2009. The primary objective of this analysis was to determine the efficacy of anastrozole compared to tamoxifen in preventing recurrences overall, and in particular in the post 5-year treatment period. Secondary endpoints included type of recurrence, breast cancer mortality, other cancers, cardiovascular disease, fractures, adverse events and non-breast cancer deaths.**Results:** After a median follow-up of 11.6 years (IQR 9.9 to 13.4), a total of 221 breast cancer recurrences (7.4%) have been recorded. No difference in overall recurrence was observed (102 (6.9%) anastrozole vs. 119 (7.9%) tamoxifen; HR=0.87 (0.67-1.14), P=0.32) overall (Table), in the 5-year treatment period (HR=0.82 (0.53-1.27), P=0.37), or the post treatment follow-up period (HR=0.91 (0.65-1.27), P=0.57). Oestrogen receptor (ER) positive breast cancers were reduced by 28% with anastrozole when compared to tamoxifen (58 vs. 82; HR=0.72 (0.52-1.01), P=0.056) but this did not reach significance. In contrast, no effect was observed for ER-negative breast cancer with anastrozole (Table). No significant difference for the reduction in invasive breast cancer recurrence was observed with anastrozole when compared to tamoxifen (Table). Invasive ER-positive breast cancer was non-significantly reduced by 24% with anastrozole when compared to tamoxifen (44 vs. 59; HR=0.76 (0.51-1.12), P=0.17). A total of 127 deaths have been reported, with no significant difference in all-cause mortality between the two treatment arms (61 vs. 66; HR=0.94 (0.67-1.33), P=0.74). Only 7 deaths from breast cancer (3 vs. 4) were reported, with so few deaths from breast cancer at 12 years, any impact on survival is unlikely to emerge with longer follow-up. 214 cancers other than breast were reported, with a non-significant decrease observed with anastrozole (97 vs. 117, OR=0.84 (0.63-1.12), P=0.22). Endometrial (2 vs. 13, OR=0.16 (0.02-0.0.69)), ovarian cancer (1 vs. 9, OR=0.11 (0.003-0.82)), and non-melanoma skin cancer (11 vs. 21) were less common with anastrozole. Significantly higher rates of fractures (181 vs. 145, OR=1.32 (1.04-1.68)) and transient ischaemic attacks (15 vs. 5, OR=3.10 (1.07-10.92)) were observed with anastrozole compared to tamoxifen. A comprehensive adverse event profile will be reported.
**Conclusions:** No clear efficacy differences were seen between the two treatments, although the data suggests possible greater efficacy for anastrozole over tamoxifen for prevention of ER-positive breast cancers. There were some clear differences in adverse events and anastrozole may be more appropriate for some women with contraindications for tamoxifen. **Table**: Number of events and Hazard Ratios (95% CI) according to treatment allocation.

| | **Anastrozole(N=1471)** | **Tamoxifen(N=1509)** | **HR (95% CI)** |
|---|---|---|---|
| Any recurrence | 102 | 119 | 0.87 (0.67-1.14) |
| ER-positive | 58 | 82 | 0.72 (0.52-1.01) |
| ER-negative | 24 | 15 | 1.63 (0.86-3.11) |
| Invasive | 66 | 76 | 0.89 (0.64-1.23) |
| ER-positive | 44 | 59 | 0.76 (0.51-1.12) |
| ER-negative | 17 | 12 | 1.44 (0.69-3.02) |
| DCIS | 35 | 42 | 0.85 (0.54-1.33) |
| ER-positive | 14 | 23 | 0.62 (0.32-1.21) |
| ER-negative | 7 | 3 | 2.38 (0.61-9.20) |
| Numbers do not add up due to missing information | | | |

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**Publication Number:** PD15-02

Cx3cl1-cx3cr1 axis in liver metastasis of triple negative breast cancer

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Triple negative breast cancer (TNBC) is a breast cancer subtype with increased risk of distant metastasis, especially to visceral organs. However, the detailed molecular mechanism underlying the visceral metastasis of TNBC is unknown. We used three patient-derived xenograft models derived from TNBC tumors with different metastatic capacities. PDX1 and PDX2 model developed distant metastasis in only lung and liver, respectively. In contrast, PDX3 tumor metastasized to both lung and liver. RNA sequencing of the primary tumor and distant metastatic sites of these three PDX models was performed. The gene expression profiles of the primary tumors of the three models showed minimally overlapping genes. However, the microenvironment gene expression profiles, measured by using the sequencing reads aligned to mouse genome, showed distinct difference between the models. Among the differentially expressed genes, we identified Cx3cr1 as a significantly upregulated gene in the liver microenvironment of the PDX models that metastasized to liver. Next, we used 4T1 syngeneic mouse mammary carcinoma model to validate the Cx3cr1 in the mouse liver tissues. Interestingly, the Cx3cr1 up-regulation occurred during the pre-metastatic period, and Cx3cl1, the ligand of the Cx3cr1, was also up-regulated in the liver tissue prior to the development of metastasis suggesting the Cx3cr1 regulates the formation of pre-metastatic niche. Cx3cl1, the ligand of the Cx3cr1, was also up-regulated in the liver tissue prior to the development of metastasis. These data suggest that Cx3cl1 and Cx3cr1-mediated tumor-microenvironment interaction is critical in developing liver metastasis in TNBC. Cx3cl1 increased the invasion and migration of Raw264.7 monocyte/macrophage cells and this effect was abrogated by the Cx3cr1 silencing in Raw264.7 cells or treating Cx3cl1 neutralizing antibody. Pathway analysis of the RNA sequencing data showed that genes involved in extracellular matrix remodeling was significantly dysregulated in the liver tissues including Lysyl Oxidase (Lox). Cx3cl1 treatment in Raw264.7 cells resulted in increased expression of Lox and MMP9 mRNA in three-dimensional culture system. The Raw264.7 cells caused increased invasion of 4T1 cells in vitro. In conclusion, our data suggest that Cx3cl1-Cx3cr1 axis plays critical role during the liver metastasis of TNBC.

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**Publication Number:** PD2-03

Treatment exposure and discontinuation in the PALLAS trial: PALbociclib CoLlaborative Adjuvant Study of palbociclib with adjuvant endocrine therapy for HR+/HER2- early breast cancer

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**Background**:Adherence to and tolerability of oral agents for the treatment of hormone receptor positive (HR+) breast cancer in the adjuvant setting may be challenging and can limit drug exposure. Palbociclib (P) is an oral CDK4/6 inhibitor; P in combination with endocrine therapy (ET) has demonstrated efficacy in HR+/HER-2 negative (HER2-) metastatic breast cancer (MBC). The global PALLAS study (NCT02513394) was designed to determine if the addition of P to adjuvant ET improves outcomes over ET alone in early breast cancer. The goal of this analysis is to describe P exposure and discontinuation in PALLAS, and explore any impact on study endpoints. **Methods**:Pts with stage II-III HR+/HER2- disease were randomized to receive 2 years of P (starting dose 125 mg daily, 3 weeks on, 1 week off) in combination with adjuvant ET (Arm A) or ET alone (Arm B). The primary objective was to compare invasive disease-free survival (iDFS) between arms; secondary endpoints included safety, quality of life, adherence, and translational science. Dose adjustments were defined per protocol in the setting of emergent toxicity. Continuous monitoring of toxicity, dose modifications, and early discontinuations was performed throughout the trial. Statistical analysis included tabulation of dose levels/reductions and reasons for treatment discontinuation, as well as landmark analysis comparing iDFS between those receiving ≥ 12 months (mo) vs < 12 mo of P. Ongoing analyses include exploration of relative dose intensity and modeling of P dose intensity/duration and impact on iDFS. **Results**:A total of 5760 pts were randomized; 83% had received prior chemotherapy; 68% initiated aromatase inhibitor and 33% tamoxifen, with or without ovarian suppression. Grade 3/4 neutropenia was more common in Arm A vs B (62% vs 0.4%); febrile neutropenia was uncommon (1%). Other all-grade adverse events (AEs) more common in Arm A included other hematologic toxicity, fatigue, upper respiratory infection, nausea, diarrhea, and alopecia. A total of 55% of pts required P dose reduction to 100mg, and 34% to 75 mg, at some point during treatment. At a median follow-up of 23.7 mo at the second interim analysis, no significant difference in iDFS was observed between the arms (3-year iDFS of 87.9% vs 88.4%, HR 0.93, 95% CI 0.76, 1.15); consequently, pts in Arm A stopped P, and all pts moved to long-term follow-up. At time of data cut-off, 32% had completed the planned 2 years of P, 26% were still receiving P, and 42% had discontinued P prematurely. P discontinuation was 18% at 6 mo, 30% at 12 mo, 38% at 18 mo, and 45% projected at 24 mo. A total of 27% of Arm A pts (770 of 2840) discontinued therapy due to AEs, primarily neutropenia (460, 16%) and fatigue (71, 3%). Other reasons for P discontinuation included non-compliance (128, 5%), recurrent disease or second malignancy (104, 4%), or withdrawal of consent (100, 3%). Last observed dose level was 125mg, 100mg, and 75mg for 45%, 22%, and 33% pts, respectively. Among those discontinuing due to AEs, dose level at time of discontinuation was 75mg for 62%, suggesting some discontinuations occurred without maximum dose reduction. Pts who received ≥ 12 mo of P had a 2-year iDFS of 96.6%; those receiving <12 mo had 2-year iDFS of 95.7% (HR 0.86, 95% CI 0.55-1.34). **Conclusions**:An early analysis of PALLAS has demonstrated that 2 years of adjuvant P in combination with adjuvant ET did not improve iDFS when compared with ET alone in pts with HR+/HER2- breast cancer. While 2 years of adjuvant P was feasible for the majority of pts, 42% discontinued P early, primarily for AEs. Further data examining drug discontinuations and relationships between drug exposure and clinical outcomes will be presented, expanding upon initial point estimates suggestive of a possible explanation of trial results.

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# Personalized ctDNA as a predictive biomarker in high-risk early stage breast cancer (EBC) treated with neoadjuvant chemotherapy (NAC) with or without pembrolizumab (P)

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**Background**: In the I-SPY 2 TRIAL, the addition of P to standard NAC resulted in more than doubling of the pathologic complete response (pCR) rates for both hormone receptor-positive (HR+)/HER2- and triple-negative (TN) early breast cancer (EBC) patients (pts) compared to NAC only (Nanda et al, JAMA Oncol, 2020). At 3 years, distant recurrence-free survival (DRFS) rates in pts with pCR following NAC+P was >95%. We hypothesized that ctDNA can serve as a predictive biomarker of response and survival in pts treated with NAC.
**Methods:** A personalized ctDNA test (Signatera) was performed on 511 serial plasma samples from 138 pts with high-risk HR+/HER2- (n=77) or TN (n=61) stage II/III EBC. Pts received P with paclitaxel (Tx) followed by AC (P arm, n=42) or standard NAC only (n=96), an exploratory subset of pts evaluated for P efficacy. Plasma was collected; pretreatment (T0), 3 weeks after treatment initiation (T1), between Tx+/-P and AC regimens (T2), and prior to surgery (T3). ctDNA was deemed positive with a minimum of 2 of the pt specific tumor mutation fragments detected in cfDNA. Association of ctDNA with response and survival was analyzed using logistic and Cox regressions with pCR and DRFS as endpoints. Median follow-up was 2.8 years.
**Results:** Detection of ctDNA decreased over time (P arm: T0-81%, T1-50%, T2-19%, T3-3%) and NAC only: T0-82%, T1-65%, T2-26%, T3-10%).
ctDNA data at T0 and T1 was available for 96% (132/138) of pts in P arm or NAC only (Table). Among ctDNA+ patients at baseline, clearance at T1 was significantly associated with pCR (OR=1.92, ctDNA+/-; OR=0.27, ctDNA+/+; LR p<0.001). This association remained significant after adjustment for HR status and treatment (LR p<0.001) and P arm or NAC only (P: LR p=0.03; NAC: LR p=0.01).
ctDNA data at T0, T1, and T2 was available for 86% (118/138) pts. (Table). Among all ctDNA+ pts at baseline, dynamics through T2 was associated with pCR (OR=1.44, ctDNA+/-/-; OR=0.33, ctDNA+/+/-, OR=0.12, ctDNA+/+/+; LR p=0.0011). This association remained significant when adjusted for HR status and treatment (LR p<0.001). Analysis within individual treatments showed significant association for NAC (LR p=0.040) and a non-significant trend in NAC+P (LR p=0.063), likely due to smaller sample size.
All pts who achieved pCR were ctDNA- at T3 (n=34). Among those who failed to achieve pCR (n=81), DRFS was significantly better in ctDNA- (n=72/81; 20 in P and 52 in NAC) versus ctDNA+ pts (n=9/81; 1 in P and 8 in NAC) (adjusted HR 0.13; 95% CI 0.05-0.37).
**Conclusions:** These exploratory results align with our previous findings that early clearance of ctDNA during NAC treatment was significantly associated with increased likelihood of achieving pCR. Additionally, we show that ctDNA clearance can be an early surrogate marker for therapy response assessment. Residual ctDNA after neoadjuvant treatment was a significant predictor of metastatic recurrence and death. Personalized monitoring of ctDNA during the course of NAC is feasible and provides information that can be combined with imaging and pathology, and may help to optimize decision making for de-escalation or escalation of therapy. Larger studies are ongoing.

ctDNA dynamics and pCR

| | ctDNA status at T0 and T1 (n=132) | | | ctDNA status at T0, T1, and T2 (n=118) | | | |
|---|---|---|---|---|---|---|---|
| | ctDNA-/- | ctDNA+/- | ctDNA+/+ | ctDNA-/-/- | ctDNA+/-/- | ctDNA+/+/- | ctDNA+/+/+ |
| Total, n (%) | 24 (18) | 28 (21) | 80 (61) | 22 (19) | 24 (20) | 43 (36) | 27 (23) |
| pCR, n (%) | 9 (38) | 15 (54) | 11 (14) | 9 (41) | 12 (50) | 8 (19) | 2 (7) |
| No pCR, n (%) | 15 (63) | 13 (46) | 69 (86) | 13 (59) | 12 (50) | 35 (81) | 25 (93) |

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# Neratinib + capecitabine sustains health-related quality of life (HRQoL) while improving progression-free survival (PFS) in patients with HER2+ metastatic breast cancer and ≥2 prior HER2-directed regimens

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**Background:** The FDA approved neratinib (N), an irreversible pan-HER tyrosine kinase inhibitor, in combination with capecitabine (C) for patients with HER2+ advanced or metastatic breast cancer who have received ≥2 prior HER2-directed regimens in the metastatic setting based on the NALA clinical study, where N+C significantly improved PFS vs. lapatinib (L)+C. Characterizing HRQoL associated with this regimen can help inform treatment decision-making for these patients. The objective of this analysis was to characterize HRQoL among patients with HER2+ metastatic breast cancer from the NALA clinical study.

**Methods:** NALA was a multinational, randomized, open-label, phase III clinical study of N+C vs. L+C in patients with HER2+ metastatic breast cancer and ≥2 prior HER2-directed regimens. From May 2013 to July 2017, patients were randomized 1:1 to N (240 mg qd) + C (750 mg/m$^2$ bid 14d/21d) with loperamide prophylaxis during the first cycle, or to L (1250 mg qd) + C (1000 mg/m$^2$ bid 14d/21d). HRQoL, a prespecified secondary endpoint of the NALA study, was measured using the EORTC QLQ-C30 and the breast cancer-specific QLQ-BR23 at baseline and every 6 weeks (±3 days) until the end of treatment (data collection through treatment cycle 19, 12.5 months). The QLQ-C30 summary and global health status scores range from 0 (worst) to 100 (best) and the systemic therapy side-effects scores range from 0 (best) to 100 (worst). Patients were included in the analysis for a particular scale if they had a baseline assessment and at least 1 follow-up assessment. For these analyses, a change of ≥10 points was considered to be clinically meaningful. Descriptive statistics summarized observed scores and changes from baseline, Kaplan-Meier and log-rank tests were used for time-to-deterioration (TTD) of ≥10 points and mixed models estimated the change over time for 7 prespecified scales: QLQ-C30 summary score, global health status, physical functioning, fatigue, constipation and diarrhea, and the EORTC QLQ-BR23 systemic therapy side effects subscale. No adjustments for multiplicity were performed.

**Results:** 621 patients from 28 countries were randomized (307 N+C; 314 L+C). The mean completion rate of the QLQ-C30 over the course of the study was 91% for both treatment arms. Discontinuation due to any treatment-emergent adverse event (TEAE) was lower in the N+C vs. L+C arm (14% vs. 18%). At baseline, the mean (SD) QLQ-C30 summary scores were 79.8 (14.1) for N+C and 79.9 (15.7) for L+C. After 19 treatment cycles, the mean (SD) QLQ-C30 summary scores were similar to baseline scores: 81.8 (16.7) for N+C and 81.3 (15.3) for L+C. There were no differences in TTD of ≥10 points for the QLQ-C30 summary score between treatment arms; the HR for N+C vs. L+C was 0.94 (95% CI 0.63-1.40). All prespecified HRQoL subscales had similar statistically non-significant results for TTD with the exception of diarrhea (HR=1.71; 95% CI 1.32-2.23). The mixed models analyzing change in HRQoL from baseline did not demonstrate persistent declines nor meaningful differences between the treatment arms.

**Conclusion:** In these results from the NALA study, among patients with HER2+ metastatic breast cancer, at study end and throughout most of the study, there were no differences observed between the two treatment arms in HRQoL scores. HRQoL was sustained over the study period despite the early transient presence of diarrhea in some patients. Discontinuation due to any TEAE was lower in the N+C vs. the L+C arm. These results may help guide healthcare providers, patients and carers in selection of optimal treatment for HER2+ metastatic breast cancer.

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Comprehensive comparative analysis of invasive ductal and lobular breast cancer cases in great lakes breast cancer consortium

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**Background:** Invasive lobular breast cancer (ILC) is the second most common histologic subtype of breast cancer following invasive ductal cancer (IDC). ILC accounts for ~10-15% of all breast cancers (~26-40,000 cases annually in the US) and ranks as the 6$^{th}$ most common cancer in women in the US. While there is increasing recognition that ILC has distinct clinical, histologic, molecular, and biological characteristics compared to IDC, it remains understudied. There are very few large cohort analyses comparing clinic-pathological features of ILC, and therefore we performed a large multi-institutional retrospective cohort study. **Methods:** Investigators from UPMC Hillman Cancer Center, James Cancer Hospital/OSU, and Cleveland Clinic Taussig Cancer Institute/CWRU formed the Great Lakes Breast Cancer consortium, and worked with their respective cancer registries to collect comprehensive data on patients with IDC and ILC seen at their institutions between 1990 and 2017. Descriptive statistics were performed to compare clinic-pathological features, treatments, metastases sites, and co-morbidities. Survival rates were analyzed using the Kaplan-Meier (KM) method and compared using the Cox proportional hazards model. A total of N=38,175 records (N=15,792 for UPMC, N=13,040 for CCF, and N=9,343 for OSU) were included in the study. **Results** Among the N=38,175 records, we identified N=30,100 unique IDC (not otherwise specific, NOS) (89.3%) and N=3,618 unique ILC cases (10.7%). There were no significant differences between IDC and ILC with respect to laterality of the cancer (IDC: Left 51%, Right 49%; 0.2% Other vs ILC: Left 51%, Right 48%, Other 0.5%) and body mass index (IDC: 28.4 vs ILC: 28.2). In contrast, we observed significant difference with respect to age - patients with ILC were significantly older (61.2 vs 57.5 years; p<0.0001), and there were significant differences in race (7.6% vs 9.2% African American patients in ILC vs IDC, respectively; p=0.004). Among ILC cases, there were fewer grade III tumors (11.4% vs 40.3% in IDC; p<0.0001). ILCs were more frequently stage III (16.6% vs 8.0% in IDC) and stage IV (3.7% vs 2.4% in IDC) (p<0.0001), and ILC were significantly larger than IDC (13.7% T3 vs 2.8% in IDC, p<0.0001). There was also significantly more lymph node involvement in patients with ILC (N2: 5.3% vs 4.0%; N3: 4.6% vs 1.5%) (p<0.0001). The ILC cohort had significantly fewer HER2+ cases (5.5% vs 18.1% in IDC) (p<0.0001), and the proportion of patients with a high recurrence score as determined by 21 gene recurrence score was significantly lower in ILC compared to IDC (1.7% vs 10.4% in IDC; p<0.0001). As expected, there was a significant enrichment of ER+ tumors in ILC (96.1% compared to IDC (76.6%) (p<0.0001). Age, stage, grade, ER, Her2, and lymph node involvement remained significantly associated with histology in a logistic regression analysis. KM analysis showed significantly shortened disease-free (p=0.041) and overall survival (p<0.0001) for patients with ER+ ILC (N=2,565) compared to ER+ IDC N=17,278). The estimated 5yr and 10yr DFS rates for patients with IDC are 0.94 and 0.89, and for ILC 0.94 and 0.86, confirming prior data of late recurrences in patients with ILC. **Conclusions:** In the largest cohort of patients with ILC made possible by multi-center collaborations we show that lobular histology carries distinct prognostic implications and that outcomes are significantly worse. This highlights the need for more ILC research and clinical trials for patients with ILC.

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# A living biobank of normal mammary organoids derived from patients at low and increased risk of developing breast cancer

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**Background:** Mutations in *BRCA1* and *BRCA2* are associated with a high risk of developing breast cancer, but the earliest molecular changes that lead to the transformation of mammary cells in the setting of *BRCA1/2* heterozygosity remain unknown. We previously demonstrated that breast organoid cultures derived from histologically normal tissues can preserve all of the major mammary epithelial lineages for further study in vitro[1]. In addition, organoid culture medium is fully defined, enabling modulation of the medium to enhance the growth of distinct mammary subpopulations. Here, we undertook the development of a large biobank of breast organoids derived from patients with and without increased breast cancer risk, including patients with inherited mutations in *BRCA1* and *BRCA2*. **Methods:** Breast samples with normal histology (taken from reduction mammoplasties or prophylactic mastectomies), were digested for ~2 hours using collagenase, embedded in basement membrane extract, and grown in a fully-defined organoid medium[1]. CyTOF profiling was performed using our previously published mammary-specific heavy metal-tagged antibody panel[1]. Lentiviral transduction was performed to knock-down BRCA1 and/or overexpress mutant p53. Murine engraftment of normal breast organoids was performed by intra-ductal injection of ~1,000 organoids into NCG mice using a modification of protocols for breast cancer cell lines[2], with removal of mammary glands after 3 months for detailed immunohistochemistry analysis. **Results:** A living biobank of > 100 normal breast organoids derived from patients with and without inherited mutations in breast cancer predisposition genes, including *BRCA1* and *BRCA2*, was established. Cultures were generated with high efficiency (>95%) and could be serially passaged with the longest cultures > 16 months. CyTOF profiling of organoids revealed the maintenance of multiple epithelial cell subtypes, with at least one subtype of luminal cells enriched in tissues and organoids from *BRCA1/2* mutation carriers. Protein and RNA expression patterns of breast organoids were found to correlate with patient tissues analyzed using a combination of single-cell analyses (CyTOF, single-cell RNA sequencing, and immunohistochemistry). The impact of factors present in the organoid medium on distinct mammary epithelial cell subtypes was assessed by CyTOF, enabling identification of conditions that promote expansion of cell populations that are enriched in tissues from *BRCA1/2* mutation carriers. Furthermore, normal breast cell types could be engrafted into the murine mammary gland, and could be modified by lentiviral transduction for gene transfer, enabling future studies of the tumorigenic potential of distinct normal and premalignant epithelial cell subtypes. **Conclusion:** We have shown that organoid cultures can be used to propagate normal breast tissues with high efficiency, preserve normal as well as potential premalignant breast epithelial cell types, and model methods to inhibit precancerous cells in vitro. Thus, organoids are a useful complement to murine and other models of breast cancer development, and can ultimately be used to identify potential cancer interception strategies for patients at high risk of developing breast cancer.

**References:**1.Rosenbluth JM, Schackmann RCJ, Gray GK, et al: Organoid cultures from normal and cancer-prone human breast tissues preserve complex epithelial lineages. Nat Commun 11:1711, 20202.Zoeller JJ, Bronson RT, Selfors LM, et al: Niche-localized tumor cells are protected from HER2-targeted therapy via upregulation of an anti-apoptotic program in vivo. NPJ Breast Cancer 3:18, 2017

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Celtil score and long-term survival outcome in early stage HER2-positive (HER2+) breast cancer treated with anti-HER2-based chemotherapy: A correlative analysis of neoALTTO trial

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**Background:** Biomarkers to help escalate or de-escalate systemic therapies are urgently needed in early-stage HER2+ breast cancer patients. The combination of high stromal tumor infiltrating lymphocytes (TILs) and low tumor cellularity at 2 weeks of anti-HER2 therapy (CelTIL score) has been associated with high rates of pathologic complete response (pCR) after completion of neoadjuvant therapy. However, the value of CelTIL as a prognostic biomarker is unknown. Here, we present an independent validation of CelTIL in the NeoALTTO phase III trial. **Methods:** NeoALTTO randomized 455 patients (pts) with HER2+ early breast cancer to receive lapatinib (arm A), trastuzumab (Arm B) or lapatinib and trastuzumab (Arm C) for 6 weeks, followed by the assigned anti-HER2 treatment combined with paclitaxel weekly for 12 weeks. After surgery, patients received 3 cycles of fluorouracil, epirubicin and cyclophosphamide, and then continued the assigned anti-HER2 treatment for 34 weeks. CelTIL was centrally evaluated in tumor biopsies performed at week 2 in arms B and C using the pre-established formula (CelTIL score = -0.8 × tumor cellularity [%] + 1.3 ×TILs [%]). The primary objective was to evaluate the association of CelTIL (as a continuous variable and using the pre-established 33.59% cut-off as defined by Nuciforo P, et al; *Ann Oncol*. 2018) with event-free survival (EFS). Secondary objectives were to evaluate the association of CelTIL with overall survival (OS) and pCR. Univariable and multivariable analyses were performed adjusting for hormone-receptor status, pre-treatment tumor size and nodal status, planned type of surgery, pCR status, and treatment arm. **Results:** The CelTIL score was evaluable in 196 samples (108 samples in arm B and 88 samples in arm C), of which 45.4% (89/196) had low CelTIL score and 54.6% (107/196) had a high CelTIL score. As a continuous score, higher CelTIL levels were independently associated with improved EFS (hazard ratio [HR]=0.84 per 10% increment; 95% CI 0.73-0.97; P=0.006), but not OS (HR=0.85; 95% CI 0.71-1.03; P=0.094). Using the pre-established cutoff, the 5-year EFS estimate was 76% (95% CI 68-85%) and 60% (95% CI 50-72%) in pts with high- and low-CelTIL, respectively (adjusted HR=0.53; 95% CI 0.30-0.94; p=0.030). Moreover, the 5-year OS rate was 86% (95% CI 80-94%) and 73% (95 CI 64-84%) in high- and low-CelTIL respectively (adjusted HR=0.43; 95% CI 0.20-0.92; p=0.029). CelTIL as a continuous score was also independently associated with higher rates of pCR (odds ratio [OR]=1.18; 95% CI 1.02-1.36; p=0.024). The pCR rate in the high-CelTIL group was 37% (40/107) versus 18% (16/89) in the low-CelTIL group (adjusted OR=2.60; 95% CI 1.31-5.14; p=0.006). **Conclusions:** CelTIL score measured at week 2 of anti-HER2 therapy is significantly associated with long-term survival outcomes in early-stage HER2+ breast cancer, independently of pCR status and other prognostic variables. Further validation of this biomarker could help select early-on pts candidates for escalation or de-escalation of systemic therapy.

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Reported concerns and acceptance of information or referrals among survivors with breast cancer seen for survivorship care planning visits: Results from the University of Wisconsin Carbone Cancer Center (UWCCC) Survivorship Program

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**Background:** Survivors diagnosed with breast cancer experience a wide range of physical, psychosocial, and socioeconomic challenges following curative-intent treatment. Given survivors' unique and complex needs, a coordinated transition from active treatment to post-treatment care is crucial and is often facilitated by survivorship care planning visits. Care planning visits are expected to identify survivors' specific needs and provide information or referrals for additional services. However, little is known about survivors' need for and acceptance of information or referrals at the end of curative-intent treatment, particularly in the context of care planning visits. To understand how we can improve delivery of post-treatment care for curatively treated survivors, we examined the frequency and patterns of concerns reported by survivors seen for care planning visits, as well as their acceptance of information and/or referrals.
**Methods:** Survivors diagnosed with Stage 0-3 breast cancer seen at the UWCCC for survivorship care planning visits at roughly one month after radiation therapy were identified using the electronic health record (EHR). An EHR data pull of a cohort seen between January 2016 to January 2020 was performed to extract discrete data on survivor demographics, clinical characteristics, concerns, and acceptance of information or referrals at the time of the initial survivorship care planning visit.
**Results**: A total of 1,016 survivors with breast cancer were seen for at least one care planning visit following radiation therapy as standard of care. Most survivors were middle-aged (mean = 58; range = 22-88), female (n = 1,014; 99.8%), and White (n = 962; 94.7%). Most survivors had private health insurance (n = 626; 61.6%) and received endocrine therapy (n = 718; 70.7%). About one-third of survivors received chemotherapy (n = 354; 34.8%). Nearly all survivors reported at least one concern (n = 975; 96.0%). Activity-related concerns, such as fatigue and desire to increase physical activity, were most commonly reported among survivors (n = 739; 72.7%), followed by concerns related to nutrition (n = 677; 66.6%) and pain or swelling (n = 630; 62.0%). Among survivors who reported a concern, most accepted information about activity or pain (n = 842; 98.6%). Acceptance of referrals to services were generally fewer in number than of information, with the most accepted referrals being for nutrition (n = 46; 6.8%). More than ninety percent of survivors who reported a concern related to activity or pain (n = 842; 98.6%), nutrition (n = 669; 98.8%), and substance use (n = 50; 92.6%) accepted information or referrals for services. Most survivors who reported a concern related to endocrine therapy (n = 221; 95.7%) and employment or insurance (n = 118; 88.7%), however, did not seek additional support.
**Conclusions:** Our analysis of discretely collected EHR data of survivors with breast cancer suggests that although survivors seen for care planning visits report a range of concerns at the end of active curative-intent treatment, they may not necessarily accept information or referrals for services to address some of their concerns. A possible reason for this occurrence may be that these routinely seen survivors have already received resources to address their concerns at visits prior to the care planning visits. Survivors may have also declined resources due to barriers to health care access, such as those related to finances, transportation, and child care. Further studies are needed to understand this discrepancy and determine how to effectively meet both the desires and needs of this population.

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# Letrozole and palbociclib versus 3rd generation chemotherapy as neoadjuvant treatment in luminal breast cancer: Survival results of the UNICANCER-NeoPAL study

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**Background** Palbociclib is a CDK4/6 inhibitor with demonstrated survival benefits in combination with endocrine therapy in advanced luminal breast cancer (LBC). Its potential role in early breast cancer is currently explored. The NeoPAL trial compared letrozole-palbociclib (LETPAL) combination to standard chemotherapy (CT) as neoadjuvant treatment in patients with high-risk LBC. Both LETPAL and CT were associated with poor pathological response, and equivalent clinical responses, while LETPAL let to encouraging biomarker responses in Prosigna®-defined high-risk LBC. We now evaluate the survival outcomes of both groups.
**Patients and Methods** NeoPAL (UCBG10/4, NCT02400567) is a randomized, parallel, non-comparative phase II study. Postmenopausal women with ER-positive, HER2-negative, Prosigna®-defined luminal B, or luminal A and node-positive, stage II-III breast cancer, not candidate for breast-conserving surgery, were randomly assigned to either letrozole (2.5 mg daily) and palbociclib (125 mg daily, 3 weeks/4) during 19 weeks (LETPAL), or to FEC100 (5FU 500 mg/m2, epirubicin 100 mg/m$^2$, cyclophosphamide 500 mg/m2) x3 21-day courses followed by docetaxel 100 mg/m$^2$ x3 21-day courses (CT). Secondary endpoints included progression-free survival (PFS) and invasive-disease free survival (iDFS), all measured from the date of randomization. Exploratory objectives aimed at evaluating the impact of PEPI score and residual cancer burden (RCB) on survival outcomes in both arms.
**Results** 53 pts were randomized in each arm (both with 11% Luminal A N+ and 89% Luminal B). 23 of the 53 pts in the LETPAL arm received postoperative adjuvant chemotherapy. Median follow-up is 40.4 months [0-56.6]. 11 progressions have been observed (10 metastatic events, 1 regional progression), of which 3 were in the LETPAL and 8 in the control arm. Two additional iDFS events were observed in the LETPAL arm (secondary malignancies). PFS (HR = 1.01; 95%CI [0.36; 2.90], p=0.98) and iDFS (HR= 0.83; 95%CI [0.31; 2.23], p=0.71) did not differ between both arms. 40 months PFS rate is 86.7% (78.0-96.4) and 87.2% (78.1-97.4) in LETPAL and CT arms respectively. PEPI (PEPI II/II vs I: HR 0.80, 95%CI 0.18-3.67) and RCB scores (RCB II/III vs 0/I: HR 1.36; 95%CI 0.17-10.6) did not appear as independent predictors of PFS or iDFS.
**Conclusions** Despite its small size, NeoPAL suggests that a neoadjuvant LETPAL strategy, together with selected postoperative administration of chemotherapy, may spare chemotherapy in some pts with luminal breast cancer while allowing very good long-term outcomes.

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Genomic profiling of breast cancer leptomeningeal metastasis (BCLM) reveals a divergent evolution and therapeutic targets

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**Background**: Leptomeningeal metastasis remains a devastating development in breast cancer, with a median survival of 3-4 months, no widely accepted standard treatment, and limited access to trials of novel therapies. In addition, lack of access to leptomeningeal metastatic material hampers the pre-clinical investigation of the disease process and molecular drivers. This project uses CSF as a liquid biopsy to characterise BCLM, through genomic analysis of the cell-free DNA (cfDNA), and the development of pre-clinical BCLM models by the expansion of CSF disseminated tumour cells.
**Methods**: CSF (surplus to clinical requirements) and blood were collected from patients undergoing evaluation of leptomeningeal metastasis. cfDNA was extracted from CSF and plasma, and subjected to ultra-low pass whole genome sequencing (ulpWGS) to assess tumour-derived cfDNA fraction. Samples with >10% tumour fraction underwent whole exome sequencing, along with matched archival primary tumour, archival extra-cranial metastatic site(s) and germline DNA. CSF cells were expanded *in vitro* (to establish 3D patient-derived organoids (PDOs).
**Results**: Cohort demographics are shown in Table 1. Whole exome sequencing (WES) in 21 patients reveals that 65.2% of variants found in CSF cfDNA were not shared with the primary tumour or other matched samples. Phylogenetic analysis shows a divergent evolution from extra-cranial metastatic sites, represented by plasma cfDNA (n = 12) and/or metastatic site tissue DNA (n = 7). The most frequently mutated cancer-associated genes in CSF were *MUC16 (*12/21), *TP53* (11/21), *CDH1* (10/21), and *KMT2D* (7/21). The common occurrence of *CDH1* loss-of-function mutations was in keeping with the large number of lobular cases, however were also discovered in CSF of two cases with E-cadherin positive ductal primary tumours. Furthermore, mutations (including frameshift indels) in JAK family proteins (*JAK1*, *JAK3* and *TYK2*) were present in 5/21 cases, and were private to CSF in 4/21. Potential actionable gene alterations private to CSF include; *IDH2* (3/21), *GLI1* (3/21), *PIK3CA* (2/21) and *PTCH1* (2/21). Further, there was an enrichment for somatic *BRCA1/2* mutations (5/21, 2 private to CSF) indicating potential for platinum and/or PARP inhibitor therapy in these individuals. Patient-derived organoids (PDOs) were established using CSF tumour cells from 3 ER+/HER2- and 2 TNBC BCLM cases. WES of PDOs revealed high concordance with genomic variants identified in the matched CSF cfDNA. Therapeutic compound testing revealed 3/5 PDOs did not display sensitivity to methotrexate, the most commonly used BCLM intrathecal treatment. Patient-derived xenograft (PDX) models have been established by mammary fat pad, intraductal, intracardiac and intracerebroventricular injection routes.
**Conclusion/future plans**: WES of CSF cfDNA provides insight into genomic changes in BCLM, including the divergent evolution, and BCLM specific alterations, some of which are potentially targetable. Parallel PDO and PDX models are being used to validate potential drivers and therapeutic targets. Treatment options beyond intrathecal methotrexate are urgently needed and in future might be molecularly tailored based on alterations discovered by CSF cfDNA sequencing.

**Table 1. Clinical demographics**

| **Demographics** | **Median, years (range)** |
|---|---|
| Age at BC diagnosis | 45 (24 – 66) |
| Time from primary BC to BCLM | 4.7 (0.7 – 14.7) |
| Time from first metastasis to BCLM | 1.2 (0.0 – 6.5) |
| **Histological Type** | **n (%)** |
| Lobular | 10 (48) |
| Ductal | 8 (38) |
| Mixed ductal/lobular | 3 (14) |
| **Immuno-histochemical phenotype** | **n (%)** |
| ER+ HER2- | 13 (62) |
| TNBC | 5 (24) |
| ER+ HER2+ | 2 (9) |
| ER- HER2+ | 1 (5) |
| **Metastatic sites** | **n (%)** |
| No other metastatic sites (BCLM only) | 3 (14) |
| Bone | 12 (57) |
| Serosal | 8 (38) |
| Brain | 6 (29) |
| Liver | 4 (19) |
| Ovary | 4 (19) |

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Differential gene expression in luminal-type invasive lobular carcinoma and invasive ductal carcinoma by MammaPrint risk stratification

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**Background:** Invasive lobular carcinoma (ILC) comprises 10-15% of breast tumors and is the second most common histological type after invasive ductal carcinoma (IDC). Patients with ILC are often diagnosed at an older age and more advanced stage than those with IDC. Late recurrences and worse long-term survival suggest the need for improved approaches to treatment optimization and exploration of molecular pathways unique to ILC. Although previous reports have described comprehensive transcriptomic profiling of ILC, these were limited by small sample sizes. Furthermore, differential gene expression between ILC and IDC within genomic risk groups and molecular subtypes has yet to be explored. Here we characterize differential gene expression between ILC and IDC in a large, age-matched patient subset categorized by 70-gene signature/MammaPrint (MP) risk and 80-gene signature/BluePrint (BP) subtype.

**Methods:** The prospective FLEX Registry (NCT03053193) includes stage I-III primary invasive breast cancer patients who receive MP/BP testing and consent to full transcriptome and clinical data collection. This sub-analysis included 450 ILC patients enrolled from 2017 to present. Compared with a random selection of IDC patients (n=450, mean age, 60 years), ILC patients were older (mean, 63 years, $p<0.001$). Thus, we selected an age-matched subset for differential gene expression analysis. There were few non-Luminal ILCs; thus, gene expression analyses were limited to BP Luminal tumors. A subset of 413 age-matched pairs (n=826) of ILC and IDC were used for analysis. Gene expression data were quantile normalized using R limma package, and differentially expressed genes (DEGs) were compared between groups. DEGs with an adjusted $p<0.05$ and $\log_2$ fold change > ± 1.0 were considered significant.

**Results:** ILC represented 13% of FLEX cases (n=450/3562), and were 81% lymph node-negative, 99% ER+, 94% HER2-negative, and 68% MP Low Risk (LR). By BP, ILC were 99% Luminal, 1% HER2, and <1% Basal type. BP Luminal ILC were predominantly grade 2 (63%), T1 (61%), node-negative (84%), and MP LR (69%). Menopausal status, nodal status, ethnicity, BMI distribution, and frequency of type 2 diabetes mellitus were similar between ILC and IDC. However, IDC were more likely to be MP HR (46% IDC vs. 31% ILC, $p<0.001$) and grade 3 (15% IDC vs. 4% ILC, $p<0.001$). ILC were more likely to be T3 (10% ILC vs. 1% IDC,
$p<0.001$). We found 4 DEGs common to all comparisons: all Luminal ILC vs. IDC, MP LR ILC vs. IDC, and MP HR ILC vs. IDC. ILC had lower expression of *CDH1* (E-cadherin) than IDC, regardless of MP risk. Including *CDH1*, 6 unique genes were differentially expressed in LR ILC compared with IDC, and 21 genes were differentially expressed in HR ILC compared with IDC. Genes with increased expression in HR ILC were related to immune cell migration/chemotaxis, hormone signaling, and growth factor signaling. HR ILCs were also enriched for TGFβ signaling and angiogenesis pathway genes.

**Conclusions:** Here we report differential clinical and molecular characteristics between ILC and IDC in a large, age-matched patient subset. Regardless of MP risk, expression of *CDH1* was lower in ILC compared with IDC. Approximately one-third of ILCs were MP HR, and we report a greater number and diversity of DEGs between HR ILC and HR IDC compared with LR tumors, in particular genes related to TGFβ signaling. TGFβ pathway genes play a variety of roles in the tumor microenvironment, including induction of angiogenesis, fibroblast growth factor stimulation, and inhibition and/or exclusion of an immune response. These results suggest that therapeutic strategies targeting the TGFβ pathway may be future avenues of exploration in ILC, although further studies are warranted to characterize underlying molecular mechanisms.

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# Double-blind placebo (PBO)-controlled randomized phase III trial evaluating first-line ipatasertib (IPAT) combined with paclitaxel (PAC) for *PIK3CA/AKT1/PTEN*-altered locally advanced unresectable or metastatic triple-negative breast cancer (aTNBC): primary results from IPATunity130 Cohort A

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**Background:** In the randomized phase II LOTUS trial [Kim, Lancet Oncol 2017], adding IPAT to PAC improved progression-free survival (PFS), with a more pronounced effect in patients with *PIK3CA/AKT1/PTEN*-altered tumors. This effect provided the rationale for the biomarker-selected IPATunity130 phase III trial. Here we report primary results from Cohort A in aTNBC. **Patients and methods:** In Cohort A of this pivotal phase III trial (NCT03337724), eligible patients had *PIK3CA*- and/or *AKT1*- and/or *PTEN*-altered measurable aTNBC, ECOG performance status 0/1, were appropriate candidates for taxane monotherapy, and had received no prior chemotherapy for aTNBC. Patients were randomized 2:1 to receive either oral IPAT 400 mg or PBO (days 1-21), both combined with IV PAC 80 mg/m$^2$ (days 1, 8, & 15). Cycles were repeated every 28 days until disease progression, unacceptable toxicity, or patient withdrawal. Stratification factors were: prior (neo)adjuvant chemotherapy (yes vs no); geographic region (Asia-Pacific vs Europe vs North America vs rest of world); and tumor alteration status (*PIK3CA/AKT1*-activating mutation vs *PTEN* alteration without *PIK3CA/AKT1*-activating mutation). The primary endpoint was investigator-assessed PFS; secondary endpoints included overall survival (OS; key secondary), objective response rate (ORR), duration of response, clinical benefit rate (CBR), patient-reported outcomes, and safety. **Results:** Between 6 Feb 2018 and 8 Apr 2020, 255 patients were enrolled, of whom 51% had received (neo)adjuvant chemotherapy and 59% had visceral disease; 51% had *PIK3CA/AKT1*-activating mutations and the remaining 49% had *PTEN* alterations (without *PIK3CA/AKT1*-activating mutations). At the clinical cut-off date (7 May 2020), median duration of follow-up was 8.3 months (range 0-26.8 months) and 33% of patients remained on treatment. Mean duration of PAC was similar in the two groups (5.5 vs 5.4 months in the IPAT vs PBO arms, respectively). There was no difference in PFS between treatment groups overall (Table) nor in any prespecified subgroups. OS results are immature (deaths in 20% of patients). Similar proportions of patients in the IPAT and PBO arms experienced grade ≥3 adverse events (AEs) (46% vs 44%, respectively), fatal AEs (1% vs 1%), and AEs leading to discontinuation of any treatment (14% vs 15%), although AEs leading to dose reduction of any treatment were more common with IPAT (35% vs 14%). The most common AEs (any grade) were diarrhea (80% vs 31%; grade ≥3 9% vs 2%), alopecia (46% vs 44%), and nausea (36% vs 23%). **Conclusions:** In contrast to results from the phase II LOTUS trial, this trial showed no PFS improvement with the addition of IPAT to first-line PAC in patients with *PIK3CA/AKT1/PTEN*-altered aTNBC. Biomarker analyses are ongoing to evaluate potential markers of IPAT benefit. Safety was consistent with previously reported results for this combination.

Summary of efficacy

| | IPAT + PAC | PBO + PAC |
|---|---|---|
| ITT population | (n=168) | (n=87) |
| PFS events, n (%) | 92 (55) | 48 (55) |
| Median PFS, months (95% CI) | 7.4 (5.6-8.5) | 6.1 (5.5-9.0) |
| PFS stratified hazard ratio (95% CI) | 1.02 (0.71-1.45) | Log-rank p=0.9237 |
| Measurable disease population | (n=167) | (n=86) |
| ORR, n (%) [95% CI] | 65 (39) [32-47] | 30 (35) [25-46] |
| CBR, n (%) [95% CI] | 78 (47) [39-55] | 39 (45) [35-56] |

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Clonal relatedness of LCIS with synchronous and asynchronous invasive disease

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**Background:** Lobular carcinoma *in situ* (LCIS) is typically clinically undetectable but is being increasingly diagnosed as a result of breast screening mammography and is often found associated with other breast pathologies such as invasive lobular breast cancer (ILC), invasive carcinoma of ductal /no special type (IDC) and ductal carcinoma *in situ* (DCIS). It is also considered a risk factor for the development of subsequent invasive breast disease. The aim of this study was to understand the genetic relationship between LCIS that presents with synchronous DCIS, IDC and/or ILC in order to ascertain whether the components have common precursors and also to understand the clonal relationship between LCIS and subsequent invasive disease. **Methods:** 25 cases of LCIS with synchronous ILC, 7 cases of LCIS with synchronous DCIS & IDC, and 8 pure LCIS that developed a subsequent invasive recurrence were identified from the GLACIER study (MREC 06/Q1702/64). DNA was extracted from archival paraffin embedded tissue and underwent copy number analysis using either the *Oncoscan™ Array (Affymetrix)* or *HumanCytoSNP FFPE-12 BeadChip (Illumina)*. Four of 7 cases of LCIS with synchronous DCIS & IDC also underwent targeted sequencing using a custom 121 breast cancer-associated gene panel (*SureSelect$^{XT\ HS}$ kit, Agilent Technologies*). Clonal relatedness was assessed using a novel methodology based on the presence of shared copy number aberration breakpoints and mutations. **Results:** Of the 25 synchronous LCIS and ILC cases, 17 appeared related, 4 were ambiguous (sharing the typical lobular signature of 1q gain and 16q loss) and 4 demonstrated no evidence of relatedness. Of the 7 cases with synchronous LCIS, DCIS and IDC, all had copy number data available and 4 had mutation data available. In 3 cases the synchronous LCIS, DCIS and IDC were clonally related according to copy number and for two there was mutation data that supported this (one sharing *PIK3CA* and *CDH1* mutations, the other a *TP53* mutation). In two cases the LCIS was not related to the DCIS or IDC, but the DCIS and IDC were related to each other; while in one case LCIS was related to IDC but not to the DCIS by copy number but all components shared the same *CHEK2* mutation. Finally in one case none of the three components were related to each other by copy number but the LCIS and IDC shared a *PIK3CA* mutation, albeit at much lower allele frequency in LCIS than in IDC. Of the 8 patients with pure LCIS, 4 developed an ipsilateral invasive recurrence of various combinations of morphologies: 1 ILC & LCIS, 1 ILC & DCIS, 1 IDC & DCIS, 1 ILC & IDC, and 4 a contralateral recurrence (1 tubular, 1 IDC, 2 ILC), with a median time to recurrence of 69 months (range 34-175). The primary LCIS was related to at least one component of the recurrent disease in all four ipsilateral cases; in two the primary LCIS and all components of the recurrent disease were related, and in the remainder we observed a variety of putative evolutionary patterns. **Conclusions:** The majority (68%) of cases of synchronous LCIS and ILC appeared to be clonally related by copy number. 50% of cases of co-existing LCIS and IDC appeared to have a common clonal origin by either copy number or targeted sequencing. As these are genomically stable tumours, copy number data may also be underestimating relatedness. In the four cases of pure primary LCIS that developed an ipsilateral recurrence, different subtypes of breast cancer were noted as the recurrence morphology, supporting the historical view that LCIS is a risk lesion rather than a true precursor. However, in all cases the preceding LCIS was found to be related to at least one component of the subsequent invasive tumour including DCIS and IDC. This data shows that clonal relatedness between LCIS and both synchronous and asynchronous invasive disease and DCIS is more complex than previously thought, with LCIS acting as a precursor lesion even in some cases of IDC.

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Comparison of pathologist reads of sp142 and sp263 with quantitative measurement of protein and mRNA in triple negative breast cancer

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**Background:** PD-L1 SP142 immunohistochemistry (IHC) assay has been approved as a companion test by the US Food and Drug Administration (FDA) to identify eligibility for atezolizumab therapy in patients with advanced triple negative breast cancer (TNBC) but a number of studies suggest the assay suffers from poor reproducibility. Using readings of 70 TNBC chromogenic FDA approved assays from 19 pathologists in a previous study as a baseline, we compared pathologist reads to quantitatively measured mRNA and protein expression **Methods:** Formalin-fixed paraffin-embedded (FFPE) slides representing primary invasive triple negative breast cancer (stage I-III) from 100 patients between 2012-16 were selected from the Yale Pathology archives. Slides were macrodissected to tumor enrichment for quantitative assessment of *CD274 (PD-L1* mRNA*)* measured using a closed-system, real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) research use only (RUO)* prototype assay on the GeneXpert® instrument. We also measured protein expression levels using the AQUA method of quantitative immunofluorescence (QIF) in both the tumor and non-tumor compartments on full sections by QIF stained using SP142 in a lab derived test (LDT). The IHC stained slides were prepared using SP142 and SP263 assays prepared exactly according the FDA approved label followed by reading by 19 pathologists. This study was approved by Yale Human Investigation IRB protocol ID 9505008219.**Results:** Previous work from our group showed overall percent agreement for both the SP142 and SP263 IHC assays read by pathologists was in the 40-50% range. We used the median *CD274* score to compare positive (IC□1) vs negative (IC<1) and found that the levels of mRNA were not statistically significantly different between the two categorical scores. However, quantitative measurement of protein expression (including both tumor and non-tumor regions) showed statistically significant differences between pathologist read PD-L1 positive/negative scoring for SP142 (*p=0.0004*) and SP263 (*p=0.0185*). Concordance of quantitative PD-L1 measurement between protein QIF scores and transcript RT-qPCR levels was modest, with a Spearman coefficient r = 0.18. **Conclusions:** By chromogenic IHC, using the FDA approved assays, pathologist read scoring shows no difference to mRNA for *CD274*. Quantitative continuous scoring of protein expression show that, on average, when pathologists score IC□1, there is more protein present than when they score IC<1. Further studies are needed to determine if RNA and protein for PD-L1 are concordant and to determine which assay(s) and cutoff values are best correlated with clinical outcomes on atezolizumab therapy.

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**Publication Number:** PD9-03

# Genomic analysis of the CALGB 40603 (Alliance) neoadjuvant trial in TNBC identifies immune features associated with pathological complete response and event-free survival

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**Purpose:** CALGB (now part of the Alliance for Clinical Trials in Oncology) 40603 was a randomized Phase II study investigating pathological complete response rates (pCR) in triple-negative breast cancer (TNBC) patients receiving neoadjuvant weekly paclitaxel followed by doxorubicin and cyclophosphamide +/- bevacizumab and/or carboplatin for which 5-year event-free survival (EFS) results are now available. This is a valuable resource to characterize clinical and genomic features associated with response and survival. **Methods:** Clinical parameters and pre-treatment tumor biopsy RNA-sequencing (RNAseq) from 295 TNBC patients were analyzed to identify features associated with pCR and/or EFS. A panel of 689 previously published gene expression signatures were evaluated to provide insights regarding potential associations between clinical endpoints and genomically determined cell types and signaling pathway activities. Additionally, B cell receptor (BCR) and T cell receptor (TCR) sequences were examined, and repertoire abundance, richness, and diversity measures were calculated to investigate correlations with pCR and EFS status. Univariate Mann-Whitney U-Tests were used for continuous variables, and Fisher's test was used for categorical features, with unadjusted p-values < 0.05 designated as significant. **Results:** While the addition of bevacizumab and carboplatin each significantly improved pCR rates, neither improved EFS. We examined outcomes according to race and no differences were seen for either pCR rate or EFS. 131 features, including high proliferation and multiple interferon signatures were significantly associated with pCR, but not with EFS. Alternatively, 69 features, including clinical factors for T stage and node status, were prognostic for EFS, but not significantly associated with pCR. Nevertheless, pCR itself was the strongest predictor of EFS, and was the only feature significantly associated with EFS after adjusting for multiple comparisons (Benjamini-Hochberg False Discovery Rate = 6.7e-3). In total, 52 genomic features were significantly correlated with both pCR and EFS, 44 of which were features of the immune microenvironment. Immune associated features included signatures of T cells, B cells and NK cells, immune checkpoint pathways (PD-1, PD-L1, CTLA4), and antigen presentation (dendritic cells, MHC-I, MHC-II). In particular, low BCR evenness, which is a measure of uniformity of unique BCR sequence abundance, was strongly associated with both pCR and EFS, suggesting that an antigen-specific adaptive immune response with clonally selected B cells is occurring in patients that have improved response and survival. Furthermore, a multivariate Cox Proportional Hazards model assessing BCR evenness along with age, T stage, N stage, grade and pCR found BCR evenness to be an independent prognostic feature for EFS in TNBC. **Conclusions:** Evidence of distinct predictors of pCR and EFS in TNBC patients treated with neoadjuvant chemotherapy suggests that, while pCR is still the strongest prognostic feature, high expression of many immune related gene expression signatures in pretreatment tumor samples are promising biomarkers of improved EFS. In addition to the important role of T cells in an anti-tumor response, these data show high IgG expression and evidence of B cell clonal selection associates with improved response and survival, supporting an important role for B cells in the adaptive response that portends a long-term benefit of chemotherapy in TNBC. **Support**: U10CA180821, U10CA180882, U24CA196171, P50-CA58223, Genentech, and The Breast Cancer Research Foundation. https://acknowledgments.alliancefound.org; **ClinicalTrials.gov Identifier:** NCT00861705

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# Dna repair imbalance and immune response in breast cancer mortality disparities

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**Background:** Black breast cancer patients have p53 loss in 60% of their tumors, compared to 35% p53 loss in white breast cancer patients. The tumor suppressor p53 has pleiotropic effects on DNA repair, as it regulates both error prone and error-free DNA repair pathways. These effects on DNA repair represent molecular vulnerabilities that influence chemotherapy response, both directly and indirectly through the activation of immune responses. While studies have begun to elucidate DNA repair imbalance and immune response in human cancer, little is known about how these pathways differ by race. **Methods:** To study DNA repair and immune response in breast cancer, we performed gene expression analysis on FFPE samples from the Carolina Breast Cancer Study (CBCS), a large population-based study that oversampled black and younger women. We curated a list of DNA repair genes representing regulators of error prone and error free DNA repair. Pathways included Nucleotide Excision Repair (NER), Fanconi Anemia (FA), Mismatch repair (MMR), Base Excision Repair (BER), Homologous Recombination (HR), Translesion Synthesis (TLS), Alternative End Joining (AEJ), Checkpoint, and APOBEC. In addition, we developed a 50-gene immune panel representing 12 individual immune cell types (B cells, T cells, Treg cells, T help cells, T follicular helper cells, CD8 T cells, NK cells, Eosinophils, Neutrophils, M1 & M2 Macrophages) and both adaptive and innate arms of the immune system. A total of 1464 patients (53% black, 53% under 50) were included in the current analysis. We used consensus clustering to identify groups of patients based on DNA repair gene expression and used linear regression to estimate the relative frequency differences between these classes and demographic and clinical characteristics. **Results:** We found that breast cancers grouped into four clusters based on DNA repair gene expression. One cluster, ‘Repair High’, represented 32% of the tumors, and had high expression of NER, NHEJ, HR, and FA genes, suggesting a broad DNA repair response. Another group, ‘HR/FA High’ represented 23% of the tumors and was enriched for high expression of HR and FA genes. An “APOBEC High” group consisted of 32% of the tumors and was enriched for high expression of APOBEC family genes (APOBEC3D, APOBEC1, APOBEC3A, APOBEC3H, APOBEC3B). Finally, 13% of tumors, had a ‘Heterogeneous Repair’ pattern of high expression of HR, NHEJ, and FA genes, but lower expression of NER genes. The HR/FA and Heterogeneous Repair groups were enriched for TP53 mutant-like tumors (93% vs. 5% and 61% vs. 38% Mutant vs. Wildtype respectively). In addition, the Heterogeneous Repair group was enriched for Hormone Receptor positive samples ([RFD] 8.2% (0.613, 15.3), 77% vs. 23% in positive vs. negative respectively), while the HR/FA High group was significantly enriched for TNBC ([RFD] HR/FA: 51.2% (45.1, 57.1), 75% vs. 25% TNBC vs. non-TNBC respectively). The Repair High group was the only group enriched for non-black race ([RFD]: 10.4% (4.0, 16.7), 42% vs. 58% in blacks vs. non-blacks respectively). Finally, DNA repair classes were associated with immune scores, with the APOBEC High tumors having a significantly higher Eosinophil score ($p = 0.021$) and Neutrophil score ($p = 0.007$) compared to the other four groups. **Conclusion:** DNA repair expression is highly variable across breast tumors and may depend upon TP53 status, tumor subtype, and race. Differential immune marker expression by DNA repair group suggests some DNA repair groups may have differential response to immune-targeted therapies. DNA repair, immune response, and race are inter-related in breast cancer and unraveling and ultimately targeting breast cancer disparities may require coordinated evaluation of these pathways.

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# A phase Ib trial of fulvestrant + CDK4/6 inhibitor (CDK4/6i) palbociclib + pan-FGFR tyrosine kinase inhibitor (TKI) erdafitinib in *FGFR*-amplified/ ER+/ HER2-negative metastatic breast cancer (MBC)

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Background: Somatic alterations in the FGFR pathway (mainly *FGFR1*, amplified in about 15% of ER+ BC) have been implicated in resistance to endocrine therapy (ET), and more recently, to CDK4/6i as well. Based on our preclinical data showing that the FGFR pan-inhibitor erdafitinib when added to fulvestrant/palbociclib resulted in marked PDX regressions, we initiated a phase Ib trial combining erdafitinib with fulvestrant/palbociclib in patients with ER+/HER2-/*FGFR*-amplified MBC (NCT03238196) to determine safety, tolerability and anti-tumor activity of this combination. Methods: Patients with evaluable ER+/HER2- MBC with *FGFR1-4* amplification (detected on tumor next generation sequencing or plasma ctDNA) exposed to at least one ET regimen (but no more than 2 lines of chemotherapy) in the metastatic setting, were treated with fulvestrant, palbociclib (standard of care dosing/ schedule) and oral erdafitinib, tested in 4 doses ranging from 4 mg to 8 mg daily. Once MTD reached, we planned to enroll 20 patients in the expansion portion of the trial. Tumor blocks were collected for *FGFR1* FISH amplification analysis, and plasma ctDNA was collected at baseline, 4 weeks and at treatment discontinuation. Tumor assessments were performed every 8 weeks. Results: Since August 2017, 26 eligible patients with evaluable ER+/HER2-/*FGFR*-amplified MBC were enrolled across 4 institutions. Patient characteristics are summarized in Table 1. Main grade 1 and 2 adverse events (AE) were consistent with on-target toxicities of erdafitinib and/or palbociclib: mucositis (67%), hyperphosphatemia (61%), dysgeusia (52%), diarrhea (48%), fatigue (48%), neutropenia (47%), hand-foot syndrome (38%), anemia (29%), and onycholysis (14%). Febrile neutropenia occurred in 5% patients, no cases of central serous retinopathy were seen. Serious AE were rare: one grade 4 elevation of transaminases (DLT; attributed to fulvestrant), one grade 3 colitis (attributed to erdafitinib), and one thromboembolic event (attributed to palbociclib). In combination with fulvestrant/ palbociclib, the MTD of erdafitinib was 6 mg. No drug-drug interaction was seen. 8 patients were deemed non-evaluable for anti-tumor effect as treatment discontinuation (mainly due to AE) occurred prior to first tumor assessment. Of the 18 evaluable patients: 7 had disease progression, 8 had stable disease (4 of which discontinued treatment due to AE), 3 have not completed their first tumor assessment, 4 are still on treatment; median PFS was 3 months and CBR at 6 months was 28%. However, higher PFS (6 months) was seen in 6/8 patients with high levels of *FGFR1* amplification (FISH FGFR1:CEP8 ratio >5; gene copy number >10) and in both patients with *FGFR3* amplification.
Conclusion: To our knowledge, this is the first time an FGFR inhibitor has been tested in combination with ET and CDK4/6i in patients with MBC harboring *FGFR* alterations. Erdafitinib-related side effects appeared to be on target, leading to treatment discontinuation in several patients despite optimal medical treatment. Clinical activity was seen in heavily pre-treated patients with molecular evidence of high *FGFR* amplification despite 100% prior exposure to ET and CDK4/6i. Full clinical and correlative work will be presented at the meeting, and a future phase II trial is being planned.

Table 1

| | |
|---|---|
| **26 / 35 patients accrued** | 13 in escalation, 13 in expansion(ongoing) |
| **Median age** | 53 (35 - 75) |
| **Race/ ethnicity** | White 22 |
| | Black 1 |
| | Asian 2 |
| | Hispanic 1 |
| **Median number of lines of treatment in the metastatic setting** | 4 (1 - 5) |
| **Prior lines of treatment in the metastatic setting** | Endocrine therapy 100% |
| | Fulvestrant 28% |
| | CDK4/6i 100% |
| | PI3K pathway inhibitor 80% |
| | 1 line chemo 65% |
| | 2 lines chemo 45% |
| ***FGFR1* amplification** | 23 |
| ***FGFR3* amplification** | 2 |
| ***FGFR4* amplification** | 1 |

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LGR4 engages a wnt-independent mechanism to enhance EGFR signaling and promote metastasis of triple-negative breast cancer

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Leucine-rich repeat-containing G-protein-coupled receptors 4/5/6 (LGR4/5/6) have crucial functions in embryonic development, adult tissue homeostasis, and diseases. LGR4/5/6 also play important roles in cancer initiation and progression. LGR4 is highly expressed in multiple types of cancer and associated with poor patient outcome. LGR4 promotes tumorigenesis and metastasis and modulates cancer stem cells, while LGR5 and LGR6 mark cancer stem cells and progenitor cells that contribute to tumor initiation. The biological functions of LGR4/5/6 are primarily attributed to their roles in potentiating Wnt signaling, which requires the binding of their four R-spondin ligands (RSPO1-RSPO4). However, it is unclear whether these proteins have Wnt signaling-independent functions. We have previously reported that LGR4 is important in mammary gland development and breast cancer progression and metastasis. Here, we demonstrate that LGR4 enhances triple-negative breast cancer (TNBC) metastasis independently of Wnt signaling. We first found that LGR4 was highly expressed in the TNBC subtype and associated with poor metastasis-free survival in TNBC patients, while a well-validated Wnt signature failed to correlate with metastasis-free survival of this same subset of TNBC patients. These bioinformatic data suggested divergent functions of LGR4 versus Wnt signaling in TNBC progression. Then we showed that depletion of *LGR4* inhibited, while inducible expression of *LGR4* promoted TNBC cell migration and invasion, without added exogenous ligands and any detectable impact on baseline Wnt signaling. Importantly, blockade of Wnt signaling by Wnt inhibitors or by genetic depletion of *Wntless* cannot abolish the effect of LGR4 on TNBC cell metastatic ability. Furthermore, we have generated non-RSPO-binding LGR4 mutants that failed to activate Wnt signaling. These LGR4 mutants that are uncoupled from Wnt signaling can still promote TNBC cell migration and invasion in vitro and TNBC lung metastasis and bone metastasis in vivo, as potently as wild-type LGR4. To identify the molecular mechanisms by which LGR4 promotes TNBC metastasis, we did computational analyses of TCGA data to search for candidate proteins associated with LGR4 and proteomics screenings to uncover protein pathways regulated by LGR4 knockdown in TNBC cells. Both in silico and proteomic analyses identified EGFR as a downstream component of LGR4 signaling in TNBC. We confirmed LGR4 enhanced EGFR signaling by immunoblot analyses and found that EGFR was the crucial mediator of LGR4's role in TNBC metastasis. Ectopic EGFR rescued migration and invasion of *LGR4* knockout cells, while EGFR knockdown and the EGFR inhibitor erlotinib attenuated LGR4-induced cell migration and invasion. In an intra-iliac injection model of bone metastasis, erlotinib also suppressed LGR4-induced TNBC bone metastasis in vivo. Mechanistically, LGR4 did not affect EGFR mRNA levels but EGFR protein stability. LGR4 interacted with EGFR and blocked EGFR ubiquitination and degradation, resulting in persistent EGFR activation. Together, these data uncover a new signaling pathway controlled by LGRs with broad implications for cancer progression and targeted therapy.

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# Predictors of pain reduction in trials of interventions for aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS)

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**Background**: Up to half of AI-treated breast cancer patients experience AIMSS, and 20-30% have severe symptoms that lead to treatment discontinuation. Multiple interventions have been examined in randomized clinical trials, including in SWOG S0927 (omega-3 fatty acids vs placebo), S1202 (duloxetine vs placebo), and S1200 (true acupuncture vs sham acupuncture vs wait list control). We hypothesized that we could identify predictors of pain reduction in AIMSS intervention trials by combining data from these trials. **Methods**: The S0927, S1200, and S1202 clinical trials had similar eligibility criteria, and all used the same patient-reported outcomes measures to assess arthralgias and endocrine symptoms. The Brief Pain Inventory (BPI) examines average pain, worst pain, and pain interference; higher numbers reflect more symptoms. Endocrine symptoms were assessed with the Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES), which includes subscales for functional and physical well-being; higher scores reflect better function. We also used validated measures to assess joint symptoms in the knees/hips (WOMAC) and hands (M-SACRAH), where higher scores indicate greater symptom severity. We analyzed the subset of patients enrolled on these three trials who had a baseline BPI average pain score of at least 4/10 (S0927, n=185; S1200, n=158; S1202, n=240). The primary outcome was 50% reduction in BPI average pain from baseline to week 12. Variable cut-point selection was performed on each continuous variable to identify a binary cut-point that optimally distinguished high versus low levels of pain reduction. Logistic regression was performed for each variable. A risk model was built by summing the number of statistically significant baseline predictors and categorizing patients by low vs. medium vs. high likelihood of pain reduction. All analyses were stratified by study and adjusted for treatment arm. **Results**: Of the 583 analyzed patients, median age was 60 years (range 27-84), median body mass index was 30 kg/m$^2$ (range 18-84), and 208 patients (35.7%) had at least a 50% reduction in BPI average pain. Factors significantly associated with at least a 50% reduction in pain included lower pain and pain interference and better physical and functional status at study enrollment (Table). Patients with 2-4 of the 7 statistically significant factors were twice as likely to experience pain reduction compared to those with fewer than 2 factors (37.8% vs. 22.5%; odds ratio [OR] 2.08, 95% CI 1.38-3.13, p<.001). Those with 5-7 factors were more than 5 times more likely to experience pain reduction (61.2% vs. 22.5%; OR 5.66, 95% CI 3.21-9.98, p<.001). **Conclusions**: Patients with AIMSS who have lower pain and better functional status are more likely to experience meaningful pain reduction in intervention trials for AIMSS. These findings suggest early intervention for treating AIMSS may be important. Baseline pain and functional status should be considered as stratification factors in future interventional trials. **Funding**: NIH/NCI Grant Award CA189974; and in part by the Hope Foundation for Cancer Research.

Association of baseline characteristics with 50% reduction in average pain from baseline to 12 weeks

| Factor | Rates of pain reduction | Odds Ratio (95% CI) | P value |
|---|---|---|---|
| Age: <70 vs ≥70 years | 37.1% vs. 26.3% | 1.66 (0.96-2.86) | 0.07 |
| BMI: <30 vs. ≥30 kg/m$^2$ | 37.9% vs. 33.6% | 1.27 (0.90-1.79) | 0.17 |
| BPI average pain: 4 vs. ≥5 | 48.6% vs. 31.7% | 1.93 (1.30-2.86) | 0.001 |
| BPI worst pain: <6 vs. ≥6 | 49.0% vs. 32.8% | 1.95 (1.26-3.02) | 0.003 |
| BPI pain interference: <3 vs. ≥3 | 47.8% vs. 31.9% | 2.21 (1.47-3.32) | 0.0001 |
| FACT-ES Functional Well-Being: ≥24 vs. <24 | 49.3% vs. 33.9% | 1.97 (1.18-3.30) | 0.01 |
| FACT-ES Physical Well-Being: ≥12 vs. <12 | 38.6% vs. 21.1% | 2.45 (1.44-4.18) | 0.001 |
| FACT-ES Endocrine Subscale: ≥42 vs. <42 | 36.7% vs. 29.7% | 1.44 (0.84-2.47) | 0.19 |
| WOMAC: <50 vs. ≥50 | 49.0% vs. 26.0% | 2.63 (1.85-3.74) | <.001 |
| M-SACRAH: <33 vs. ≥33 | 45.6% vs. 27.4% | 2.18 (1.54-3.10) | <.001 |

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Correlative biomarker analysis of intrinsic subtypes and efficacy across the MONALEESA Phase III studies

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**Background:** The prognostic and predictive value of the 4 main intrinsic subtypes of breast cancer (ie, luminal A [LumA], luminal B [LumB], human epidermal growth factor receptor 2 enriched [HER2E], and basal-like) in hormone receptor-positive, HER2− advanced breast cancer (ABC) treated with endocrine therapy (ET) and ribociclib (RIB) is currently unknown. The MONALEESA-2, -3, and -7 trials all showed a significant benefit in progression-free survival (PFS) with RIB over placebo (PBO; Hortobagyi et al. *Ann Oncol*. 2018; Slamon et al. *J Clin Oncol*. 2018; Tripathy et al. *Lancet Oncol*. 2018). Here, we correlate ABC intrinsic subtypes with the PFS benefit of RIB in the MONALEESA trials. **Methods:** Patient samples from the MONALEESA-2, -3, and -7 trials underwent PAM50-based subtyping (blinded from clinical data), and the correlation between intrinsic subtype and PFS was analyzed. Gene expression profiling of formalin-fixed, paraffin-embedded tumor samples was performed using a customized NanoString nCounter GX 800-gene panel. The prognostic and/or predictive relationship of PAM50-based subtypes with PFS and the risk of tumor progression by subtype were evaluated using univariate and multivariable Cox proportional hazards models. Multivariable models were adjusted for known clinical prognostic factors, including age, prior chemotherapy, prior ET, ECOG performance status, visceral disease (presence of liver/lung metastases), bone-only metastases, histological grade, number of metastatic sites, and de novo metastatic disease. **Results:** A total of 1160 tumor samples from both the RIB (n = 672) and PBO (n = 488) treatment arms of the MONALEESA trials were profiled. Subtype distribution was generally consistent across treatment arms (**Table**). The associations between intrinsic subtypes and PFS were statistically significant in both treatment arms (*P* < .0001). Compared with patients with LumA subtype, which is the subtype that is the most prevalent and has the best prognostic outcome, patients with LumB, HER2E, and basal-like subtypes had a 1.41, 2.30, and 3.97 times higher risk of tumor progression, respectively, after adjusting for other clinical-pathologic variables and treatment arm. In terms of treatment benefit, all subtypes except for basal-like showed a significant PFS benefit with RIB treatment (**Table**). Patients with HER2E (hazard ratio [HR], 0.389; *P* < .0001), LumB (HR, 0.521; *P* = .0001), LumA (HR, 0.633; *P* = .0007), and normal-like (HR, 0.467; *P* = .0005) subtypes all derived benefit from RIB treatment, with HER2E demonstrating the greatest benefit. Patients with the basal-like subtype (n = 30) did not derive benefit from RIB (HR, 1.15; *P* = .767), although these results should be interpreted with caution due to the small sample size (RIB: 2%; PBO: 3%). **Conclusions:** This is the largest analysis evaluating the correlation of intrinsic ABC subtype with efficacy outcomes in patients treated with CDK4/6 inhibitors. Patients with HER2E, LumA, LumB, and normal-like subtypes all exhibited a consistent PFS benefit with RIB treatment, while patients with basal-like ABC (RIB: 2%; PBO: 3%) did not. The HER2E subtype (RIB: 14%; PBO: 11%) exhibited the greatest relative reduction in risk of progression or death (61%) with RIB plus ET.

**Table.**

| Subtype | Treatment Arm | Distribution, n (%) | Median PFS, months, (95% CI) | HR | *P* Value |
|---|---|---|---|---|---|
| Luminal A | RIB | 320 (48) | 29.60 (23.03-NA) | 0.63 | .0007 |
| | PBO | 222 (45) | 19.48 (15.61-24.80) | | |
| Luminal B | RIB | 154 (23) | 22.21 (18.79-NA) | 0.52 | < .0001 |
| | PBO | 124 (25) | 12.85 (10.98414.82) | | |
| HER2-enriched | RIB | 95 (14) | 16.39 (12.71-24.6) | 0.39 | < .0001 |
| | PBO | 52 (11) | 5.52 (3.12-9.17) | | |
| Basal | RIB | 16 (2) | 3.71 (1.91-13) | 1.15 | .77 |
| | PBO | 14 (3) | 3.58 (1.87-NA) | | |
| Normal | RIB | 87 (13) | 22.34 (16.56-NA) | 0.47 | .0005 |
| | PBO | 76 (16) | 11.10 (7.39-16.56) | | |

NA, not achieved.

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Recurrent active *ESR1* fusions render a diagnostic transcriptional signature in metastatic breast cancer

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**Background:** We recently reported two *ESR1* fusions (ESR1-YAP1 and ESR1-PCDH11X) that drive endocrine therapy (ET) resistance and metastasis in estrogen receptor positive (ER+) metastatic breast cancer (MBC) (PMC6171747). Here, we report the functional properties of additional *ESR1* fusions in ET-resistant MBC with an emphasis on the identification of a transcriptional signature designed to diagnose the presence of an active *ESR1* fusion for targeted therapies directed against *ESR1* fusion-driven biology. **Methods:** *ESR1* fusions were detected by RNA-seq in ER+ MBC samples. *ESR1* fusions were reproduced as cDNA constructs and expressed in ER+ breast cancer cell lines. Hormone-independent cell growth was detected by an Alamar blue assay and activated cell motility by a scratch wound assay. The transcriptional properties of *ESR1* fusions was studied by RNA-seq followed by qPCR-based validation. Signature performance was evaluated using a ROC analysis on ER+ patient derived xenografts (PDX) harboring a variety of *ESR1* somatic events. **Results:** All *ESR1* fusions studied encoded the first six exons of *ESR1* fused in-frame to diverse partner genes, thus replacing the *ESR1* drug/ligand binding domain (LBD). Fusions involving a known transcription factor (TF) or coactivator (CoA) gene, including ESR1-YAP1, ESR1-SOX9 and ESR1-ARNT2 drove fulvestrant-resistant cell growth and hormone-independent cell motility. Other ESR1-e6 fusions, including ESR1-DAB2, ESR1-GYG1, ESR1-PCMT1 and ESR1-ARID1B did not induce these properties. From these examples, a functional rule is emerging whereby inter-chromosomal *ESR1* translocations fused in-frame to 3' partner genes with a positive role in transcription are active. Intra-chromosomal fusions with genes with no transcriptional roles are likely inactive. The ESR1-PCDH11X fusion is an exception, suggesting the need for continued functional study of non-TF/CoA partner ESR1-e6 fusions. RNA-seq of T47D cells expressing the full panel of gene fusions demonstrated an overlapping pattern of transcriptional activation focused on estrogen response and epithelial-to-mesenchymal transition (EMT) genes driven by active fusions. This gene signature was well-preserved in a PDX naturally expressing the ESR1-YAP1 fusion. Interestingly, further study showed that a series of ET-resistant PDXs bearing a variety of *ESR1* LBD point mutations induced a similar pattern to the active *ESR1* fusion signature suggesting overlapping transcriptional regulatory events between *ESR1* fusions and *ESR1* LBD mutations. The ESR1-D538G mutation conferred the most comparable gene dysregulation to *ESR1* fusions. The Y537S/N and E380Q mutations also reproduced the signature driving hormone-independent growth but with exceptions. Two PDX lines bearing either a fully heterozygous Y537S or L536P mutations were surprisingly completely estrogen-dependent. Neither of these examples exhibited the *ESR1* fusion gene signature, suggesting an unknown secondary event needed to fully express the phenotype of some *ESR1* mutants. The gene signature distinguished *ESR1* mutations (constitutively active fusions and point mutations) from wild-type *ESR1*, with a 92.0% Area Under Curve. **Conclusion:** Here, we show that *ESR1* fusions are recurrent somatic mutations that lead to drug resistance and metastasis by transcriptional reprogramming. We describe a fusion gene signature that may be useful to determine whether an *ESR1* fusion or mutation is transcriptionally active and is capable of driving hormone-independent growth and endocrine therapy resistance.

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# Molecular mechanism of ipatasertib (IPAT) and its combination with atezolizumab (atezo) in patients (pts) with locally advanced/metastatic triple-negative breast cancer (aTNBC)

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**Background:** Phase 3 trials (IMpassion130, KEYNOTE-355) have shown improved efficacy with the addition of immune checkpoint modulators to chemotherapy in PD-L1 +ve aTNBC. However, unmet need remains in the ~60% of pts with aTNBC who have PD-L1 -ve tumors. Preliminary data from a multicenter phase 1b study (NCT03800836) evaluating the safety and efficacy of the oral AKT inhibitor IPAT + atezo + paclitaxel/nab-paclitaxel showed promising antitumor activity (73% confirmed objective response rate) irrespective of PD-L1 status [Schmid, AACR 2019], suggesting a potential role for the triplet independent of PD-L1 status. We report on-treatment changes in the tumor microenvironment in Cohort 2.
**Methods:** In Cohort 2, pts with aTNBC and ≤2 prior lines of chemotherapy for aTNBC received oral IPAT 400 mg on d1-28 of cycle 1 (35-d cycle) and on d1-21 of subsequent cycles (28-d cycles). IV atezo 840 mg was given on d8 & 22 of cycle 1 and on d1 & 15 of subsequent cycles. Biopsies were collected before treatment administration during cycle 1 on d1 (C1D1) & d8 (C1D8), and on d15 of cycle 2 (C2D15). PD-L1 (VENTANA SP142 immune cell ≥1%) and CD8 expression was assessed by immunohistochemistry (IHC); % immune infiltrate was measured by H&E staining. Changes in gene expression were assessed by RNA-Seq. Gene set enrichment analysis was used to study molecular pathway activation (enrichment score [ES] >0 to 1) or inhibition (ES -1 to <0).
**Results:** In Cohort 2, 11 pts had PD-L1 -ve tumors at baseline and are included in the analyses below, 2 had PD-L1 +ve tumors and 3 were unevaluable for PD-L1. IHC analysis of serial biopsies from pts with PD-L1 -ve tumors showed a statistically significant increase in immune infiltrates (mean % infiltrates C1D8/C1D1=1.44; p=0.042) and a trend toward increased CD8 protein expression (mean CD8 % staining C1D8/C1D1=1.75; Kruskal-Wallis p=0.16) at the tumor center during the first week of single-agent IPAT compared with the baseline biopsy. An increase in PD-L1 expression (mean PD-L1 % infiltrating immune cells C2D15/C1D1=4.33; Kruskal-Wallis p=0.044) was seen during IPAT + atezo combination treatment. No significant changes in immune infiltrates or CD8 expression were observed after initiating atezo versus IPAT alone. As expected, MTORC1 activity decreased (ES=-0.43; p<0.005) in response to IPAT. IPAT (± atezo) enhanced key immunogenic pathways, including antigen processing and presentation (ES=0.49; p<0.005), allograft rejection (ES=0.47; p<0.0001), inflammatory response (ES=0.34; p<0.05), and NK cell activation (ES=0.66; p<0.05). In addition, IPAT + atezo enhanced TCR signaling (ES=0.52; p<0.0005) and interferon gamma response (ES=0.30; p<0.05). IPAT treatment was associated with decreased expression of gene sets predicting pathway upregulation, including E2F signaling, G2M checkpoint, and MYC activity. IPAT was also associated with apoptotic pathway enrichment. Using a syngeneic melanoma mouse model, we validated clinical findings and identified additional molecular changes after treatment with IPAT and/or anti-PD-L1. To date, 3 enrolled pts achieved a partial response and 6 had stable disease. Clinical and preclinical studies are ongoing to explore associations between treatment-driven molecular changes and clinical response.
**Conclusion:** Inhibition of AKT signaling may remodel the microenvironment of PD-L1 -ve tumors by increasing immune infiltration, priming immune pathways, promoting tumor cell apoptosis, and inhibiting oncogenic cell proliferative pathways. To our knowledge, these are the first reports evaluating molecular changes during AKT-targeted therapy for aTNBC in the context of immunotherapy irrespective of PD-L1 status. IPAT warrants further investigation combined with atezo as treatment for PD-L1 -ve aTNBC.

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[$^{89}$Zr]-pertuzumab pet imaging reveals paclitaxel treatment efficacy is positively correlated with her2 expression in human breast cancer xenograft mouse models

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**Introduction:** Paclitaxel (PTX) is one of the most commonly used first-line chemotherapies in the treatment of breast cancer. However, it is reported that overall PTX response rate is between 30-60% for the treatment of metastatic breast cancer. Thus, novel discoveries of molecular mechanisms that account for ineffective response is critical in breast cancer treatment. [$^{89}$Zr]-Pertuzumab (antibody that targets HER2 receptors) and 2-deoxy-2-[fluorine-18] fluoro-D-glucose ([$^{18}$F]-FDG) positron emission tomography/computed tomography (PET/CT) imaging allows us to noninvasively measure the amount and heterogeneity of HER2 expression and tumor glucose metabolism. These methods are clinical translatable and can provide insight into tumor biology changes during the course of therapy. This study evaluates whether HER2 expression level is correlated with PTX treatment efficacy in controlled pre-clinical mouse models of HER2+ breast cancer. **Experimental Design:** BT474 ($1\times10^7$), MDA-MB-361 ($6\times10^6$), or MDA-MB-231 ($2\times10^6$) cells were subcutaneously injected into athymic nude mice (N = 7 per cell line). When the tumor volume reached approximately 200 mm$^3$, mice were enrolled in the study. Tumor size was measured with calipers weekly until enrolled and every 3 days after experiment started. *In vivo* HER2 expression level was determined by [$^{89}$Zr]-Pertuzumab PET/CT imaging at one week prior to initiation of treatment and confirmed with immunohistochemistry staining. PTX (15 mg/kg) was administered via i.v. on days 0 and 3. *In vivo* tumor metabolism was quantified by [$^{18}$F]-FDG PET/CT imaging on day 0, 3 and 6. Mean, standard deviation, sum, and frequency histogram of standard uptake value (SUV) were quantified. Tumors were harvested at day 6 for histological analysis. Hematoxylin and eosin (H&E) and cleaved caspase 3 immunohistochemistry (IHC) staining were used to determine tumor apoptosis. Pearson's correlation and ANOVA were used as statistical analysis. **Results:** [$^{89}$Zr]-Pertuzumab $SUV_{mean}$ of BT474 (HER2+) tumors were 4.9±1.5, MDA-MB-361 (HER2+) tumors were 1.4±0.2 ($p<0.0001$, compared with BT474), and MDA-MB-231 (HER2-) tumors were 1.1±0.4 ($p<0.0001$, compared with BT474). [$^{18}$F]-FDG SUV sum was positively correlated with tumor volume ($R^2=0.1669$, $p=0.0250$). Tumor volumes showed no significant changes during the treatment. However, normalized [$^{18}$F]-FDG SUV concentration changes from day 0 to day 3 was negatively correlated with baseline [$^{89}$Zr]-pertuzumab SUV concentration ($R^2=0.3654$, $p=0.05$). **Conclusion:** Preliminary results show paclitaxel treatment efficacy is positively correlated with HER2 expression level in human breast cancer mouse models. [$^{89}$Zr]-Pertuzumab PET/CT imaging quantitively measured HER2 expression level *in vivo*, and [$^{18}$F]-FDG PET/CT imaging revealed the early signals of drug treatment efficacy. This discovery will help identify chemotherapy responders and potentially enhance clinical decision making.
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# Ipsilateral invasive cancer risk after diagnosis with ductal carcinoma in situ in patients with and without index surgery: The effects of endocrine therapy and radiation treatment

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**Background.** Ongoing clinical trials are evaluating active surveillance as a potential alternative to immediate surgery in patients diagnosed with low-risk ductal carcinoma in situ (DCIS). Among women undergoing lumpectomy, the risk of ipsilateral invasive breast cancer (iIBC) after a diagnosis of DCIS can be reduced with adjuvant therapy, including endocrine therapy (ET) and radiation treatment (RT). Here we characterize the effects of ET and RT on iIBC risk after diagnosis with DCIS in a national cohort, in patients who received breast conserving surgery (BCS) within 6 months of diagnosis (BCS group) compared to patients who did not receive any locoregional treatment within 6 months of diagnosis (surveillance [SV] group). **Methods**. A treatment-stratified random sample of patients diagnosed with biopsy-confirmed DCIS in 2008-14 was selected from 1,330 Commission on Cancer-accredited facilities (20/site). Patients who received a mastectomy within 6 months of diagnosis were excluded. Subsequent breast events were abstracted up to 10 years after diagnosis. Primary outcomes were the population-averaged 8-year absolute risks of iIBC for the following five treatment modalities: BCS alone, SV alone, BCS + ET, SV+ET, BCS+RT, and BCS+ET+RT (where ET was defined as ≥5 years of continuous treatment). Secondary outcomes were the average treatment effects (ATE) of SV+ET vs SV, BCS+RT vs SV+ET, and BCS+RT+ET vs SV+ET. A propensity score (PS) model for treatment choice BCS vs SV was fitted with sampling design (SD) weighting and random effects for patients within facilities. Relative treatment effects (hazard ratios [HR]) for the five treatment groups were obtained using multivariable Cox proportional hazards models adjusted for tumor and patient characteristics. The models were weighted by SD and PS and included a robust sandwich covariance estimator to account for clustering of patients within facilities. Population-averaged risks and ATEs were derived from the marginal outcome probabilities: assuming that the entire population received the treatment of interest, each patient's counterfactual probability of an iIBC event by 8 years was predicted, and then averaged across the weighted population. 95% confidence intervals (CI) were obtained by bootstrapping. **Results.** The final analytic cohort contained 14,245 (88.2%) BCS and 1,914 (11.8%) SV patients. Overall, median age at diagnosis was 61 years (IQR: 52-69) and median follow-up was 5.8 years (95% CI 5.7-6.1). The majority of patients were Caucasian (81.9%), with hormone receptor-positive (79.9%), and nuclear grade I/II (54.5%) DCIS. Uptake of any ET was 48.5% and 23.7% in BCS and SV patients, respectively. The relative treatment effects (HR) for the receipt of BCS, RT and ≥5 years of ET were 1.65 (95% CI: 1.14-2.39), 0.40 (95% CI: 0.27-0.61) and 0.55 (95% CI: 0.17-1.72) respectively. The 8-year population-averaged iIBC risks and corresponding ATEs are shown Table 1. **Conclusion.** The 8-year risk of iIBC was below 7% for all six management options. Relative and absolute treatment effects of ET and RT were comparable to previously reported estimates. In SV patients, receipt of ≥5 years of ET nearly halved the 8-year risk, indicating a substantial risk reduction potential for ET in patients who do not receive immediate surgery after diagnosis.

| **Treatment** | **iIBC risk (%)** | **95% CI** |
|---|---|---|
| Surveillance | 6.90 | 6.79-7.01 |
| Surveillance + ET | 3.90 | 3.83-3.96 |
| BCS | 4.26 | 4.21-4.31 |
| BCS + RT | 1.76 | 1.73-1.79 |
| BCS + ET | 2.39 | 2.35-2.43 |
| BCS + ET + RT | 0.98 | 0.96-0.99 |
| **Treatment comparison** | **ATE (%)** | **95% CI** |
| SV+ET vs SV | 3.0 | 2.95-3.04 |
| BCS+RT vs SV+ET | 2.14 | 2.11-2.17 |
| BCS+RT+ET vs SV+ET | 2.92 | 2.78-2.97 |

***Table 1:*** *Population-averaged 8-year iIBC risk and ATEs.*

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# Triple-negative breast cancer (TNBC) risk with pathogenic variants (PV) in hereditary cancer predisposition genes

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**BACKGROUND:** TNBC is among the most aggressive subtypes of invasive breast cancer (BC), and accounts for approximately 10-15% of incidental BC diagnoses. TNBC is associated with early age of onset (median age of diagnosis <50) and disproportionately affects African American women. Breast MRI is currently recommended to screen for BC in women with at least a moderate-to-high lifetime risk of BC (a 2-fold or higher increased risk), and may also be superior to mammogram to screen for TNBC. TNBC has been most closely associated with germline PVs in *BRCA1*. However, recent studies have suggested that PVs in other genes previously associated with invasive BC may specifically confer high risks of the TNBC subtype. **METHODS:** Results were analyzed from 627,219 women undergoing clinical multi-gene panel testing at a single US-based commercial laboratory between 5/2013 and 2/2020, including genes associated with hereditary BC and other cancers. Demographic and personal/family history data were collected on a test requisition form. Individuals who had single- or founder-site testing, or prior *BRCA1* or *BRCA2* testing, were excluded. Multivariable regression analysis was used to examine the association between PVs/suspected PVs and personal history (PHx) of TNBC . Models were adjusted for age, personal/family cancer history, and ancestry. Odds ratios (OR) with 95% confidence intervals (CI) excluding 1.0 were considered significant. **RESULTS:** In total, 22.4% (140,467/627,219) of women tested reported PHx of BC, of whom 12.8% (17,951/140,467) reported PHx of TNBC. Elevated risks of TNBC were identified in carriers of PVs in 10 genes (see Table). While the highest TNBC risk was associated with PVs in *BRCA1* (OR 21.24, 95% CI 19.71-22.88), high risks were also seen for *BARD1* (OR 7.05, 95% CI 5.71-8.71), *TP53* (OR 5.64, 95% CI 3.08-10.33), *PTEN* (OR 5.52, 95% CI 2.35-13.00) and *PALB2* (OR 5.27, 95% CI 4.55-6.10). Moderate-to-high risks (2-5-fold increased risk) of TNBC were also seen for carriers of PVs in *RAD51C*, *RAD51D*, *BRCA2*, and *CDKN2A/P16*. By contrast, PVs in *NBN*, *ATM*, and *CHEK2* were all associated with an apparent decreased risk of TNBC. **CONCLUSIONS:** PVs in several hereditary cancer genes routinely tested on multi-gene panel tests are associated with high risks (OR>5.0) and moderate-to-high risks (OR 2.0-5.0) of TNBC. These findings can inform practice guidelines about which genes to test when evaluating breast cancer risk and which PV carriers may benefit from intensive breast screening with magnetic resonance imaging (MRI).

Odds ratios for TNBC in germline carriers of PV in hereditary cancer risk genes

| Risk Gene | PV Positive with TNBC | OR | 95% CI | p-value |
|---|---|---|---|---|
| High Risk | | | | |
| *BRCA1* | 1193 | 21.24 | 19.71-22.88 | <0.001 |
| *BARD1* | 125 | 7.05 | 5.71-8.71 | <0.001 |
| *TP53* | 12 | 5.64 | 3.08-10.33 | <0.001 |
| *PTEN* | 6 | 5.52 | 2.35-13.00 | <0.001 |
| *PALB2* | 231 | 5.27 | 4.55-6.10 | <0.001 |
| Moderate-to-High Risk | | | | |
| *RAD51C* | 86 | 4.92 | 3.86-6.26 | <0.001 |
| *RAD51D* | 45 | 4.64 | 3.34-6.45 | <0.001 |
| *BRCA2* | 488 | 4.43 | 4.02-4.89 | <0.001 |
| *CDKN2A* (p16) | 17 | 2.52 | 1.52-4.18 | <0.001 |
| Moderate-to-Low Risk | | | | |
| *BRIP1* | 77 | 1.92 | 1.51-2.44 | <0.001 |
| Protective Effect | | | | |
| *NBN* | 14 | 0.55 | 0.32-0.94 | 0.030 |
| *ATM* | 40 | 0.51 | 0.37-0.70 | <0.001 |
| *CHEK2* | 49 | 0.44 | 0.33-0.58 | <0.001 |
| *HOXB13* | 5 | 0.33 | 0.14-0.81 | 0.015 |

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# An automated DNA methylation assay for monitoring treatment response in patients with metastatic breast cancer

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**BACKGROUND:** Previously, we demonstrated the clinical validity of cMethDNA, a circulating methylated tumor DNA (ctDNA) assay, in serum samples from TBCRC 005 (J Clin Oncol, 2017; 35:751-758) to predict progression free- and overall-survival, and to monitor therapeutic response in patients with stage IV breast cancer. Here, Johns Hopkins (JH) and Cepheid partnered to develop an automated GeneXpert (GX) cartridge-based system to provide quantitative measures of DNA methylation within 5 hours.**METHODS:** With a goal of discriminating stage IV breast cancer from healthy and benign breast disease with high sensitivity and specificity, we evaluated breast cancer-specific DNA methylation markers (selected through comprehensive methylome analysis) in STRECK tube plasma of 46 patients with metastatic breast cancer enrolled in Individualized Molecular Analyses Guide Efforts in Breast Cancer (IMAGE II trial), 17 benign breast disease and 9 healthy normal controls (J0888 repository). Blood from IMAGE II participants was collected upon disease progression. A newly designed GX Breast Cancer Monitoring Assay for research use only (RUO*) first converted unmethylated CpG sites in ctDNA from 1 ml plasma with bisulfite. The sample was then split into two methylation detection cartridges, which quantitated DNA methylation of 9 markers along with an ACTB reference. Cumulative methylation (CM) of the 9-gene panel was calculated using a novel algorithm. Performance was assessed based on Receiver Operating Characteristic (ROC) curves and Mann-Whitney analyses.**RESULTS:** The GX Breast Cancer Monitoring Assay (RUO)* showed that the 9-gene panel was significantly more methylated in cancer compared to normal/benign plasma samples (median for cancer: 428.0 CM units versus for benign: 0.0 CM units; $P< 0.0001$), and revealed a sensitivity of 85% and specificity of 92%, using a cumulative methylation threshold of 35.5 units based on ROC area under the curve (AUC) = 0.909 (95% CI 0.836 – 0.982, $P<0.0001$). We will present comparisons of the GX results to cMethDNA, the gold standard assay, which reported 85-90% sensitivity at 90% specificity.**CONCLUSIONS:** We identified a panel of methylated DNA markers that discriminates stage IV breast from benign breast disease and healthy normal subjects using ctDNA. Our automated cartridge-based assay prototype demonstrates high sensitivity and specificity for detecting invasive breast cancer. Its ability to assess changes in DNA methylation will be tested next with clinical trial samples collected longitudinally during treatment. This assay has potential clinical utility in monitoring therapeutic response and predicting disease recurrence.* *For Research Use Only. Not for use in diagnostic procedures. Not reviewed by any regulatory body.*

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# Ribociclib + letrozole in male patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer (ABC): Subgroup analysis of the phase IIIb CompLEEment-1 trial

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**Background:** While the incidence of breast cancer in men is up to 100-fold less than in women, it is estimated that in 2020, 2,620 men in the United States will be diagnosed with breast cancer, and 520 will die from this disease. However, male patients are rarely included in breast cancer clinical trials and treatment guidelines for this population are often proposed based on data from female patients. Ribociclib (RIB), an oral, selective cyclin-dependent kinase 4/6 inhibitor, is approved for use in combination with endocrine therapy (ET) in women with HR+, HER2- ABC. Here, we present a subgroup analysis of male patients from the Core Phase of CompLEEment-1 (NCT02941926), a Phase IIIb trial of RIB in combination with letrozole (LET) in patients with HR+, HER2- ABC. In order to reflect a more typical real-world clinical setting, the eligibility criteria for this study allowed for a more diverse and broader patient population than those of previous Phase III trials of RIB + LET. **Methods:** CompLEEment-1 included women of any menopausal status and men with HR+, HER2- ABC treated with ≤1 line of prior chemotherapy and no prior hormonal therapy for advanced disease. Pts received RIB (600 mg QD, 3 weeks on/1 week off) in combination with LET (2.5 mg QD, continuous). Men and premenopausal women received a luteinizing hormone-releasing hormone agonist (3.6 mg goserelin or 7.5 mg leuprolide, Q28D). This subgroup analysis assessed the primary outcomes (safety and tolerability) and secondary outcomes of time to progression (TTP), overall response rate (ORR), and clinical benefit rate (CBR) in male patients. **Results:** At the data cutoff date (November 8, 2019), 39 male patients (1.2%; N = 3,246) had been evaluated, with a median duration of exposure to RIB of 19.2 months. Adverse events (AEs) were reported in 38 (97.4%) patients; with all but two experiencing a treatment-related AE. Grade ≥ 3 AEs were reported in 26 (66.7%) patients; serious AEs were reported in 6 patients. There were no treatment-related fatal AEs. The most common all-grade AEs were neutropenia (53.8%), hot flush (33.3%), and diarrhea (25.6%), with the most common grade ≥ 3 AE being neutropenia (41.0%). Overall, 7 patients (17.9%) had ≥ 1 dose reduction of RIB, all of whom had at least 1 due to an AE, and 18 patients (46.2%) permanently discontinued treatment, 4 (10.3%) due to AEs. Median TTP was not estimable (95% CI, 16.8-NE); event-free probability was 61.4% (95% CI, 38.4-77.9) at 30 months. For the 32 patients with measurable disease, ORR was 46.9% (95% CI, 29.1-65.3%) and CBR was 71.9% (95% CI, 53.3-86.3). **Conclusions:** In this subgroup analysis of male patients - a rare population who are often excluded from clinical trials - efficacy results support the use of RIB + LET in HR+, HER2- ABC in a close to real-world setting. The safety profile associated with RIB + LET was manageable, with very few patients discontinuing treatment due to AEs, consistent with previous Phase III trials of RIB + LET.

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# Examining a decade of racial disparity in partial mastectomy and oncoplastic surgery

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BACKGROUND: Breast Conservation Surgery (BCS) includes either partial mastectomy or oncoplastic surgery, of which oncoplastic surgery has become increasingly prevalent. Previous studies have examined BCS rates and post-operative complications, however, no known study has analyzed racial disparity in BCS utilization rates. Understanding racial disparity is crucial to addressing health equality and access to care. Therefore, our study aims to examine racial differences in BCS utilization rates within an 11-year period to determine how these rates have changed over time. METHODS: This retrospective cohort analysis utilized the NSQIP (National Surgical Quality Improvement Program) database to identify women who underwent BCS procedures between 2008-2018. All patients were diagnosed with ductal carcinoma in situ or invasive breast cancer. BCS was further sub-divided into partial mastectomy and oncoplastic surgery. Patient demographics were recorded, and racial utilization trends were analyzed using a Cochran-Armitage test and Index of Disparity analysis, which is a method for summarizing proportional changes within a group's population and its subgroups. RESULTS: In the 11-year period, 180,700 women underwent a breast cancer resection, of which 46% underwent BCS. Within BCS, 92% underwent a partial mastectomy and 8% received oncoplastic procedures. For both BCS subgroups, Caucasian women held the highest sample size (82%), followed by African Americans (12%), and Asian Americans (5%). Within the total sample size, BCS utilization increased from 38% in 2008 to 53% in 2018. Within the BCS subgroup, the proportion of patients having oncoplastics increased from 3.5% in 2008 to 10% in 2018, leading to a declining proportion of partial mastectomies: 96.5% to 90.0% (all $p<0.01$). When stratified by race, oncoplastic utilization between 2008 and 2018 increased from 4% to 10% in Asian and Caucasian patients, and 1% to 10% in African American patients ($p<0.01$). Overall, the racial index of disparity for BCS patients decreased from 17.1% to 9.7%. Interestingly, the index of disparity has remained relatively unchanged for partial mastectomies (1.2% to 0.2%), but significantly decreased in oncoplastics (35% to 1.6%) suggesting an improvement in racial disparities for this surgical option. CONCLUSION: As breast conservation surgery becomes the mainstay for early-staged breast cancer interventions, it is crucial to understand the potential for novel procedures to worsen healthcare inequalities. This study demonstrates promising progress within the field of breast conservation surgery with a decreasing index of disparity among races especially in oncoplastic surgery.

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# Neoadjuvant nab-paclitaxel weekly versus dose-dense paclitaxel followed by dose-dense EC in high risk HR+/HER2- early BC by: Results from the neoadjuvant part of ADAPT HR+/HER2- trial

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**Background:** Pathological complete response (pCR) is associated with improved outcome in patients with high-risk HR+/HER2- breast cancer (BC) but the use of (neo)adjuvant chemotherapy in early HR+/HER2- BC remains controversial. Oncotype DX / Recurrence Score (RS) and dynamic Ki67 response after short preoperative endocrine therapy are potentially predictive for pCR. Still, no prospective data are available so far to predict chemotherapy efficacy in this key patient group. Use of dose-dense chemotherapy is associated with improved outcome in meta-analysis, but its use in the neoadjuvant setting is less studied. Furthermore, use of nab-paclitaxel instead of solvent-based paclitaxel has shown promising results in some studies. Here, we present for the first time data from a randomized prospective trial comparing these risk-selection strategies according to RS and Ki67 decrease in high-risk HR+/HER2- BC. **Methods:** High-risk BC patients [cN0-1 with RS>25 or (RS 12-25 AND (centrally measured) post-endocrine Ki67 >10%] OR [cN2-3 status] OR [G3 AND Ki67>40%] were randomized to (neo)adjuvant 4x paclitaxel$_{175}$ q2w or 8xnab-paclitaxel 125 mg/m$^2$q1w followed by 4x $E_{90}C_{600}$ q2w. pCR was defined as no invasive tumor in breast and lymph nodes. **Results:** 858 patients with available surgery data randomized to neoadjuvant Pac-EC (N=423) or nab-Pac-EC (N=435) were analyzed. Median age was 51 years; median RS was 30 (N=572); 34% had node-positive; 46% (locally) G3 tumors. Baseline characteristics were well balanced between study arms. Patients receiving nab-Pac-EC had higher pCR than those with Pac-EC (20.3% vs. 12.3%, p=.002); patients with RS<25 (about 27%) had a lower pCR rate than those with RS>25 (6.5% vs. 15.8%, p=.003). The association of RS with pCR appeared more pronounced in premenopausal women, but a test of interaction was not significant; RS was about 3 points higher (mean 32.9 vs. 29.8, p<.001) in postmenopausal cases (p=.001). Clinical tumor stage cT2-4 was reported in 65%, with a lower pCR rate than in cT1 tumors (14% vs. 20%, p=.02). RS was moderately correlated (R=.45) with baseline Ki67. In multivariable analysis with tumor stage, RS, Ki67, menopausal status, and ER and PR positivity, higher RS and cT1 stage were favorable for pCR. Excluding RS, higher Ki67 and lower ER (as well as cT1) were favorable. In patients with RS<25, there was no pCR with Pac-EC (0/72 pCR); pCR was almost 20% with RS>25 and nab-Pac-EC. Further details and data including impacts of Ki67 dynamics and additional markers on pCR will be presented at the meeting. **Conclusions:** Use of neoadjuvant nab-paclitaxel instead of solvent-based paclitaxel appears promising within a short (16-weeks) dose-dense chemotherapy schedule in high-risk HR+/HER2- BC. For the first time, data from a large neoadjuvant randomized trial confirm RS could help to select patients for neoadjuvant chemotherapy in high-risk HR+/HER2- breast cancer (BC).

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# Interim safety and efficacy analysis of phase IB / II clinical trial of tucatinib, palbociclib and letrozole in patients with hormone receptor and HER2-positive metastatic breast cancer

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**Background:** In hormone receptor-positive / HER2-positive (HR+/HER2+) breast cancer, the HER2 and estrogen receptor (ER) signals merge on the cyclin D1-CDK4/6-RB1 pathway. Thus, a combined pharmacological intervention with individual drugs targeting HER2, ER and CDK4/6 is warranted. Here, we present the safety and efficacy results of the combination of tucatinib with letrozole and palbociclib in patients (pts) with HR+/HER2+ metastatic breast cancer (MBC) (NCT03054363).

**Methods:** Pts with HR+/HER2+ MBC previously treated with at least 2 HER2-targeted agents were enrolled in this phase IB/II clinical trial. Pts with untreated asymptomatic or stable treated brain metastasis (BM) were included. Pts with treated progressing BM were enrolled after local treatment and classified as treated stable. Treatment consisted of tucatinib 300mg PO BID and letrozole 2.5mg PO daily continuously, and palbociclib 125mg PO daily 21 days on, 7 days off. Due to drug-drug interaction issues found in the middle of the trial and not related to this study, the dose of sensitive CYP3A4 substrate palbociclib was reduced to 75mg for all study participants, as it became evident that tucatinib is a strong CYP3A4 inhibitor. The primary end-points were assessment of safety using CTCAE v.4.03 criteria, and progression free survival (PFS). Secondary end-points included pharmacokinetic evaluation (PKs) and objective response rate by RECIST 1.1. BM response was evaluated using RANO-BM criteria. All pts who received at least one cycle of therapy were assessed for safety.

**Results:** Between 11.21.2017 and 04.20.2020, we enrolled 42 pts of whom 40 were evaluable. Median age was 52.5 years (range, 22 to 82) and the median number of prior lines of therapy for MBC was 2 (range, 0 to 7); 23 pts (58%) had visceral disease and 15 (38%) had BM. All pts had prior therapy with trastuzumab and pertuzumab and 18 pt (45%) had prior T-DM1. As of 06.15.2020 data cut off, 14 patients were on active therapy while 26 were off study (22 due to progressive disease [PD], 1 due to toxicity and 3 for other reasons). Median follow up time was 6 months. The combination was well tolerated with manageable and expected adverse events (AEs). The most common grade ≥3 AEs were neutropenia (25 pts, 60%), leukopenia (10 pts, 24%), diarrhea (8 pts, 19%), fatigue (6 pts, 14%), and infections (6 pts, 14%). One pt came off study due to asymptomatic grade 4 elevated LFTs that resolved without sequelae. There were no deaths due to AEs. Among 26 pts with measurable disease at the time of data cut-off, 8 pts (31%) had partial response, 16 pts (62%) had stable disease (SD) (7 pts [27%] had SD for ≥ 6 months and 6 pts [23%] have not yet reached 6 months of follow up) and 2 pts (8%) had PD. Among 14 patients with BM and evaluable disease by RANO-BM, 1 pt had complete response in the brain, 6 pts had SD in the brain for ≥6 months, and 7 pts had SD for 2-6 months (4 pts on active therapy have not yet reached 6 months of follow up). Median PFS is 8.7 months (10.1 months for pts without BM and 6.0 months for those with BM). Updated analysis including PKs, tumor response, and PFS will be presented.

**Conclusion:** The combination of tucatinib with letrozole and palbociclib showed a tolerable and manageable safety profile and evidence of considerable anti-tumor activity that warrant further clinical investigation in pts with HR+/HER2+ MBC.

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# Assessing the impact of 12 months lifestyle interventions on breast cancer secondary prevention: A modeling approach

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**Background** Healthy lifestyle, including caloric restriction, balanced diet and physical activity, is important in primary and secondary prevention of breast cancer (BC). It is known that Mediterranean diet reduces metabolic syndrome and insulin resistance that are associated with increased risk of BC onset and recurrence. Physical activity decreases BMI, blood concentrations of testosterone, estrogens, insulin, its resistance and strengthens anti-inflammatory pathways against tumor cells. Since January 2014, at our Institution we promoted a project named “Lifestyle Program” for high risk BC patients underwent to primary surgery. Here we presented the results of 12 months of “Lifestyle Program”. **Patients and methods** Since January 2014 we have prospectively enrolled all high risk patients between 18 and 70 years treated to our department for invasive early-stage breast cancer (stage I-III). High risk has been defined by one or more of the following inclusion criteria: body mass index (BMI) > 25, diagnosis of metabolic syndrome, increased level of blood testosterone and/or insulin. All high risk patients receive a periodical personalized educational intervention by a physiatrist for physical activity and by a nutritionist for a mediterranean diet low in animals fat and enriched of fibers, fruits and vegetables. All patients underwent to screening for anxiety and depression through HADS questionnaire scores. All data were analyzed by Chi-square test assuming statistical significance at $p<0.05$. **Results** 98 BC patients were included; 21.4% of them had a metabolic syndrome. Median age was 56 years old (range 27-75). Most of patients enrolled had ER+ (85.7%), Her2/neu negative (79.6%), stage I (48%) BC. We observed a statistically significant reduction of BMI (BMI>25 in 94.9% of pts at baseline vs 63.2% after 12 months of lifestyle; p=<0.0001), glycemic (>110 mg/dl in 23.5% of pts at baseline vs 10.2% at 12 months; p=<0.0001), insulin levels (>27 uU/ml in 20.6% of pts at baseline vs 2.9% after 12 months; p<0.0001), testosterone (>1,2 ng/ml in 17.6% of pts at baseline vs 4.1% at 12 months; p<0.0001), cholesterol (>200 mg/dl in 46.9% of pts at baseline vs 35.7% at 12 months; p<0.0001), triglycerides (>170 mg/dl in 13.3% of pts at baseline vs 10.2% at 12 months; p<0.0001) and arthralgia (37.7% at baseline vs 17.3% at 12 months; p=0.0008). We also noted a significantly reduction of anxiety and depression after 12 months of lifestyle program (25.4% and 12% respectively at diagnosis vs 13.4% and 4.5% at 12 months respectively; p=0,0064 and p<0.0001). **Conclusions** Promoting healthy lifestyle can reduce risk factors involved in BC recurrence and ensure psychological benefit and compliance to endocrine therapy. A multidisciplinary approach allows greater adherence to healthy attitudes in BC high risk patients.

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Prognostic value of clinical treatment score post-5 years (CTS5) and late relapse risk in hormone receptor-positive HER2-positive breast cancer in the North Central Cancer Treatment Group (NCCTG) N9831 (Alliance) and NSABP B-31 (NRG) trials

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**Background:** Although risk of late relapse in hormone receptor-positive (HR+) breast cancer is well established, most existing data pertain to the HR+ HER2-negative (HER2-) subgroup. CTS5 is one of the models for predicting risk of late relapse in HR+ HER2- breast cancer. However, the value of this model in HR+ HER2+ disease is less known, particularly in the context of adjuvant trastuzumab. Here, we evaluated CTS5 in patients with early stage HR+ HER2+ breast cancer treated in the NCCTG N9831 (Alliance for Clinical Trials in Oncology) and NSABP B-31 (NRG) trials. **Methods:** Stage I-III HR+ (ER+ and/or PR+) HER2+ breast cancer patients who were free of recurrence after 5 years in N9831 and B-31 trials were included. The online CTS5 calculator was used to determine CTS5 score and risk group (low, intermediate, and high) based on age, tumor size, grade, and number of involved nodes. Kaplan-Meier (KM) estimates, Cox regression models, and C index were used for analysis. N9831 and B-31 trials were analyzed separately. **Results:** 1,204 patients in N9831 and 658 patients in B-31 met the entry criteria. Baseline characteristics were similar between both trials, including median age, tumor size, and follow up. Similar distribution within CTS5 risk group was observed in both trials; 68.2% and 70.1% patients were high risk, 24% and 21.9% as intermediate risk, as well as 7.8% and 8.1% as low risk classified in N9831 and B-31, respectively. Using univariate Cox regression analysis, CTS5 score as a continuous variable was associated with recurrence-free survival (RFS) in the entire study cohort, including patients who received chemotherapy alone or in combination with trastuzumab, (HR 1.37, 95%CI 1.03-1.81, p=0.03, C index 0.57 in N9831 and HR 1.36, 95%CI 1.06-1.76, p=0.02, C index 0.54 in B-31), but not in patients who received concurrent trastuzumab (HR 1.19, 95%CI 0.73-1.2, p=0.49, C index 0.54 in N9831 and HR 1.35, 95%CI 0.96-1.9, p=0.08, C index 0.54 in B-31). As categorical variable in the entire study cohort, CTS5 risk group was not significantly associated with RFS among patients with intermediate vs. low (HR 0.47, 95%CI 0.18-1.22, p=0.12 and HR 1.61, 95%CI 0.66-3.92, p=0.29) and high vs. low (HR 1.23, 95%CI 0.57-2.67, p=0.6 and HR 1.93, 95%CI 0.85-4.41, p=0.12) with the C index of 0.58 and 0.53 in N9831 and B-31 respectively. There was also no significant difference in RFS among 3 CTS5 risk groups with Kaplan-Meier estimates. Among patients who received concurrent trastuzumab, similar trends were observed with no statistical difference in RFS between high vs. low (HR 0.68, 95%CI 0.24-1.97, p=0.48 and HR 1.44, 95%CI 0.52-3.96, 0.49) with the C index of 0.55 and 0.51 in N9831 and B-31, respectively. Paradoxically, patients with intermediate risk had better RFS than low risk (HR 0.18, 95%CI 0.03-0.97, p=0.05) in N9831 but no significant difference in B-31 (HR 1.31, 95%CI 0.44-3.95, p=0.63). **Conclusions:** While CTS5 score as a continuous variable was associated with outcome in overall HR+ HER2+ population, this model was not prognostic in patients receiving adjuvant trastuzumab in both N9831 and B-31 trials. Furthermore, the correlation (C index) was modest and CTS5 risk group as a categorical variable could not stratify outcome in this group of patients. This study underlines the need to develop a new prognostic model to better delineate the risk of late relapse in HR+ HER2+ breast cancer patients receiving trastuzumab as this model can facilitate clinical decision for extended adjuvant endocrine therapy. **Support:** BCRF-19-161, U10CA180821, U10CA180868 and U10CA180822 (NRG), Genentech. https://acknowledgments.alliancefound.org

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Fertility preservation for breast cancer patients before chemotherapy

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**Background:** Various strategies of fertility preservation for breast cancer patients have been purposed for women at childbearing age. Ovarian stimulation protocols for oocyte/embryo cryopreservation are common means, but are introduced differently and detail regimens vary widely. Protocols for better oocyte cryopreservation outcomes and patients' hormone stability remain to be determined. **Research Objectives and Rationale:** To compare oocyte/embryo cryopreservation outcomes after random-start ovarian stimulations with conventional ones as well as to investigate the effects after double ovarian stimulation cycles, co-administration of aromatase inhibitors or tamoxifen on stabilizing breast cancer patients' estrogen level, the efficiency of oocyte in vitro maturation for fertilization and the impact of patients' genetic background on fertility preservation outcomes. **Methods:** A systematic review followed by a meta-analysis was performed to identify all relevant studies published before June 2020. The primary outcomes were the numbers of retrieved oocytes. The secondary outcomes were the numbers of mature oocytes and peak serum estradiol levels. **Outcomes:** A total of 29 studies met the inclusion criteria. Random-start ovarian stimulations resulted in comparable numbers of retrieved oocytes as conventional protocols did (retrieved oocytes: 503 patients, weighted mean difference [WMD]: -0.01, 95% CI: -2.08 - 2.06, P = 0.99; $I^2$= 0%). Two cycles of ovarian stimulation have significant higher numbers of total retrieved oocytes compared to a single cycle (102 patients, WMD: 7.91, 95% CI: 3.42 -12.40, P = 0.0006; $I^2$= 0%). Both co-administration of letrozole and tamoxifen showed similar results of retrieved oocytes compared to those without (letrozole versus without: 681 patients, WMD: -0.68, 95% CI: -1.96 - 0.61, P = 0.30; $I^2$= 0%) (tamoxifen versus without: 87 patients, WMD: 0.67, 95% CI: -1.29 - 2.64, P = 0.50; $I^2$= 45%). Significant lower peak serum estradiol level was observed in letrozole-based groups compared to letrozole-free groups (301 patients, WMD: -1.05, 95% CI: -1.21 - -0.89, P < 0.00001; $I^2$= 0%). No significant differences were found in peak serum estradiol level between those co-treated with tamoxifen and those without (87 patients, WMD: 0.21, 95% CI: -0.01 - 0.43, P = 0.07; $I^2$= 26%). Regarding breast cancer patients with different BRCA gene background, lower AMH levels were discovered in those with BRCA mutations (831 patients, WMD: -0.63, 95% CI: -1.18 - -0.08, P = 0.03; $I^2$= 47%); however, no significant differences were found in the numbers of retrieved oocytes (retrieved oocytes: 550 patients, WMD: -1.33, 95% CI: -2.72 - 0.05, P = 0.06; $I^2$= 0%). **Wider implications:** We systematically investigated various aspects of ovarian stimulation for oocyte retrieval in breast cancer patients undergoing fertility preservation prior to chemotherapy, our review indicated that (1) random-start controlled ovarian stimulation protocol showed comparable oocyte yields with minimal delays of referral to initiate ovarian stimulation; (2) two ovarian stimulation cycles results in higher numbers of retrieved oocytes while back-to-back and conventional two cycles showed no significant differences; (3) combinations with letrozole demonstrated a safer way over tamoxifen and anastrozole in terms of lowering estradiol level during stimulation processes; (4) in vitro maturation of immature oocytes can maximize the numbers of oocytes for cryopreservation; and (5) regarding patients' genetic backgrounds, those with BRCA mutations have lower AMH levels, but similar in numbers of retrieved oocytes to those without BRCA mutations. Nonetheless, we look forward to higher evidence-level studies to understand the clinical relevance of these protocols for ovarian stimulation in breast cancer patients desiring fertility preservation before chemotherapy.

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Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib

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**Background:** MONALEESA-7 (NCT02278120), the first large randomized phase III clinical trial dedicated to investigating a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) plus ET vs ET + placebo (PBO) in pre- or perimenopausal patients with HR+/HER2− ABC, previously demonstrated a statistically significant improvement in OS with the addition of ribociclib (RIB) to ET vs PBO + ET (median, not reached vs 40.9 months; HR, 0.71 [95% CI, 0.54-0.95]; *P* = .00973; Im SA, et al. *N Engl J Med*. 2019). This concluded the protocol-defined final analysis of OS and the patients and investigators were unblinded to their treatment assignment allowing patients on the PBO arm to cross-over to RIB treatment. Longer follow-up allows for more events to further characterize the long-term survival benefits. Here we report an exploratory update of OS after a minimum of ~ four years of follow-up, an additional 20 months since the last report. **Methods:** Pre- or perimenopausal patients with HR+/HER2− ABC were randomized 1:1 to receive RIB or PBO plus goserelin with either a nonsteroidal aromatase inhibitor (NSAI; letrozole or anastrozole) or tamoxifen. RIB is approved in combination with an NSAI in pre- or perimenopausal patients. Patients who had received a prior CDK4/6i or ET in the advanced setting were excluded. Patients who received ET in the (neo)adjuvant setting or ≤ 1 prior line of chemotherapy for advanced disease were eligible to enroll. Updated OS were evaluated by Cox proportional hazards model and summarized using Kaplan-Meier methods. Additional post-progression endpoints such as progression-free survival 2 (PFS2), time to chemotherapy (CT) and CT-free survival were also evaluated and summarized. **Results:** The data cutoff for this updated OS analysis was 29 June 2020, and the median follow-up was 53.5 mo (min, 46.9 mo). These updated results with extended follow-up demonstrated an OS benefit with RIB + ET vs PBO + ET (median, 58.7 vs 48.0 mo; HR, 0.76 [95% CI, 0.61-0.96]). In patients receiving an NSAI, a similar OS benefit was observed with RIB + NSAI vs PBO + NSAI (median, 58.7 vs 47.7 mo; HR, 0.80 [95% CI, 0.62-1.04]). The survival benefit shown in subgroup analyses was consistent with the intent-to-treat (ITT) population. PFS2, time to chemotherapy (CT), and CT-free survival for the ITT and NSAI populations are in the Table. Among the patients who discontinued study treatment, 77.3% and 78.1% in the RIB + ET vs PBO + ET arms received a subsequent antineoplastic therapy, respectively, and 12.9% and 26.1% received a subsequent line of CDK4/6i. Additionally there were 15 patients in the PBO arm that crossed over to the RIB arm following unblinding and prior to disease progression. **Conclusions:** With an extended follow-up of more than 4 years, RIB + ET continued to demonstrate a clinically relevant OS benefit compared with ET alone in pre- or perimenopausal patients with a median OS ~5 years with RIB +ET in HR+/HER2− ABC. A similar benefit with RIB was observed for PFS2, time to CT, and CT-free survival.

| | **ITT** | | **NSAI cohort** | |
|---|---|---|---|---|
| | RIB + ETn=335 | PBO + ETn=337 | RIB + NSAIn=248 | PBO + NSAIn=247 |
| **PFS2** | | | | |
| Events, n (%) | 177 (52.8) | 221 (65.6) | 131 (52.8) | 159 (64.4) |
| Median, mo | 44.2 | 31.0 | 43.6 | 30.4 |
| HR (95% CI) | 0.68 (0.56-0.83) | | 0.69 (0.55-0.87) | |
| **Time to first CT** | | | | |
| Events, n (%) | 144 (43.0) | 173 (51.3) | 107 (43.1) | 129 (52.2) |
| Median, mo | 50.9 | 36.8 | 50.9 | 36.0 |
| ITT HR(95% CI) | 0.69 (0.56-0.87) | | 0.66 (0.51-0.85) | |
| **CT-free survival** | | | | |
| Events, n (%) | 190 (56.7) | 236 (70.0) | 139 (56.0) | 169 (68.4) |
| Median, mo | 42.4 | 26.4 | 42.5 | 25.9 |
| HR (95% CI) | 0.67 (0.55-0.81) | | 0.64 (0.51-0.81) | |

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# Clinical-grade detection of breast cancer in biopsies and excisions using machine learning

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**Background:** Pathologists reviewing breast tissue slides must identify the presence of many salient features within each slide, including invasive and in situ breast cancer as well as various forms of atypia. In breast pathology particularly, the large volume of slides poses significant challenges for workload management and pathologist productivity (Johnson et al. 2019). The shift to a digital workflow in pathology, augmented by machine learning algorithms, has the potential to increase the efficiency, and productivity of pathologists by identifying cancer and pre-cancerous lesions in digitized slides. While there has been extensive work using machine learning algorithms to detect breast cancer metastasis in lymph nodes (Liu et al. 2018; Steiner et al. 2018), almost no research has been done on using such systems to detect breast cancer in biopsies and excisions.
**Methods**: We created and assessed Paige Breast Alpha, a machine learning system for the detection of breast cancer in hematoxylin and eosin (H&E) stained whole slide images (WSIs) of glass slides. The system is a binary classifier, intended to draw a pathologist's attention to concerning features. Concerning features (the positive category) consisted of invasive breast cancer, in situ breast cancer, and various forms of atypia (atypical ductal hyperplasia, atypical lobular hyperplasia, etc. ). The deep learning system is based on the method proposed in Campanella et al. (2019). It learns directly from diagnosis using multiple instance learning, without the need for pixel-wise annotations. Paige Breast Alpha was trained on 17354 images from 3378 patients, and was assessed on 7921 images from 2443 patients. All slides were scanned on a Leica Aperio AT2.
**Results:** For detecting invasive or in situ cancer at the part level, the system achieved an overall sensitivity of 97.3% and a specificity of 98.0% in biopsies and 96.1% sensitivity and 91.5% specificity in excisions. Each part had between 1—10 slides.
**Conclusions:** We hypothesized that a machine learning system trained to detect predefined types of breast cancer and pre-cancerous lesions could be applied to a range of breast biopsy and resection WSIs to detect for the presence of these lesions. Herein we showed that the presence of these predefined features can be detected with high accuracy. Future studies are being initiated to assess the potential benefits of such a system when used by a pathologist. Additional systems are under development that would have the capability of subtyping the lesion present, in addition to acting as an overall binary classifier.

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# A FOXA1/FRA1-centered transcriptional axis regulates interferon signaling in high FOXA1-associated endocrine-resistant and metastatic breast cancer

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**Background**: Forkhead box A1 (FOXA1) is an essential pioneer transcription factor (TF) evoking other key TFs-mediated lineage-specific transcriptional programs in several endoderm-derived organs. Aberrant FOXA1 augmentation, via genetic alterations, occurs in 10-15% of ER+ primary and metastatic breast cancer (BC). We have recently shown that high levels of FOXA1 (H-FOXA1) induces enhancer and transcriptional reprogramming to promote endocrine-resistant (EndoR) and pro-metastatic phenotypes. Using the core transcriptional regulatory circuitry (CRC) mapping method, we identified the AP-1 TF JUNB as a key CRC component in BC cells expressing H-FOXA1. In this study, we aimed to further characterize key AP-1 components that play a role in mediating H-FOXA1-induced transcriptional reprogramming in EndoR and metastatic BC. **Methods**: The ROSE and HOMER tools were used to identify super-enhancers (SEs) and the predicted SE-harboring TFs in MCF7-parental (P) cells with ectopic FOXA1 overexpression (OE), and in MCF7 tamoxifen-resistant (TamR) cells with endogenous *FOXA1* amplification and OE. Cell growth, migration, and co-immunoprecipitation assays, were performed using ER+ BC P cells with ectopic FRA1 OE. A FOXA1 core gene signature (GS) was deduced using the BETA.plus algorithm to analyze our previously reported RNA-seq and ChIP-seq data derived from MCF7-P cells with ectopic FOXA1 OE. Additional RNA-seq analyses include MCF7-P cells with ectopic FRA1 OE, FOXA1 OE and simultaneous FRA1 siRNA knockdown (KD), and MCF7-TamR cells with FRA1 KD. We identified a FOXA1/FRA1-centered GS and its clinical relevance was examined using expression profiles of TCGA, METABRIC, and a metastatic biopsy study from cohort of patients with ER+ metastatic BC from Dana-Farber Cancer Institute.**Results**: We identified FRA1 as one of the top TFs selectively harboring SEs at their gene loci in MCF7-TamR vs. P cells. Both FRA1 and JUNB expression was elevated in TamR vs. P cells and altered concordantly with FOXA1 in P and TamR cells upon FOXA1 OE or KD, respectively. As we identified JUNB as a CRC component with binding sites enriched at the SEs in BC cells expressing H-FOXA1, we hypothesized that FRA1 and JUNB form a feed-forward transcriptional axis amplifying H-FOXA1-induced enhancer reprogramming. We found that JUNB co-immunoprecipitated with FRA1 in MCF7-TamR and MCF7-P cells with ectopic FRA1 OE, suggesting that FRA1 forms a heterodimer with JUNB to exert AP-1 activity. Ectopic FRA1 OE reduced P cell endocrine sensitivity, increased cell migration, and elicited a transcriptome enriched for the FOXA1-induced core GS. In P cells with ectopic FOXA1 OE, we identified a FRA1-dependent GS ($n$ = 27) that is highly enriched for interferon signaling. This FOXA1/FRA1 GS was highly expressed in luminal B vs. A subtype of primary tumors, further elevated in ER+ metastases, where its expression was positively correlated with FRA1 mRNA levels. Notably, this FOXA1/FRA1 GS was not dependent on FRA1 in P cells without FOXA1 OE, suggesting its relevance in the context of H-FOXA1.**Conclusions**: Here we show that a FOXA1/FRA1-centered transcriptional axis induces an interferon signaling-enriched GS associated with poor outcome of ER+ BC and metastasis. A FRA1/JUNB AP-1 complex may form a feed-forward transcriptional axis to amplify H-FOXA1 signaling. The FOXA1/FRA1-centered GS could be used to stratify patients with ER+ BC who may need additional targeted therapies. Further studies are warranted to elucidate the interplay between FOXA1 and FRA1/JUNB in regulating interferon signaling, which may guide approaches to improve patient outcomes, possibly with immunotherapy using immune checkpoint inhibitors.

**Publication Number:** SS2-03

Patterns of medical behavior in the management of breast cancer during COVID-19. Mexican Experienc

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**Objective**. This survey was conducted with medical oncologists treating breast cancer and explores how the COVID-19 pandemic has impacted their approach to managing breast cancer.**Method.** A questionnaire of ten questions was sent electronically to 123 medical oncologists throughout the Mexican Republic from June 25 to 29, 2020, a critical moment in our patient with the highest reports of new cases of patients with COVID-19.**Results.** Of the respondents, 47.1% work in a public and private hospital, 21.9% and 30.0% exclusively in the public and private respectively. Modification of treatment schemes due to the pandemic is reported in 42.5% (51) and 34.1% (41) occasionally. The dose modification has occurred mainly in the palliative context 71.3%. The modification of intravenous to oral chemotherapy was confirmed in 78.2% of the respondents, but this was in less than 30% of the patients. Only 27.1% of doctors have prolonged their chemotherapy schedules. To the question of postponing visits in patients under surveillance or in adjuvant with endocrine therapy, 80% of the doctors answered confirmatory. Private online consultation has been implemented in 57.8% of doctors. When asked to have patients with breast cancer and a positive test for COVID-19, 37% (43 doctors) confirmed having had patients. Delays in diagnostic protocols for breast cancer were reported in 74.5% (85). Finally 37.7% reported that less than 25% of their patients did not attend their scheduled appointment and 32.4% of the doctors reported that between 25% to 50% of their patients postponed the medical visit. (See images of results).**Conclusion.** In Mexico, like many countries, the treatment and follow-up of patients with breast cancer has been affected by the pandemic, a factor that impacts the results is that in our country we have a shortage of oncological drugs for more than a year, including sometimes cyclophosphamide, anthracyclines and taxanes that are essential for this disease. Management and diagnosis protocols have been delayed since medical care has been prioritized for patients with COVID-19. Unfortunately, there is no national registry of cancer patients, much less the association of cancer with COVID-19. The study, however, reflects similarity of results with other countries in medical behavior.

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# A longitudinal study assessing sexual dysfunction in postmenopausal women with breast cancer undergoing adjuvant treatment

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According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), Female Sexual Dysfunction is defined as a sexual problem associated with personal distress. It can be caused by any of the following: lack of sexual desire, impaired arousal, inability to achieve orgasm, or pain with sexual activity.

Several studies have demonstrated the negative impact chemotherapy has on sexual functioning, short term and long term in women undergoing breast cancer treatment. Most of the research that has been done in this area only evaluated this problem in premenopausal women. The limited studies investigating this in postmenopausal women have found similar effects in this population group.

The goal of this study is to assess sexual dysfunction in high risk postmenopausal women with breast cancer undergoing adjuvant therapy. We want to define this problem in this poorly studied subgroup, and to assess the degree of dysfunction, time course over which it occurs, and the particular sexual domains this occurs in. T

This longitudinal study will assess sexual functioning utilizing two survey tools- the Female Sexual Function Index (FSFI), and the Female Sexual Distress Scale (FSDS-R). The FSFI is a 19- item questionnaire that assesses six domains of sexual functioning: desire, arousal, lubrication, orgasm, satisfaction, and pain The FSFI has been proven to have excellent validity and reliability in determining sexual dysfunction in healthy women, as well as women with various cancers including breast cancer. It was designed to be easy to use, and can be used in heterosexual, as well as homosexual women. To be consistent with the DSM 5's definition of sexual dysfunction regarding personal distress, which is not evaluated in the FSFI, the FSDS-R will be utilized. This is a 13-item questionnaire, which has demonstrated excellent validity and reliability in determining sexual distress associated with sexual dysfunction.

Participants will serve as their own control while assessing any change in sexual functioning over the course of the administration of 2-3 survey sets. The 1st set of surveys will be administered prior to receiving any treatments, this will serve as a baseline assessment for future comparison. The last 1-2 survey sets will be administered 6 months to 1 year after the initiation of adjuvant therapy.

Data will be analyzed with a Repeated Measures ANOVA if statistical assumptions are met. If statistical assumptions are not met the Friedman ANOVA will be used. Post-Hoc testing will be conducted if significant main effects are found.

At this time, 13 patients are currently enrolled in this trial. The number of participants for this study to achieve statistical power was calculated to be n=42. This calculation was based on one treatment group, with three observations across time, a correlation amount of repeated measures of 0.5, and a non-sphericity correction of 1.0. The

assumed effect size was small to moderate with an F=0.20, an alpha of 0.05, and a beta of 0.20.

**Eligibility Criteria for this trial:** •Must be a postmenopausal female •Diagnosed with Stage I, II, or III breast cancer •Not currently receiving endocrine therapy or chemotherapy•Plans with their physician to receive adjuvant therapy

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# Inflammation and coagulation biomarkers associated with physical resilience in older women receiving chemotherapy for early breast cancer

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**Background:** Physical resilience, the ability to resist decline and maintain functional status despite a stressor such as chemotherapy, is a central aspect of successful aging. Understanding clinical and biological factors associated with resilience in older women receiving chemotherapy for early breast cancer may facilitate the development of targeted interventions to maintain an individual's robustness.**Methods:** Women age ≥65 (N=406) with Stage I-III breast cancer who were part of a clinical study of neo/adjuvant chemotherapy in older women were recruited from 16 sites (NCT01472094, R01AG037037). The Deficit Accumulation Index (DAI), a continuous score (0-1) calculated based on 51-items from geriatric assessment data (Cohen et al Cancer 2017), was measured before and after receipt of chemotherapy. DAI was categorized as robust (0.0<0.2), prefrail (0.2<0.35) and frail (≥0.35). Baseline blood biomarkers of inflammation (interleukin-6 [IL-6], C-reactive protein [CRP]) and coagulation (D-dimer) were measured and defined as elevated if values were ≥median values in this cohort. The population of interest was older women who were robust prior to initiation of chemotherapy. The primary outcome was resilience (Yes/No); yes, defined as retaining robustness [DAI 0.0<0.2] before and ≤1 month after chemotherapy. Demographic, disease, and pretreatment variables associated with resilience in univariate analysis with p<0.1 were further adjusted using multivariable logistic regression to examine the associations between baseline biomarkers and resilience. **Results:** Before starting chemotherapy, 324 of 406 (80%) older women were robust. The median age was 70 (range 65-86), 61% had stage II or III disease, 29% had HER2+ disease, 22% had TNBC, 37% received an anthracycline-based regimen, 49% had planned duration of treatment > 12 weeks, and 74% received primary prophylaxis with WBC growth factors. Among these 324 robust older women, 253 (78%) remained robust (resilient) at the end of chemotherapy, 63 (19%) became prefrail, and 8 (3%) became frail. In univariate analyses, patients treated with anthracycline (OR=0.63, p=0.09), planned duration of treatment > 12 weeks (OR=0.56, p=0.04), elevated IL-6 ≥2.7 pg/ml (OR=0.59, p=0.05), elevated CRP ≥4.3 µg/ml (OR=0.57, p=0.04), elevated D-dimer ≥0.7 µg/ml (OR=0.61, p=0.07), or at least one elevated biomarker (OR=0.18, p<0.001) at baseline were less likely to be resilient after systemic chemotherapy. Adjusting for anthracyclines and treatment duration, patients who had one or more elevated biomarker were still significantly less likely to be resilient (OR=0.15, 95 CI 0.04-0.49, p=0.002) compared to those with no elevated biomarkers at baseline.

Table 1. Multivariable associations between baseline blood biomarkers and resilience

| | Resilient (n=253) No. % | Non-resilient (n=71) No. % | Multivariable OR (95%CI) | P value |
|---|---|---|---|---|
| # of elevated biomarkers* | | | | |
| 0 | 64 (25) | 4 (6) | 1.00 | |
| 1 | 90 (36) | 29 (41) | 0.16 (0.05-0.55) | 0.004 |
| 2 | 55 (22) | 22 (31) | 0.14 (0.04-0.49) | 0.002 |
| 3 | 44 (17) | 16 (23) | 0.14 (0.04-0.51) | 0.003 |
| No elevated biomarker | 64 (25) | 4 (6) | 1.00 | |
| At least one elevated | 189 (75) | 67 (94) | 0.15 (0.04-0.49) | 0.002 |

*Biomarkers were defined as elevated using the entire cohort median value as cut off points (IL-6 ≥2.7 pg/ml, CRP ≥4.3 µg/ml, and D-dimer ≥0.7 µg/ml). Combined effects of biomarkers were examined by creating a four-level categorical combination variable: 0=all three biomarkers are <median; 1=one of the biomarkers ≥median; 2=two of the biomarkers ≥median; and, 3=all three biomarkers ≥median. A dichotomized variable was also created comparing none (all three biomarkers are <median) vs at least one biomarker elevated (≥median).

**Conclusions:** In this cohort of older women with early breast cancer who were robust prior to initiation of chemotherapy, 22% became prefrail or frail at end of treatment. Resilience to chemotherapy was related to inflammatory and coagulation biomarkers. Further research is needed to examine the mechanism underlying why some older women are resilient and retain their robustness after receiving treatment, whereas others experience decline, and further explore the role of inflammation/coagulation in this phenomenon.

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# Active surveillance for DCIS: Clinical outcomes at 5.6 years mean follow-up

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**Introduction:**
Standard treatment for ductal carcinoma in situ (DCIS) involves surgical excision with radiation and often endocrine therapy. However, not all DCIS progresses to invasive ductal carcinoma (IDC); thus, surgical intervention may constitute overtreatment for DCIS that has low risk for progressing to IDC. A period of active surveillance (AS) with magnetic resonance imaging (MRI) monitoring may offer the opportunity to stratify lesions with high and low risk for invasion and to avoid overtreatment of DCIS. The purpose of this study was to characterize the outcomes of a cohort of women who elected to go on AS to avoid surgical intervention and to identify whether clinical and imaging features would identify patients who should convert to operative management.

**Methods:**
The clinicopathologic variables and outcomes of patients with DCIS who prospectively enrolled in MRI monitoring studies between 2002 and 2019 were retrospectively analyzed with IRB approval. We included 64 cases among 63 women who declined standard operative management for DCIS and had at least two breast MRIs. Clinicopathologic data and physician recommendations regarding continuing surveillance versus converting to operative management were recorded from the medical record. Those who had surgical excision showing IDC were considered to have progressed; those with only DCIS at excision or no operative intervention were considered to have stable disease.

**Results:**
Women in the cohort were an average of 53.6 years (29.8 - 78.9) old, and nearly all cases of DCIS with estrogen receptor (ER) status were ER+ (98.3%). Of the 64 cases in the cohort, 57 received endocrine therapy (89.1%). Average length of time on AS was 2.7 years (.2 – 11.9) with a median of 3 (2 – 18) MRIs performed and mean follow-up time 5.6 years (0.9 – 15.3).
A total of 31 cases (48.4%) eventually had surgical excision while 33 (51.6%) remained on AS. There were 17 cases with IDC at surgery (26.6%). The IDC was an average of 1.5 cm (0.1 – 9.0) and most commonly ER + (88.2%), HER2 + (53.3%), grade 2 (58.9%), and node negative (82.4%). Only 7 women did not take endocrine therapy, but 3 of those women had IDC (42.9%). In 15 of the 17 cases with IDC (88.2%), the physician noted concern for progression in their clinic note and recommended surgical excision. This occurred a mean of 1.9 years (0.2 – 6.5) from the start of AS, with 47%, 67%, and 87% of cases identified within 1, 2 and 3 years from the start of AS. Suspicion of progression was based on an increase in lesion size or prominence on MRI and/or increase in calcifications on mammography. Of those that were identified as good candidates to continue AS with no concern for progression (n = 49), 16 chose to undergo surgical excision (32.7%) and 2 had IDC (4.1%).

**Conclusion:**
After over a decade of following women who seek alternatives to surgery for DCIS, we have identified clinicopathologic and imaging features that discriminate good candidates for AS and
endocrine risk reducing therapy from those best treated with surgical excision. In our cohort of mostly ER+ patients receiving endocrine therapy on AS, over half of the cohort (51.6%) avoided surgical intervention. Her2 status, Oncotype DCIS, and Mammaprint scores of IDC is in process and will be presented. Our data support the study of AS as a method to stratify the risk of IDC and avoid overtreatment. We will present a personalized AS algorithm (based on biology and imaging) that we intend to prospectively test in the ATHENA network and NCI funded MCL consortium.

**Table 1: Cohort Characteristics**

| | **Full Cohort (n=64)** | **No evidence of IDC (n=47)** | **IDC at surgery (n=17)** |
|---|---|---|---|
| **Age at Diagnosis (years)** | 53.6 (29.8 - 78.9) | 52.9 (29.8 - 74.5) | 55.5 (41.9 - 78.9) |
| **Time on AS (years)** | 2.7 (.2 - 11.9) | 2.8 (.2 - 11.9) | 2.2 (.3 -5.9) |
| **Follow-Up (years)** | 5.6 (0.9 - 15.3) | | |
| **Menopausal Status** | | | |
| Premenopausal | 26 (40.6%) | 22 (46.8%) | 4 (23.5%) |
| Postmenopausal | 35 (54.7%) | 24 (51.1%) | 11 (64.7%) |
| Unknown | 3 (4.7%) | 1 (2.1%) | 2 (11.8%) |
| **Breast Composition** | | | |
| Fatty | 4 (6.3%) | 3 (6.4%) | 1 (5.9%) |
| Scattered | 14 (21.9%) | 9 (19.1%) | 5 (29.4%) |
| Heterogeneous | 27 (42.2%) | 19 (40.4%) | 8 (47.1%) |
| Extreme | 17 (26.5%) | 14 (29.8%) | 3 (17.6%) |
| Unknown | 2 (3.1%) | 2 (4.3%) | 0 (0.0%) |
| **ER Status** | | | |
| Positive | 57 (89.1%) | 41 (87.2%) | 16 (94.1%) |
| Negative | 1 (1.6%) | 0 (0.0%) | 1 (5.9%) |
| Unknown | 6 (9.3%) | 6 (12.8%) | 0 (0.0%) |
| **PR Status** | | | |
| Positive | 50 (78.1%) | 36 (76.6%) | 14 (82.3%) |
| Negative | 5 (7.8%) | 3 (6.4%) | 2 (11.8%) |
| Unknown | 9 (14.1%) | 8 (17.0%) | 1 (5.9%) |
| **Grade** | | | |
| High | 20 (31.3%) | 15 (31.8%) | 5 (29.4%) |
| Intermediate | 32 (50.0%) | 21 (44.6%) | 11 (64.7%) |
| Low | 10 (15.6%) | 9 (19.1%) | 1 (5.9%) |
| Unknown | 2 (3.1%) | 2 (28.5%) | 0 (0.0% |
| **Hormone Therapy** | | | |
| Yes | 57 (89.1%) | 43 (91.5%) | 14 (82.4%) |
| No | 7 (10.9%) | 4 (8.5%) | 3 (17.6%) |

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Safety and efficacy of veliparib plus carboplatin/paclitaxel in patients with HER2-negative metastatic or locally advanced breast cancer: A subgroup analysis of germline *BRCA1* or *BRCA2* mutations from the phase 3 BROCADE3 trial

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**Background:** Veliparib (Vel) is a potent PARP1/2 inhibitor with demonstrated antitumor activity when administered alone or combined with carboplatin and paclitaxel (C/P). The phase 3 randomized, double-blind, multicenter BROCADE3 study (NCT02163694) evaluated the efficacy and safety of Vel + C/P treatment compared with placebo (Pbo) + C/P treatment in patients (pts) with germline *BRCA1/2* mutations and HER2-negative metastatic or locally advanced breast cancer (BC). Vel + C/P significantly prolonged progression-free survival (PFS) compared with Pbo + C/P treatment (14.5 months [mo] vs 12.6 mo, hazard ratio [HR]=0.71 [95% CI: 0.57, 0.88]; *P*=0.002). Previous studies have identified increased acute hematologic toxicity in response to chemotherapy in pts with BC carrying *BRCA1* mutations compared with *BRCA2* mutations or wildtype *BRCA1/2*. Herein we report a subgroup analysis of the efficacy and safety of Vel + C/P treatment in pts with *BRCA1*- or *BRCA2*-positive BC.
**Methods:** Pts ≥18 years of age who received ≤2 prior lines of cytotoxic chemotherapy for metastatic disease were randomized 2:1 to receive Vel + C/P or Pbo + C/P: Vel (120 mg PO BID) or Pbo on days -2 to 5, C (AUC 6 IV) on day 1, and P (80 mg/m$^2$ IV) on days 1, 8, and 15 in 21-day cycles. Pts who discontinued C/P in the absence of disease progression could continue receiving Vel or Pbo monotherapy (300-400 mg BID continuous). Subgroup analysis of PFS stratified by *BRCA1/2* status was preplanned. The primary endpoint was investigator-assessed PFS. Adverse events (AEs) were graded according to NCI CTCAE version 4.0. Ten pts with both *BRCA1* and *BRCA2* mutations were excluded from the analyses presented here.
**Results:** In the intent-to-treat population, 256 pts had *BRCA1* mutations and 243 pts had *BRCA2* mutations. The proportion of as-treated pts with *BRCA1* or *BRCA2* mutations was comparable between the Vel + C/P (51.4% *BRCA1*, 48.6% *BRCA2*) and Pbo + C/P (50.9% *BRCA1*, 49.1% *BRCA2*) study arms. Investigator-assessed PFS for the Vel + C/P and Pbo + C/P arms was 14.2 mo vs 12.6 mo, respectively, in the *BRCA1* subgroup (HR=0.75 [95% CI: 0.55, 1.03]; *P*=0.073) and 14.6 mo vs 12.6 mo, respectively, in the *BRCA2* subgroup (HR=0.69 [95% CI: 0.50, 0.95]; *P*=0.021). Safety data in the as-treated population are presented in the **Table**. Regarding any grade AEs, thrombocytopenia and anemia were slightly more frequent in pts in the *BRCA1* subgroup compared with the *BRCA2* subgroup, whereas pts in the *BRCA2* subgroup experienced slightly more frequent nausea, fatigue, and neuropathy.

| | ***BRCA1*-Positive Subgroup (n=253)** | | ***BRCA2*-Positive Subgroup (n=241)** | |
|---|---|---|---|---|
| | **Vel + C/P (n=168)** | **Pbo + C/P (n=85)** | **Vel + C/P (n=159)** | **Pbo + C/P (n=82)** |
| **Any grade AE [≥50% of pts], n (%)** | | | | |
| Any event | 167 (99.4) | 85 (100) | 158 (99.4) | 82 (100) |
| Neutropenia | 151 (89.9) | 78 (91.8) | 140 (88.1) | 74 (90.2) |
| Thrombocytopenia | 140 (83.3) | 66 (77.6) | 124 (78.0) | 54 (65.9) |
| Anemia | 139 (82.7) | 64 (75.3) | 122 (76.7) | 52 (63.4) |
| Nausea | 118 (70.2) | 49 (57.6) | 119 (74.8) | 58 (70.7) |
| Alopecia | 89 (53.0) | 43 (50.6) | 89 (56.0) | 41 (50.0) |
| Fatigue | 79 (47.0) | 37 (43.5) | 87 (54.7) | 48 (58.5) |
| Peripheral sensory neuropathy | 69 (41.1) | 37 (43.5) | 82 (51.6) | 49 (59.8) |
| **Any grade ≥3 AE [≥30% of pts], n (%)** | | | | |
| Any event | 164 (97.6) | 82 (96.5) | 152 (95.6) | 77 (93.9) |
| Anemia | 73 (43.5) | 31 (36.5) | 67 (42.1) | 35 (42.7) |
| Leukopenia | 54 (32.1) | 20 (23.5) | 44 (27.7) | 25 (30.5) |
| Neutropenia | 136 (81.0) | 72 (84.7) | 131 (82.4) | 67 (81.7) |
| Thrombocytopenia | 72 (42.9) | 30 (35.3) | 59 (37.1) | 18 (22.0) |
| **Serious AEs, n (%)** | 58 (34.5) | 26 (30.6) | 56 (35.2) | 22 (26.8) |
| **AEs of special interest, n (%)** | | | | |
| Infections within 14 days of neutropenia | 64 (38.1) | 34 (40.0) | 59 (37.1) | 25 (30.5) |
| Hemorrhages within 14 days of thrombocytopenia | 14 (8.3) | 5 (5.9) | 17 (10.7) | 7 (8.5) |
| **Any AE leading to study drug discontinuation not due to disease progression, n (%)** | 16 (9.5) | 5 (5.9) | 15 (9.4) | 4 (4.9) |
| **Any AE leading to study drug interruption, n (%)** | 153 (91.1) | 77 (90.6) | 139 (87.4) | 67 (81.7) |
| **Any AE leading to study drug reduction, n (%)** | 28 (16.7) | 6 (7.1) | 27 (17.0) | 7 (8.5) |
| **Any AE leading to death with reasonable possibility related to study drug, n (%)** | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

AE, adverse event; *BRCA*, breast cancer susceptibility gene; C/P, carboplatin plus paclitaxel; Pbo, placebo; pts, patients; Vel, veliparib.

**Conclusions:** Globally, there was no clinically relevant difference in toxicity between *BRCA1* and *BRCA2* subgroups. Comparisons between treatment arms were generally consistent with findings in the overall study population, with more frequent thrombocytopenia and anemia of any grade reported in the Vel + C/P arm within both the *BRCA1* and *BRCA2* subgroups. Vel + C/P treatment improved PFS similarly in both *BRCA1* and *BRCA2* subgroups over C/P alone.

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Changes in body mass index (BMI) over the life course are associated with gene expression in postmenopausal women

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**Introduction**: Changes in body mass index (BMI) over the life course are associated with both mammographic breast density and breast cancer risk in postmenopausal women. The underlying biological mechanisms driving these associations are, however, yet to be elucidated. Understanding these mechanisms could provide important insights into breast cancer prevention early in life. To provide insight into the biological mechanisms underlying the associations of BMI change over the life course and breast cancer risk in postmenopausal women, we comprehensively investigated the associations of BMI change from ages 10 and 18 to current age with gene expression of biomarkers that have previously been associated with breast cancer risk: growth factors (IGF1, IGFBP3, FGF1, FGF12, TGFB1), sex hormones (PRL, PGR, ESR1, STAT1, STAT5), and receptor activator of nuclear factor-κB (RANK) pathway (RANK, RANKL, OPG, BMP2, TNFRSF13B, TNFRSF18) gene expression in postmenopausal women. **Methods**: We investigated these in 372 postmenopausal women free from breast cancer recruited during annual screening mammogram. We estimated BMI at age 10 using a validated 9-level pictogram. Gene expression levels were measured using NanoString nCounter system. We investigated the associations of BMI change with gene expression in multivariable linear regression models, adjusted for confounders. **Results**: The mean age of study participants was 58 years. Increase in BMI over the life course was associated with an increase in BMP2 gene expression but a decrease in RANK, RANKL, and TNFRSF13B gene expression. Compared to women who had a BMI gain of 0.1-5 kg/m$^2$ from age 10, BMP2 gene expression increased in women who had a BMI gain of 5.1-10 kg/m$^2$ (beta coefficient [β] = 0.48, 95% confidence interval [95% CI] = 0.04 to 0.92); BMI gain of 10.1-15 kg/m$^2$ (β = 0.47, 95% CI = 0.03 to 0.91); and BMI gain of > 15 kg/m$^2$ (β = 0.58, 95% CI = 0.15 to 1.02) (p-trend = 0.04). Similar results were observed for BMI gains from age 18 (p-trend < 0.01). Compared to women who had a BMI gain of 0.1-5 kg/m$^2$ from age 10, RANK gene expression decreased in women who had a BMI gain of 5.1-10 kg/m$^2$ (β = -0.21, 95% CI= -0.51 to 0.09); BMI gain of 10.1-15 kg/m$^2$ (β = -0.29, 95% CI= -0.59 to 0.00); and BMI gain of >15 kg/m$^2$ (β = -0.37, 95% CI= -0.66 to -0.07) (p-trend < 0.01). Similar results were observed for weight gains from age 10 and RANKL and TNFRSF13B gene expression, although the associations were weaker for RANKL gene expression. Changes in BMI over the life course were not associated with OPG, growth factors or sex hormone gene expression. **Conclusions**: Changes in BMI from childhood, late adolescence, and early adulthood were associated with RANK pathway gene expression in postmenopausal women. Our findings offer important and innovative new insights into how childhood adiposity may confer long-term protection against breast cancer risk in postmenopausal women.

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# Breast complications in patients who received intraoperative radiation therapy compared to other forms of radiation therapy following breast conserving surgery

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**Introduction:** Intraoperative radiation therapy (IORT) is a convenient treatment option for appropriate women with early stage breast cancer. Some patients undergoing IORT also need adjuvant whole breast radiation therapy due to adverse final pathologic features. Although there are various reports of the complication rates with patients undergoing IORT, comparisons with patients undergoing other forms of radiation therapy such as whole breast or accelerated partial breast radiation are sparse. **Methods:** A total of 293 patients underwent breast conserving surgery at the study institution between January 2016 and December 2019 for either ductal carcinoma in situ (DCIS) or invasive breast cancer. Three patients had bilateral breast cancer and one patient had a local recurrence having refused adjuvant treatment following breast conserving surgery, for a total of 297 treated breasts. 124 received whole breast radiation therapy, 70 did not receive radiation therapy, 47 received IORT alone, 15 received IORT and whole breast radiation therapy, 30 received accelerated partial breast radiation using external beam radiation (APBI-EB), and 9 received Ir-192 based high dose rate accelerated partial breast radiation (APBI-HDR). One patient with bilateral breast cancer did not complete whole breast radiation therapy to either breast. Complications included cellulitis, wound drainage, symptomatic seroma, delayed wound healing, and wet desquamation. Interventions included observation, antibiotics, wound packing, debridement, fluid aspiration, hydrogel dressings, and wound vacuums. **Results:** For the entire group, the incidence of wound complications was 20%. The risk of complications was 27.4% for those undergoing IORT (with or without whole breast radiation) compared to 18.3% for those not receiving IORT, which was not statistically different at the 5% significance level. For those who received both IORT and whole breast radiation, however, the proportion having complication was 53.3% versus 18.4% in the other groups. The difference was significant with a p-value 0.0032. **Conclusion:** Patients who undergo both IORT and whole breast radiation have an increased risk for wound complications.

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# Continued efficacy of neratinib in patients with HER2-positive early-stage breast cancer: Final overall survival analysis from the randomized phase 3 ExteNET trial

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**Background:** Neratinib (NERLYNX®) is an irreversible pan-HER inhibitor that significantly improves invasive disease-free survival (iDFS) compared with placebo when given as extended adjuvant therapy in patients with HER2-positive (HER2+) early breast cancer after trastuzumab-based adjuvant therapy. In the phase 3 ExteNET trial, an absolute iDFS benefit of 2.5% and distant disease-free survival (DDFS) benefit of 1.7% were observed with neratinib after 5 years' follow-up. As reflected in the approved indication by the European Medicines Agency (EMA), patients with hormone receptor-positive (HR+) disease who initiated neratinib treatment within 1 year of completing trastuzumab (HR+/≤1 year) experienced an absolute iDFS benefit of 5.1% and DDFS benefit of 4.7% at 5 years. In HR+/≤1 year patients with residual disease after neoadjuvant therapy, absolute 5-year iDFS and DDFS benefits of 7.4% and 7.0%, respectively, were observed. Here we report the final protocol-defined, event-driven analysis of overall survival (OS) from ExteNET, and provide descriptive analyses of subgroups of primary interest according to the EU label and current clinical practice in early-stage HER2+ disease.
**Methods:** ExteNET was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial of women with early-stage HER2+ breast cancer who had completed neoadjuvant or adjuvant trastuzumab plus chemotherapy (NCT00878709). Patients were randomly assigned to oral neratinib 240 mg/day or placebo for 1 year. Hazard ratios (HR) for OS were estimated from Cox proportional hazards models, and survival rates by the Kaplan-Meier method. The OS analysis was event-driven and powered for the intention-to-treat (ITT) population with a target of 248 events. Descriptive analyses were performed in the HR+/≤1 year subgroup per the approved indication in the EU, and in higher-risk patients, i.e. HR+/≤1 year who have residual disease after neoadjuvant therapy [i.e. those who did not achieve a pathologic complete response (pCR)]. Cut-off date: July 2019.
**Results:** 2840 patients were randomized to study treatment (1420 per group). After a median follow-up of 8.1 years, 127 (8.9%) and 137 (9.6%) patients in the neratinib and placebo ITT groups had died, respectively. The 8-year OS rates were 90.1% (95% CI, 88.3–91.6) in the neratinib group and 90.2% (95% CI, 88.4–91.7) in the placebo group (absolute difference at 8 years -0.1%; stratified HR=0.95; 95% CI, 0.75–1.21; p=0.6914). A positive trend was seen in the prespecified HR+ subgroup (n=1631; absolute difference at 8 years 1.5%; HR=0.80; 95% CI, 0.58–1.12), and within this population, descriptive analyses suggested greater benefits with neratinib in the HR+/≤1 year subgroup (n=1334; absolute difference at 8 years 2.1%; HR=0.79; 95% CI, 0.55–1.13) and in the HR+/≤1 year subset with no pCR after neoadjuvant therapy (n=295; absolute difference at 8 years 9.1%; HR=0.47; 95% CI, 0.23–0.92). No new safety signals were reported with this long-term follow-up to 8 years.
**Conclusions:** In this final OS analysis of ExteNET, there were fewer deaths with neratinib than placebo in the ITT population, but the results did not reach statistical significance. Analyses showed greater OS improvements with neratinib in subgroups including HR+/≤1 year, and HR+/≤1 year with residual disease after neoadjuvant therapy. These findings are consistent with the results based on the primary endpoint of iDFS, and support the use of neratinib in clinical practice in these patients.

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# Can genomic profiling eliminate the need for SLNB in ER positive, T1-2 breast cancer?

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Background: As tumor biology has taken precedence over anatomic staging, NCCN guidelines now allow for genomic profiling to make adjuvant treatment recommendations for Nmi-N1 breast cancer (BC). This makes nodal status, determined by sentinel lymph node biopsy (SLNB), less influential. Although generally safe, SLNB adds an incision, operative time, monetary costs, and carries risks of chronic paresthesia (9%) or lymphedema (2-6%). We hypothesized that, if ultrasound (US) excludes occult nodal metastasis and genomic profiling is used in making chemotherapy recommendations for N0-N1 disease, SLNB will be the sole indicator of a need for chemotherapy in <5% of patients.
Methods: This was a retrospective data and tissue analysis of patients treated at our breast center (11/2011 – 12/2015). Postmenopausal women with ER positive, HER2 negative, pT1-2 BC with non-suspicious axillary US who underwent SLNB without preoperative chemotherapy were included. For each patient, we compared recommended adjuvant therapy (per NCCN guidelines) based on SLNB results, versus the recommendation had SLNB been negative. For N0-N1 cases, we used Oncotype DX Breast Recurrence Score® test to determine chemotherapy. For Nmi-N1 cases, chemotherapy was considered for Recurrence Score® (RS) 18-25 and recommended for RS > 25. When not in the electronic medical record (EMR), RS result was obtained from stored specimens, with patient consent. Patients without a RS result were excluded from the chemotherapy outcomes analysis.
Results: Of 217 included patients, nodal status was as follows: N0, n=184 (85%); Nmi-N1, n=29 (13%); N2-3, n=4 (2%). Therefore, in 85% of patients SLNB did not influence any adjuvant treatment recommendation. In 4.1% of patients, SLNB resulted in a recommendation for axillary lymph node dissection (Table). In 15.2% of patients (n=33), SLNB resulted in a consideration (13.4%) or recommendation for (1.8%) nodal irradiation. RS result was available in 147 patients (68% of cohort). However, only 8 of those with unknown RS result (4% of cohort) were node-positive; for node-negative patients, RS would not affect any study outcome (change in treatment based on SLNB). Among patients with RS result, based on actual SLNB result, chemotherapy was recommended or considered in 30 patients. In 23 of these, chemotherapy would have been recommended regardless of SLNB result based on RS > 25. Therefore, SLNB made a difference in whether to recommend or consider chemotherapy in 4.7% of patients (7/147).
Conclusions: SLNB changed the recommendation whether to receive chemotherapy (no to yes, or no to consider) in only 4.7% of patients. More often, SLNB influenced the chemotherapy regimen recommended (2nd vs. 3rd generation), or local therapy recommendations. With increasing role for genomic profiling, the role of SLNB in determining adjuvant therapy is diminishing. When chemotherapy would not be considered, omission of SLNB may be considered in postmenopausal patients with ER positive, T1-2 BC and negative axillary US. If genomic profiling were performed prior to surgery, the results could change surgical management. In women with RS 0-11, SLNB is highly unlikely to alter the recommendation against chemotherapy. In women with RS > 25, chemotherapy is recommended regardless of SLN status, but a positive SLN would affect the regimen recommended. SLNB is most influential in patients with RS 18-25. Use of genomic profiling preoperatively to tailor whether SLNB is performed should be prospectively validated.

Table. Comparison of adjuvant treatment recommendations based on SLNB result vs. presumed negative SLNB

| | Based on presumed negative SLNB | Based on actual SLNB result | % for whom SLNB would change treatment recommendation[8] |
|---|---|---|---|
| Axillary lymph node dissection recommended[1] | 0 | 9 | 4.1% (9/217) |
| Nodal irradiation recommended[2] | 0 | 4 | 1.8% (4/217) |
| Nodal irradiation considered[3] | 0 | 29 | 13.4% (29/217) |
| Chemotherapy recommended[4] | 23 | 24 | 0.6% (1/147) |
| Chemotherapy considered[5] | 0 | 6 | 4.1% (6/147) |
| Third-generation chemotherapy recommended[6] | 0 | 6 | 4.1% (6/147) |
| Third-generation chemotherapy considered[7] | 0 | 6 | 4.1% (6/147) |

1)For >2 positive SLN, or gross extranodal extension (ENE). Since surgeon determination of gross ENE was not consistently available, > 2 mm of ENE on pathology was used to defined “gross” extension. 2)For N2-3 disease 3)For Nmi-N1 disease 4)For RS > 25, or N2-3 5)For Nmi-N1 disease, with RS 18-25 6)For Nmi-N1 disease with RS > 25; or N2-3; this group is a subset of those for whom chemotherapy would be recommended 7)For Nmi-N1 disease with RS 18-25; this group is a subset of those for whom chemotherapy would be recommended 8)Patients without Recurrence Score result were excluded from analysis of chemotherapy outcomes; fractions are included to show the denominator used for each calculation.

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# Utility of rapid- immunohistochemistry using an alternating current electric field for intraoperative diagnosis of sentinel lymph nodes in breast cancer

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Axillary lymph node status and pathological diagnosis of sentinel lymph nodes (SLNs) is an important factor that influences management of postoperative therapy. Recent reports indicate that one-step nucleic acid amplification (OSNA) and hematoxylin and eosin (HE)-stained frozen sections are effective for intraoperative diagnosis of SLNs. In the present study, we report a rapid-immunohistochemical staining (R-IHC) method that enables intraoperative detection of SLN metastases within 16 min using an anti-cytokeratin antibody. With this R-IHC system, we apply a high-voltage, low-frequency AC electric field to lymph node sections while they are incubating with the antibodies. The antibodies are mixed within microdroplets and the opportunity for contact between the antibody and antigen is increased. This greatly reduces the time required for the antigen-antibody reaction. This is the report on SLN diagnosis using R-IHC in patients with breast cancer. We prospectively examined 632 dissected SLNs from 260 breast cancer patients who underwent surgery at our institute between July 2014 and March 2020. The dissected SLNs were sectioned and conventionally stained with HE or immunohistochemically labeled with anti-cytokeratin antibody using R-IHC procedures. Intraoperative R-IHC analyses were completed within 16 min, after which diagnoses were made by two pathologists. The total time required for intraoperative diagnosis was about 20 min. In this study, R-IHC detected four metastatic SLNs that were undetected using conventional HE staining (10/52, 19.2%). Compared with subsequent permanent diagnosis, R-IHC offered 98.0% sensitivity, 100% specificity and 99.8% accuracy while those values for intraoperative HE were 80.4%, 100%, 98.4%, respectively (isolated tumor cells were counted as negative). These findings indicate R-IHC is a clinically applicable technique that enables precise, and quick intraoperative detection of micro- and macrometastases in breast cancer. Moreover, R-IHC is cost-effective method: it's cost is less than a quarter of OSNA and previous report showed that the concentration of primary antibody could be reduced by more than 90% by using R-IHC because AC mixing activated antigen-antibody reaction. Another benefit is its ability to shorten the time needed for microscopic diagnosis itself. When using R-IHC, pathologists are able to readily find metastatic lesions, even within low-power fields (e.g. 40x). This reduces not only the time needed for intraoperative diagnosis, but also the effort necessary to find unclear lesions like small cancer cells (even though it is macrometastasis), micrometastasis, and artifacts of frozen section. This study was conducted at a single institute. Further investigation in a multi-institutional collaborative prospective study will be needed to confirm the utility of this method. But for now, R-IHC appears to be a cost-effective and clinically applicable method for diagnosis of breast cancer and SLN metastasis.

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# Estrogen receptor (ER) and NFkB activity determines cancer stem cell properties in ER positive breast cancer

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Approximately 50% of estrogen receptor (ER) positive breast cancer patients will experience relapse. One explanation for this is the presence of breast cancer stem cells (BCSCs), which have self-renewal capability and can contribute to therapy resistance, metastasis, and relapse. Previously, we have shown that cells with active ER and NFκB gain stem cell properties. They are characterized by higher mammosphere (MS) forming efficiency and increased expression of stem-associated markers. NFκB has been previously described as a player in BCSC biology. However, the role of ER remains unclear since some studies have suggested that BCSCs are ER negative. In order to study the role of ER and NFκB in BCSCs in more detail, we utilized single cell RNA sequencing of MS. Dimensionality reduction of single cells identified 4 clusters with unique transcriptional signatures. In order to determine which cluster of these 4 represents BCSCs, we ran functional enrichment analysis (FEA) using MsigDB as a source of various stem cell signatures. Results of FEA showed 1 of 9 stem cell signatures enriched in Cluster 0. Whereas clusters 1, 2 and 3 demonstrated increasing enrichment of different stem cell signatures, respectively. Further analysis of stem cell signatures and genes revealed that cluster 1 included not only classical stem markers (ALDH1A3, KRT8, CD36), but also was enriched for PI3K and p53 signaling pathways. The cluster 2 stem cell signature was associated with DREAM complex activity and BRCA1 mutation. Cluster 3 was enriched for expression of NANOG and SOX2 targets. We also ran FEA to determine ER and NFκB activity in each population. Cluster 0 showed no activity of either ER or NFκB, whereas Cluster 1 was enriched for both, cluster 2 was enriched for ER only, and cluster 3 was enriched for NFκB only. Taken together this data suggests that ER and NFκB may play different roles in promoting BCSC properties. In order to determine how both pathways effect BCSC features, we made a dual reporter cell line expressing ERE-mCherry and NFκB-RE-GFP. It was found ERE activity was constant throughout MS formation, whereas NFκB-RE activity increased proportionally to MS growth over time, suggesting these pathways have different dynamics and further supporting unique roles for each in MS development. To determine which cell population has the capacity to seed MS, an indication of stemness, we sorted cells by reporter activity and tested MS forming efficiency. We discovered that ERE+ cells, either with or without NFκB activity, are more stem-like, whereas activation of NFκB alone is not sufficient to drive MS development. This finding was verified by stem cell-associated gene expression. These data suggest that ER activity is a key driver for BCSC properties and that NFκB may play a supporting role. Furthermore, a novel mechanism of ER regulating the DREAM complex, which is known to be involved in cancer progression and used to evaluate the risk of recurrence in breast cancer, is suggested as a potential ER-mediated mechanism for driving BCSCs. Taken together, our findings suggest novel roles for ER and NFκB in BCSC biology, which could be exploited to target BCSCs therapeutically in ER+ breast cancer patients in order to improve their outcome.

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Contribution of tumor and immune cells to PD-L1 as a predictive biomarker in triple-negative breast cancer (TNBC): Analysis from KEYNOTE-119

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**Background:** Pembrolizumab monotherapy did not significantly improve overall survival (OS) as second- or third-line treatment for metastatic TNBC vs chemotherapy in the randomized, open-label, phase 3 KEYNOTE-119 study (NCT02555657; N = 622). However, the benefit of pembrolizumab compared with chemotherapy appeared to be greater with increasing PD-L1 expression as quantified by combined positive score (CPS; defined as the number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). In the current exploratory analysis, we aimed to determine whether expression of PD-L1 on tumor cells contributes to the value of PD-L1 as a predictive biomarker in metastatic TNBC.**Methods:** Patients with centrally confirmed TNBC and 1 or 2 prior systemic treatments for metastatic disease were enrolled in KEYNOTE-119. Patients were randomly assigned 1:1 to pembrolizumab 200 mg Q3W or investigator's choice of single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). PD-L1 expression in tumor samples was assessed using PD-L1 IHC 22C3 pharmDx and quantified per tumor proportion score (TPS; defined as the percentage of PD-L1–expressing tumor cells [partial or complete membrane staining] relative to total number of tumor cells) and CPS. Quantitative immune cell density (QID) was defined as CPS minus TPS. QID isolates immune cells but may be truncated when TPS is high. The ability of each scoring method (TPS, CPS, and QID) to predict objective response rate (ORR) with pembrolizumab, including receiver operating characteristics (ROC) analysis, and OS hazard ratios (HRs; pembrolizumab vs chemotherapy) was evaluated.**Results:** Tumor samples were available for 601 patients (pembrolizumab, 309; chemotherapy, 292) in KEYNOTE-119. ORR was 9.7% (30/309) with pembrolizumab and 11.3% (33/292) with chemotherapy when PD-L1 expression status was not considered. In the pembrolizumab arm, the area under the ROC curve (AUROC; 95% CI) was 0.69 (0.58-0.80) for tumor samples scored for CPS, 0.66 (0.55-0.77) for QID, and 0.55 (0.46-0.64) for TPS. ROC analysis is shown in the **Table**. At each cutoff, QID had lower estimated sensitivity (ie, missed responders) and a lower Youden Index compared with CPS. The number of missed responders (of 30 total in the pembrolizumab arm) for QID relative to CPS were 2, 5, 5, 6, 2, and 2 at cutoffs of 1, 10, 20, 30, 40, and 50, respectively. Across all practical cutoffs, the OS HR tended to be slightly smaller for CPS than QID. At cutoffs corresponding to the upper percentiles of 10, 20, 40, and 60, OS HRs were 0.497, 0.658, 0.758, and 0.850, respectively, for CPS vs 0.572, 0.712, 0.814, and 0.863, respectively, for QID. QID appeared to be orthogonal to TPS (r = -0.03 for all 601 observations; r = -0.04 after eliminating 7 potentially truncated values).**Conclusions:** Trends estimated using KN119 suggest that tumor cell expression is an important component of PD-L1 as a predictive biomarker of pembrolizumab efficacy in metastatic TNBC. In this exploratory analysis, when immune cells alone were used to measure PD-L1 expression, a meaningful number of responders was missed and OS benefit trended toward higher HR estimates. Tumor and immune cell PD-L1 expression may represent distinct (presumably negative modulatory) mechanisms.

Table. ROC Analysis

| Cutoff | CPS Sens | CPS Spec | CPS YI | CPS Prev | QID Sens | QID Spec | QID YI | QID Prev | TPS Sens | TPS Spec | TPS YI | TPS Prev |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| 1 | 0.833 | 0.366 | 0.199 | 0.654 | 0.767 | 0.416 | 0.182 | 0.602 | 0.300 | 0.789 | 0.089 | 0.220 |
| 10 | 0.567 | 0.717 | 0.284 | 0.311 | 0.400 | 0.814 | 0.214 | 0.207 | 0.200 | 0.892 | 0.092 | 0.117 |
| 20 | 0.500 | 0.849 | 0.349 | 0.184 | 0.333 | 0.925 | 0.258 | 0.100 | 0.167 | 0.932 | 0.099 | 0.078 |
| 30 | 0.367 | 0.892 | 0.259 | 0.133 | 0.167 | 0.957 | 0.124 | 0.055 | 0.100 | 0.943 | 0.043 | 0.061 |
| 40 | 0.200 | 0.935 | 0.135 | 0.078 | 0.133 | 0.986 | 0.119 | 0.026 | 0.067 | 0.953 | 0.020 | 0.049 |
| 50 | 0.200 | 0.957 | 0.157 | 0.058 | 0.133 | 0.993 | 0.126 | 0.019 | 0.067 | 0.968 | 0.034 | 0.036 |

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# Tucatinib favourably modulates the immune microenvironment and synergises with anti-PD1 therapy in a trastuzumab resistant HER2+ murine model

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**Background**: The efficacy of PD-(L)1 inhibitors in patients with trastuzumab-resistant advanced HER2$^+$ breast cancer is poor. Although many HER2 targeted therapies are used clinically, their effect on the tumor immune microenvironment (TME) and whether this contributes to efficacy is not understood. Tucatinib is a potent, highly selective, HER2 small molecule tyrosine kinase inhibitor with proven clinical benefit in the advanced setting.

**Methods**: We used two immunocompetent, HER2$^+$ murine cancer models (trastuzumab-sensitive H2N113 and trastuzumab-resistant fo5) to investigate the effects of tucatinib on tumor growth kinetics, as well as tucatinib anti-tumor efficacy in combination with trastuzumab and PD-1 checkpoint blockade. Effects of tucatinib on the tumor infiltrating lymphocytes were analysed using flow cytometry. To identify genes that were modulated by tucatinib treatment, we performed bulk RNA sequencing on fo5 tumors treated with vehicle or tucatinib. We evaluated healthy donor peripheral blood T cells treated with tucatinib for 96 hours and analysed secreted cytokine levels using cytometric bead array.

**Results:** Treatment of CD4$^+$ and CD8$^+$ T cells with tucatinib together with TCR stimulation resulted significantly higher levels of IFNγ and TNFα compared with stimulated controls ($p < 0.0001$), suggesting tucatinib can directly modulate human T cell function. In both murine models, tucatinib significantly inhibited tumor growth in a dose-dependent manner and was observed at doses of 25 mg/kg, 50 mg/kg and 100 mg/kg ($p < 0.05$ between each dose). Median survival was 16 days in the vehicle group vs 50 days with 100 mg/kg of tucatinib ($p < 0.0001$). Ex vivo analysis of tumors by flow cytometry showed increased infiltration of NK cells ($p=0.01$) and, CD8$^+$ T cells with high PD-1 ($p = 0.001$), TIM-3 ($p = 0.009$), IFNγ ($p = 0.003$) and Ki67 ($p = 0.0003$) expression in Tucatinib treated mice compared to vehicle treated mice. Concomitant with these changes there was a significant reduction in numbers of neutrophils ($p = 0.0085$) and MHC-II low expressing macrophage populations ($p < 0.0001$) following tucatininb treatment with an increase in frequency of MHC-II expressing dendritic cells ($p < 0.0001$) and macrophages ($p < 0.0001$) suggesting an increase in anti-tumor immunity.

Similarly, in the fo5 model tucatinib treated tumors had significantly higher interferon-γ (IFNγ) produced by CD8$^+$ T cells ($p = 0.005$). Gene expression profile analysis shows significant enrichment in pathways associated with immune activation, including antigen binding and presentation ($p = 0.0002$), adaptive immune responses ($p = 0.0002$) including IFNγ ($p = 0.0002$) and IFNα ($p = 0.0002$). In this model, tucatinib in combination with trastuzumab demonstrated significantly better anti-tumor activity ($p = 0.03$) and survival ($p < 0.0001$) compared with tucatinib alone, with 33% of mice achieving complete tumour regressions. Tucatinib in combination with PD-1 inhibition also demonstrated significantly greater anti-tumor efficacy compared to tucatinib alone ($p = 0.0079$) with increased survival ($p = 0.05$) and 50% of mice achieving complete tumor regression.

**Conclusions**: This study suggests an anti-tumor immune response may be an important component of the efficacy of tucatinib. This is supported by *in vitro* data demonstrating tucatinib stimulated human peripheral T cells and *in vivo* data showing favorable effects on the TME mediated by tucatinib treatment. These changes were associated with improved efficacy when tucatinib was combined with PD-1 inhibition or trastuzumab in the setting of trastuzumab resistance. These findings suggest that the combination of tucatinib and PD-1 inhibition is a rational combination that warrants investigation in the clinical setting, particularly for trastuzumab resistant HER2+ breast tumors.

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Clinical and pathological characteristics and screening outcome for secondary cancers in breast cancer patients with li-fraumeni syndrome attending the MD anderson li-fraumeni education and early detection program clinic

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**Background:** Germline TP53 mutations predispose to early onset breast cancer (BC) and are associated with Li-Fraumeni syndrome (LFS) Published data on the clinical and pathological characteristics and screening outcome for secondary cancers among women with BC and TP53 mutations is limited. The UTMD Anderson's Li-Fraumeni Education and Early Detection (LEAD) program conducts comprehensive cancer screening for patients with LFS. Here we report characteristics and screening outcome of patients with BC and LFS who were referred to the LEAD program.
**Methods:** Patients with BC and LFS were identified from a prospective BC database between 2001 to 2018. Patients had genetic testing at The University of Texas MD Anderson Cancer Center (MDACC) Clinical Cancer Genetics (CCG) program and confirmed to have germline TP53 mutations. Data reviewed included clinical and pathological characteristics of their BC, the pattern of referral to the LEAD program, adherence to screening recommendation and rate of secondary cancer detection in the LEAD program.
**Results:** A total of 78 female patients with positive germline TP53 mutation and BC diagnosis were identified. The clinical and pathological characteristics of these patients are provided in table 1. Out of the 78 patients, 62 patients were referred and followed at the LEAD clinic. 50 were referred after BC diagnosis and 12 were referred to LEAD clinic before BC diagnosis. A total of 137 cancers were diagnosed in the total population. The cancers were further grouped into diagnosed before or after BC diagnosis. (table 2). 24 cancers were diagnosed in LEAD clinic including 12 breast cancers, 2 soft tissue tumors, 2 thyroid cancers, 2 acute myeloid leukemia, 1 brain tumor, 1 lung cancer, 1 pancreatic cancer, 1 melanoma, 1 parotid cancer and 1 Merkel cell cancer. Adherence to follow up and recommended screening in the first year was 77%, second year 75% and third year 65%. 6 patients, who were diagnosed with leukemia, had received adjuvant chemotherapy with anthracycline and/or cyclophosphamide-based therapy for breast cancer with median time from chemotherapy to leukemia diagnosis of 9 years (5-10yrs). 8 patients developed chest wall sarcoma in the same location of prior radiation therapy for breast cancer with median time from radiation therapy to chest wall sarcoma diagnosis of 7 years (3-11yrs).
**Conclusion:** Patients with LFS associated breast cancer are at significant increased risk to develop secondary cancers. Increased surveillance for secondary cancers in a dedicated program can increase adherence to screening, lead to early detection that could potentially lead to improved outcomes. Patient outcome of this cohort will be presented at the meeting.

Table 1: Clinical and Pathological Characteristics of Women with Breast cancer and LFS

| | | **N(%)** | | | **N(%)** |
|---|---|---|---|---|---|
| **Median Age (Range)** | 33 (20, 63) | ------ | **Hormonal receptor/HER-2 status** | +/+ | 22(31.4%) |
| **Race** | Asian/Pacific islander | 7(9%) | | +/- | 27(38.6%) |
| | Black | 8(10.3%) | | -/+ | 14(20%) |
| | Hispanic | 12(15.4%) | | -/- | 7(10%) |
| | White | 51(65.4%) | **Menopausal status at the time of BC diagnosis.** | Pre-menopausal | (72%) |
| **Stage** | 0 | 13(16.9%) | | Post-menopausal | (28%) |
| | I | 21(27.3%) | **Histology** | DCIS | 12(15.6%) |
| | II | 31(40.3%) | | IDC | 49(63.6%) |
| | III | 9(11.7%) | | ILC | 3(3.9%) |
| | IV | 3(3.9%) | | LCIS | 1(1.3%) |
| **Breast cancer diagnosis** | MRI | 4(5.2%) | | Mixed | 8(10.4%) |
| | Palpated lesion | 51(66.2%) | | Mucinous | 2(2.6%) |
| | Screening mammogram | 22(28.6%) | | Phyllodes | 2(2.6%) |

Table 2: Cancer diagnosed in the total population N=78 grouped into before and after to BC diagnosis

| **Cancer diagnosed before BC diagnosis** | **N** | **Cancer diagnosed after BC diagnosis** | **N** |
|---|---|---|---|
| Soft tissue sarcoma | **13** | Soft tissue sarcoma | **18** |
| CNS | **1** | Lung | **2** |
| Thyroid | **3** | Thyroid | **3** |
| leukemia | **2** | Merkel cell | **1** |
| Adrenal | **2** | Leukemia | **6** |
| Uterus | **1** | CNS | **3** |
| Renal | **1** | pancreas | **1** |
| | | Melanoma | **1** |
| | | Parotid | **1** |

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Prospective evaluation of patients with metaplastic (Mp) triple negative breast cancer (TNBC): Molecular characteristics and outcomes with neoadjuvant therapy (NAT)

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Background: MpBC is a rare breast cancer subtype that is commonly triple-negative and associated with a diminished response to NAT in published retrospective data sets, prompting some clinicians to recommend surgical resection followed by adjuvant therapy. Methods: The ARTEMIS trial (NCT02276443) uses imaging response and molecular profiling to personalize NAT in early stage TNBC. Patients with sensitive disease after 4 cycles of AC receive standard taxane-based NAT as the second phase of NAT, while those with resistant disease are offered biomarker-guided therapeutic trials. Pathologic response is assessed at surgical resection. Prospective data from 195 patients with early-stage TNBC (MpTNBC: N=37; Non-MpTNBC: N=158) enrolled on the ARTEMIS trial were evaluated. Due to short duration of follow-up, restricted mean survival time up to four years of follow-up was used to evaluate event-free survival (RM-EFS), metastasis-free survival (RM-MFS) and overall survival (RM-OS). RNAseq and whole exome sequencing (WES) were performed on pre-NAT core biopsies (155 and 158 non-MpTNBC respectively; 20 MpTNBC). Stromal tumor infiltrating lymphocytes (sTIL) and PD-L1 staining were also compared. Results: Pathologic complete response (pCR) rates were significantly lower in MpTNBC vs non-MpTNBC (18.9% vs. 41.4%, p=0.013). Among MpTNBC without pCR (n=30, 81%), 21 were detected early to have progression (PD) or suboptimal response to standard therapy with ultrasound and clinical exam and were offered the opportunity to participate in clinical trial. Notably, 6 patients (16.2%) had PD after 2 cycles of AC. There was a non-statistically significant trend of lower RM-EFS, RM-MFS, and RM-OS in MpTNBC; however, MpTNBCs with pCR had similar RM-OS compared to non-MpTNBCs with pCR. MpTNBCs had lower rates of high TIL (≥20%) compared to non-MpTNBCs (16% vs. 36%, p=0.02) but similar rates of PD-L1+ disease. Compared to non-MpTNBCs, using Vanderbilt classification methods, MpTNBCs were more frequently M/MSL subtype (50% vs 22%, p=0.011) and less frequently BL-1 subtype (p=0.028). By RNAseq, MpTNBC tumors had significantly lower gene expression of epithelial markers CDH1, EPCAM, ESRP1, and increased expression of EMT inducer TWIST1. WES identified PIK3CA missense mutations in 15% of MpTNBCs. Unsupervised clustering based on expression profiles revealed that 85% of MpTNBCs had a Mp-like expression signature. Interestingly, the Mp-like expression signature was identified in 12% of histologically defined non-MpTNBC. The pCR rate was lowest in the MpTNBC (18.9%) but similar between Mp-like TNBC (36.8%) and non-MpTNBC (42.2%). Conclusion: Early-stage MpTNBC has lower rates of pCR with NAT however those with pCR appear to have similar survival rates to non-MpTNBC with pCR. Notably, 16.2% of MpTNBC had PD after 2 cycles of AC NAT suggesting that a neoadjuvant approach with frequent imaging would reduce unnecessary exposure to inactive chemotherapy. 81% of MpTNBCs had either PD or suboptimal response to AC chemotherapy, thus novel treatment strategies need to be developed for this chemorefractory subtype of TNBC. PAM (PI3K/mTOR/AKT) pathway alterations were frequently detected in MpTNBCs and novel inhibitors should be further tested.

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Immune checkpoint blockade reprograms tumor microenvironment and systemic immune landscape in obesity associated triple negative breast cancer

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Few targeted therapies exist for triple negative breast cancer (TNBC), an aggressive and deadly subtype. Obesity exacerbates poor outcomes in TNBC due to elevated invasion and metastasis leading to increased mortality. Obesity has paradoxically been shown to improve immune checkpoint therapies in other cancers, yet the underlying mechanisms are unclear. Despite being an inflammatory state, obesity increases immune checkpoint ligands PD-1 and PD-L1 which drives immunosuppression. Thus, we tested the hypothesis that obesity-driven changes to the immune milieu will improve ICB efficacy in TNBC. Syngeneic tumors were generated via orthotopic engraftment of E0771 basal-like TNBC cell line into age-matched immune-competent C57BL/6J female littermates on obesogenic or low fat diets. Mice were treated with anti-mouse anti-PD-1 or isotype control (IgG2a) every 3rd day until sacrifice. Obese mice gained almost 2-fold great body weight and 3.6-fold greater adiposity compared to lean mice and immunotherapy did not impact weights or body composition. Obesity led to immunosuppression systemically in bone marrow and spleen in tumor-free mice, which was exacerbated in tumor-bearing mice. Obese mice had significantly greater tumor progression and fewer regressed tumors at endpoint vs. lean mice. Anti-PD-1 significantly reduced tumor progression in obese mice with 4.2-fold reduction in volume and 5.7-fold reduction in tumor weights in obese mice vs. isotype controls. Anti PD-1 significantly reduced immunosuppressive cells including M2-like tumor associated macrophages and monocytic and granulocytic myeloid derived suppressor cells (MDSC) and raised anti-tumor M1-like macrophages, cytotoxic CD8+ T cells, and dendritic cells. Last, the microbiome has potent effects on responses to anti-tumor therapies such as chemotherapy and immune checkpoint blockade. Obesity is a major regulator of the gut microbiome. We found that beneficial bacteria belonging to genus *Bifidobacterium* was higher in lean compared to obese mice, which could limit tumor progression and lead to greater regression through robust anti-tumor immunity. In obese mice, beneficial bacteria belonging to genus *Ruminococcus, Adlercreutzia, Corpococcus* that promote anti-tumor immunity increased with anti PD-1 immunotherapy. In sum, we show for the first time that obesity-induced systemic and microenvironmental immunosuppression augmented tumor incidence and tumor progression. Furthermore, anti-PD-1 immune checkpoint blockade successfully reduced tumor progression in obese mice through reprogramming not only the TME but systemic immune milieu as well. Immunosuppressive targets unique to the obese TME could be targeted in concert with checkpoint inhibitors in future interventions to enhance durable anti-tumor immunity.

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# Impact of low versus negative estrogen/progesterone receptor status on clinico-pathologic characteristics and survival outcomes in HER2 negative breast cancer

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**Background:** Triple negative breast cancer is defined by lack of expression of ER/PR (immunohistochemistry expression <1%) and absence of *HER2* gene amplification. However, data regarding endocrine therapy benefit in patients with low levels (1-10%) of ER/PR expression are lacking. Furthermore, gene expression studies show tremendous similarities between HER2 negative tumors with low and negative ER/PR status. Accordingly, the 2020 ASCO/CAP guideline designates that ER expression of 1-10% be reported as a distinct “ER low positive” category. Utilizing data from a prospective registry, the aim of this study was to determine the impact of low versus negative ER/PR status on clinico-pathologic characteristics and survival outcomes in patients with HER2 negative breast cancers. **Methods:** 516 subjects with stage I-III HER2 negative breast cancer and ER/PR IHC ≤10% were enrolled in an IRB-approved multisite prospective registry between 2011 and 2019. Demographic, clinical, pathologic, and treatment information was collected, and patients were followed for recurrence and survival. Patients were categorized according to ER/PR expression into two groups: TNBC (ER and PR <1%) and Low-ER (ER and/or PR 1-10%). Recurrence free survival (RFS) and overall survival (OS) were estimated according to the Kaplan-Meier method and compared among groups by log-rank test, followed by Cox regression analysis. **Results:** TNBC and Low-ER groups comprised 451/516 (87.4%) and 65/516 (12.6%) patients, respectively. Demographic, clinical, pathologic, and treatment characteristics of the two groups are described in Table 1. Median follow-up was 39 months. Three-year RFS was 82% for both TNBC and Low-ER groups (p=0.70). Three-year OS was 88% and 83% for TNBC and Low-ER groups, respectively (p=0.63). Twenty percent of patients in the Low-ER group received adjuvant endocrine therapy, and endocrine therapy use did not impact outcomes in the Low-ER group (RFS: p=0.32; OS: p=0.88). On multivariate analysis, T stage, nodal status, and age significantly impacted RFS (T stage 3/4 vs 1/2, HR=2.7, p<0.001; nodal status positive vs negative, HR=2.4, p<0.001; age above vs below median, HR=1.8, p=0.006) and OS (T stage 3/4 vs 1/2, HR=3.6, p<0.001; nodal status positive vs negative, HR=2.8, p<0.001; age above vs below median, HR=1.026, p=0.01). For patients who received neoadjuvant chemotherapy, achievement of pathological complete response (pCR) was associated with superior RFS (3-year RFS of 95% and 67% in those with and without pCR, respectively, HR=0.18, p<0.001). **Conclusions:** Patients with TNBC and Low-ER HER2 negative breast cancer present with similar clinico-pathologic characteristics, including prevalence of germline *BRCA1/2* mutation. Prognosis and rate of pCR (with neo-adjuvant chemotherapy) in patients with Low-ER HER2 negative breast cancer is similar to those with TNBC. The role and efficacy of adjuvant endocrine therapy in patients with Low-ER breast cancer is unclear. These findings support consideration for inclusion of patients with Low-ER disease along with TNBC for future clinical trial eligibility and planning.

Table 1. Demographic, clinical, pathologic, and treatment characteristics

| **Characteristics - N (%)** | | **All N=516** | **TNBC (ER & PR <1%) n=451** | **Low-ER (ER or PR 1-10%) n=65** | ***p*** |
|---|---|---|---|---|---|
| **Age at diagnosis, years - median (range)** | | 53 (23-97) | 54 (23-97) | 51 (28-76) | 0.61 |
| **Race** | **White** | 386 (75%) | 335 (74%) | 51 (79%) | 0.69 |
| | **Black** | 101 (20%) | 89 (20%) | 12 (19%) | |
| | **Asian** | 8 (2%) | 8 (2%) | 0 (0%) | |
| **Menopausal status** | **Pre** | 214 (42%) | 181 (41%) | 33 (51%) | 0.25 |
| | **Post** | 295 (58%) | 263 (59%) | 32 (49%) | |
| **Histological grade** | **I** | 2 (0.4%) | 2 (0.4%) | 0 (0%) | 0.82 |
| | **II** | 86 (17%) | 76 (17%) | 10 (15%) | |
| | **III** | 428 (83%) | 373 (83%) | 55 (85%) | |
| **T stage** | **T1-2** | 446 (87%) | 388 (87%) | 58 (89%) | 0.56 |
| | **T3-4** | 67 (13%) | 60 (13%) | 7 (11%) | |
| **N status** | **Positive** | 177 (34%) | 158 (35%) | 19 (29%) | 0.36 |
| | **Negative** | 339 (66%) | 293 (65%) | 46 (71%) | |
| **TNM stage** | **I** | 179 (35%) | 150 (33%) | 29 (44%) | 0.10 |
| | **II** | 263 (51%) | 232 (52%) | 31 (48%) | |
| | **III** | 74 (14%) | 69 (15%) | 5 (8%) | |
| **Germline *BRCA1/2* mutation** | **Yes** | 70 (14%) | 64 (14%) | 6 (9%) | 0.53 |
| | **No** | 357 (69%) | 309 (69%) | 48 (74%) | |
| | **Unknown** | 89 (17%) | 78 (17%) | 11 (17%) | |
| **Chemotherapy** | **Neoadjuvant** | 357 (69%) | 318 (71%) | 39 (60%) | 0.23 |
| | **Adjuvant** | 147 (29%) | 123 (27%) | 24 (37%) | |
| | **None** | 12 (2%) | 10 (2%) | 2 (3%) | |
| **Surgery type** | **Mastectomy** | 308 (60%) | 275 (61%) | 33 (51%) | 0.10 |
| | **Lumpectomy** | 205 (40%) | 173 (39%) | 32 (49%) | |
| **Adjuvant endocrine therapy** | **Yes** | 20 (4%) | 7 (2%) | 13 (20%) | <0.001 |
| | **No** | 496 (96%) | 444 (98%) | 52 (80%) | |
| **pCR (in patients with neoadjuvant chemotherapy, n=357)** | | 176 (49%) | 157 (49%) | 19 (49%) | 0.94 |

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# Standard temperature husbandry increases tumor aggressiveness via chronic cold stress in murine mammary cancer models

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Correct interpretation of disease progression and therapeutic responses in mouse models of breast cancer requires interrogation of models and conditions that faithfully recapitulate human disease and conditions that mimic clinical intervention. Historically, standard temperature (ST) for *in vivo* murine research has been approximately 70-72°F (21-22°C), mimicking ambient temperatures in laboratories that are comfortable for researchers. However, previous work from the Repasky lab demonstrated that ST housing results in chronic cold stress and immune suppression mediated by an increase in norepinrephrine (NE) levels, leading to increased tumor aggressiveness. In contrast, syngeneic murine mammary tumors in mice housed at higher temperatures [~ 82°F] grew more slowly and resulted in fewer metastases. Based on these findings, we investigated tumor progression and metastasis in a temperature dose response in two syngeneic murine mammary tumor models: the balb/c-4T1 model and the c57bl6/E0771-LMB (a lung metastatic variant of E0771 cells) model.Mice were acclimatized in rooms with three different ambient temperaures and challenged with tumor cells. ST was maintained at 70-72°F, while mid-temperature (MT) was maintained at 78-80°F, and high temperature (HT) was maintained at 84-85°F. Compared to ST and MT, an ambient temperature of 84-85°F resulted in a statistically significant delay in tumor formation and decreased primary tumor growth by unpaired t-test (p=.0006) At day 13, when 4T1 tumors are typically well-initiated and measurable by caliper, mean tumor volumes in the ST-housed mice were significantly larger than the HT group. At day 21, ST tumors means were 4 times larger than HT. In the E0771-LMB model, mean tumor volumes on day 14 were nearly 3 times larger in ST-housed mice than HT. At day 27, the mean tumor volumes were 2 times larger in the ST group compared to HT-housed mice. Data on metastasis will be presented at the meeting. Mean NE levels in mice housed at ST were twice as high as those at HT, providing ancillary evidence that traditional “standard” temperatures are a significant stressor for mice (p=.0091).These data demonstrate the potential for misleading interpretations of biological significance of chronic cold stress when modeling immunocompetent tumor progression [conditions almost universally employed in most studies]. Furthermore, these data demonstrate that the presence of chronic cold stress and its immunosuppressive effects call into question the interpretation of many previous studies completed at or near standard temperature and may suggest the need to increase ambient temperatures in syngeneic experiments in order to more accurately model human disease.

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# Association between patient derived xenograft (PDX) take rate and breast cancer recurrence in the prospective breast cancer genome guided therapy study (BEAUTY)

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Background: Patient derived xenografts are a standard tool used to study cancer biology and evaluate drug response phenotypes. It is well known that PDX take rate is associated with more aggressive clinical features [higher grade, biologic subtype (e.g. TNBC vs luminal)]. Previous data from a small retrospective cohort of patients (pts) with no prior chemo (n=24) suggested that primary breast tumor PDX take rate was associated with reduced overall survival. (Derose Nat Med. 2011) However, whether take rate is prognostic in newly diagnosed pts receiving standard of care neoadjuvant chemotherapy (NAC) is unknown. From the prospective BEAUTY clinical trial of pts treated with NAC in which PDX was attempted from pre-NAC as well as after chemo (post-NAC), we recently reported no difference in take rate comparing pts with or without a pathologic complete response (pCR) (Yu Breast Canc Res 2018). Herein we report the association between PDX take rate and recurrence from tumor samples implanted pre-NAC as well as post-NAC (time of surgery). Methods: The BEAUTY study is a prospective NAC study which enrolled breast cancer pts (Stage I-III; n=140) treated with neoadjuvant weekly taxane +/-trastuzumab followed by anthracycline-based chemotherapy. Percutaneous tumor biopsies were obtained prior to NAC and tumor samples from residual disease at surgery were additionally used to establish PDXs. Tumor take rate was defined as percent of pts with the development of at least one stably transplantable (passed at least for four generations) xenograft that was pathologically confirmed as breast cancer. Time to breast cancer recurrence was defined as the time from surgery to documentation of a local, regional, or distant recurrence. Gray's test was used to assess whether the cumulative incidence (CI) of a breast cancer recurrence differs with respect to either pre-NAC PDX take or post-NAC PDX take. Results: Of 140 pts enrolled in the BEAUTY study, tumor tissue for PDX from the pre-NAC tumor was available for implantation in 113. As previously published, PDX take rate from pre-NAC tumor was 27.4% (31/113), and varied according to tumor clinical subtype [51.3% (20/39) in triple negative breast cancer (TNBC), 26.5% (9/34) in HER2+, 5.0% (2/40) in Luminal]. With median follow up of 5.7 years (range: 3 months to 6.75 years), 17 pts developed local, regional or distant disease relapse (4 of whom had a PDX established pre-NAC). The cumulative incidence of breast cancer relapse after surgery was not found to differ according to pre-NAC PDX take (5 yr CI rate: 13.6% no take; 13.4% take; p=0.8911). In pts with TNBC, the group with the highest take rate, there was also no significant difference in incidence of BC recurrence between those without PDX take and those with PDX take (5 yr CI rate: 21.4% vs 16.2% p=0.7314). PDXs were established from residual tissue from surgery (post-NAC) in 6 of 34 pts (17.6%), [specifically, TNBC: 5/9; Her2+: 1/8; and Luminal: 0/17]. Nine of these 34 pts developed a local, regional or distant recurrence. There was a tendency for pts who had a PDX established from their residual disease to have a higher incidence of a breast event (p=0.1092). The 5 year cumulative incidence of a breast event was 19.6% for pts whose post-NAC PDX did not take and 50.0% for pts whose post-NAC PDX took. Discussion: In pts receiving NAC for breast cancer, we observed no significant difference between establishment of a pre-NAC PDX and breast cancer relapse. In contrast, post-NAC PDX take rate (from residual tumor obtained from the breast at surgery) was associated with a tendency to have a higher incidence of a breast cancer event. PDXs remain a valuable tool for the evaluation of tumor biology and development of new therapeutics, especially those models established from pts with chemotherapy resistance.

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De-escalation of radiation therapy in patients with stage I, node-negative, HER2-positive breast cancer: Patterns of care and survival outcomes using the national cancer database

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**Background**: In the modern era, highly effective anti-HER2 therapy is associated with very low local-regional recurrence (LRR) rates for early-stage HER2+ breast cancer. One recent prospective study of T1-2N0 HER2+ breast cancer patients treated with lumpectomy and adjuvant paclitaxel+trastuzumab followed by whole breast radiation (RT) demonstrated 7-year LRR-free survival of 99% raising the question of whether local therapy de-escalation by RT omission is possible. To evaluate existing data on radiation omission, we used the National Cancer Database (NCDB) to test the hypothesis that RT omission results in equivalent overall survival (OS) in stage 1 (T1N0) HER2+ breast cancer.**Materials/Methods:** We identified patients with stage I (T1N0) HER2+ breast cancer treated with lumpectomy, adjuvant chemotherapy and anti-HER2 therapy from 2013 (the first year anti-HER2 therapy receipt was reliably collected) to 2015. We excluded patients that received neoadjuvant systemic therapy. We then stratified the cohort by receipt of adjuvant RT. The primary endpoint was OS as LRR is not captured by the NCDB. OS was analyzed by the Kaplan-Meier method (RT and RT omission groups compared by the log-rank test) and multivariate cox regression including variables with p<0.20 on univariate analysis (hazard ratios [HR], and 95% confidence intervals [CI] are reported). Propensity score matched (PSM) analysis with patients matched on age (≥70 vs. <70), comorbidities (≥1 vs. 0), grade (3 vs. 1-2), tumor size (>1 cm vs. ≤1 cm), ER/PR status (ER-/PR- vs. ER+ and/or PR+), facility type (academic vs. non-academic), and income (<$46,000/yr vs. ≥46,000/yr) was performed as an independent test of the Cox regression analysis.**Results:** We identified 6,897 patients that met the study criteria (6,388 RT; 509 no RT). Patients that did not receive RT tended to be older (mean age 64.0 years v. 59.2 years, p<0.0001), have ≥1 comorbidity (21.4% vs. 14.8%, p<0.0001), and live in lower income areas (60.1% vs. 52%, p=0.0004). Median follow-up was 29.4 months (IQR=19.5-39.9 months) with 155 deaths (95 RT; 60 RT omission). The 2-year OS was significantly worse for patients with RT omission (89.0% vs. 99.2%, p<0.0001). Factors associated with OS on univariate analysis included RT omission (p<0.0001), age≥70 (p<0.0001), ≥1 comorbidity (p=0.0002), tumor size>1cm (p=0.14), grade 3 tumors (p=0.14), academic facility (p=0.16) and lower income (p=0.02) but not ER-/PR- status (HR=1.01, p=0.95), distance to treatment facility (p=0.42) or tumor laterality (p=0.66). On multivariate analysis, RT omission (HR=7.55, 95% CI 5.36-10.63, p<0.0001), age≥70 (HR=2.30, 95% CI 1.63-3.23, p<0.0001), and ≥1 comorbidity (HR=1.45, 95% CI 1.00-2.09, p=0.05) remained independently associated with higher risk of death. The PSM cohort consisted of 509 pairs of patients with 73 deaths (13 RT; 60 RT omission) and median follow-up 26.4 months (IQR, 16.5-37.3 months). RT omission remained associated with a 5.42-fold (95% CI 3.02-9.73, p<0.0001) increased risk of death in the PSM cohort.**Conclusion:** This study demonstrates that RT omission is independently associated with an increased risk of death in patients with stage I, HER2+, node-negative breast cancer treated with lumpectomy, adjuvant chemotherapy and anti-HER2 therapy. Patients that did not receive RT tended to be older, have more comorbidities and live in lower income areas. While other selection biases that influence RT omission likely persist, these data should give caution to RT omission in stage I, node-negative HER2+ breast cancer.

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# Long-term risks of cerebrovascular accidents (CVAs) in patients with breast cancer

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**Background:** Previous survivorship research has focused primarily on treatment-related risks of coronary artery disease (CAD) and congestive heart failure (CHF) even though they share common pathogenic mechanisms with CVAs. However, there are limited data on the latter. This real-world evidence study aimed to assess the associations of breast cancer treatments with subsequent development of CVAs.
**Methods:** We identified patients diagnosed with stage I-III breast cancer in a large Canadian province from 2004 to 2017. Data from the population-based registry were linked with data from administrative sources to identify a diagnosis of CVA during follow-up after cancer treatment. Adjuvant treatment was classified as receipt of none, one, two or three depending on the number of treatment modalities (chemotherapy, radiotherapy and hormone therapy) administered. Patients with pre-existing cardiovascular disease including CAD, CHF, arrythmias and CVAs were excluded. Multivariable logistic regression analysis was performed to determine the associations of number of adjuvant treatment modalities with CVAs.
**Results:** A total of 23,259 patients were eligible for analysis. The median age was 58 years (interquartile range, 22-101 years) and 0.5% were men. Stage distribution included 49.6% with stage I, 37.1% with stage II, and 13.4% with stage III breast cancer. Chemotherapy, radiotherapy and hormonal therapy was administered in 45.0%, 60.6%, and 68.1% of patients, respectively. While 11.0% received no adjuvant treatment, 28.7%, 35.9% and 24.4% received one, two and three modalities. At a median follow-up of 5.9 years, 1,586 (6.8%) developed new onset CVAs. The median time from diagnosis of breast cancer to CVA was 3.1 years (interquartile range, 2.7-3.5 years). In comparison, the incidence of CVAs was higher in those who received any chemotherapy (8.2% vs 5.1%, P<.001), any radiotherapy (8.3% vs 5.9%, P<.001), and any hormonal therapy (7.8% vs 6.4%, P<.001). The incidence of CVAs was 4.9%, 5.9%, 8.2% and 10.5% in patients who received none, one, two and three adjuvant treatment modalities (P<.001). After adjusting for age, patients who received two or three modalities (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.03-1.41; P=.020 and OR, 1.46; 95% CI, 1.21-1.75; P<.001) experienced a higher likelihood of CVAs, compared to those who received no adjuvant therapy, while those who received one modality were at similar risk (OR,1.00; 95% CI, 0.86-1.17, P=.974) . In multivariable Cox regression models adjusting for stage and treatment, patients who developed CVAs were at increased risk of death (hazard ratio, 1.44; 95% CI, 1.30-1.58; P<.001).
**Conclusions:** The risk of CVAs in patients with resected breast cancer increases with adjuvant treatment administration. It was highest in those who received a combination of chemotherapy, radiotherapy and hormone therapy. While breast cancer survivors are monitored for coronary events and cardiomyopathy, they may benefit from surveillance of risk factors for CVAs.

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Therapeutic considerations in microsatellite instability high (MSI- H) breast cancers (BC) identified by comprehensive genomic profiling (CGP)

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**Background:** Non-colorectal MSI-H tumors are increasingly identified by CGP. Rare types such as MSI-H BC remain poorly defined with an evidence gap on how to optimally sequence or combine with standard of care treatment. MSI can be measured by either IHC, PCR, or CGP and can be caused by both sporadic and germline variants within different tumor types. Prior studies in BC have shown evidence of dMMR by IHC cases MSS based on PCR. This could be due to intra-tumor heterogeneity, specific microsatellite loci evaluated, or penetrance of germline, somatic, or epigenetic alterations. Published data suggests carriers of germline pathogenic MMR variants have a BC risk equivalent to the normal population and currently germline testing is recommended only for *BRCA*. Currently in advanced BC, standard tumor biomarker testing includes IHC, PCR, and FISH; however, with increasing use of CGP we demonstrate additional actionable biomarkers as well as potential germline variants in MSI-H BC. **Methods:** DNA was extracted and hybrid capture CGP was performed on 29,160 BC cases. TMB was determined on 0.8-1.2 Mb of DNA and MSI status on 95-114 loci. Genomic LOH was also evaluated. Comparative analysis was done with 101 MSI-H BC, 841 MSS BC and 4,988 non-breast MSI-H cancers. Histological subtype was obtained from the pathology along with orthogonal testing for ER/PR/HER2 status. Somatic-germline-zygosity (SGZ) status was predicted using a published research use algorithm. Select case reports with clinical outcomes will be presented. **Results:** We identified 101 (0.35% of total) MSI-H BC cases: 29 ER+/HER2-, 5 HER2+, 29 TNBC, and 28 unknown. Amongst BC cases with known subtype, TNBC was enriched for MSI-H vs MSS (53.4 vs 35.8%, p=0.005). The median TMB in MSI-H BC (26.1 mut/Mb, IQR 17.4;42.8) was significantly lower than that of MSI-H colon (46.1mut/MB) and higher than that of MSI-H uterine tumors (22.6mut/Mb) in our comparison group (p<0.001 for both, Kruskal-Wallis test). Pathogenic variants in an MMR gene were found in 61.4% of MSI-H BC with *MLH1* loss being the most common (13.6%) and much higher vs. the non-breast MSI-H cohort (2.4%, p<0.0001). Germline mutations in MMR genes in BC are rare yet 5/52 MMR short variants identified in 101 MSI-H BCs were predicted to be germline, 34 somatic, and 13 could not be determined. We identified 21 MSI-H BC patients with a total of 25 pathogenic *BRCA1/2* alterations of which 4 were likely germline, 10 were homozygous, and were enriched in TNBC. These were mainly frameshift mutations, including *BRCA2* T3033fs* in 5/18 (28%) cases; however, 7/25 were deletions, rearrangements, or nonsense mutations. Median gLOH was significantly higher in *BRCA* altered (19.7%) compared to *BRCA* wild-type MSI-H BC cases (9.6%) (p=0.007, Wilcox test). Additional potentially targetable biomarkers included 26 CDx eligible *PIK3CA* mutations, 11 *ERBB2* activating point mutations in the TKD or ECD domain, 1 *FGFR2* rearrangement, and 6 *AKT1* E17K mutations. Four cases also had concurrent *(CD274*) PD-L1 amplifications. **Conclusion:** MSI-H BC is rare but CGP can identify additional therapeutic options for rational combination with targeted therapies such as PI3K, PARP, and HER2 inhibitors. *BRCA* alterations may be of germline or somatic origin and they may be targetable, as demonstrated by gLOH, rather than passenger mutations. Further characterization of these tumors and comparison to both MSS BC and non-breast MSI-H tumor types, combined with treatment outcomes, can provide insights on rationale combinations and/or sequencing of therapeutic agents.

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# Impact of delayed initiation of adjuvant chemotherapy in early breast cancer: Analysis from Taiwan National breast cancer registry database

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**Background:**In 2017, there are more than 14,000 cases of newly diagnosed breast cancer in Taiwan. With the popularity of early screening policy and social-awareness, the proportion of early breast cancer has increased significantly in the last decades. For the high risk group with early breast cancer, adjuvant systemic chemotherapy could provide lower breast cancer recurrence rate and better overall survival rate. In Taiwan, every citizen must join the National Health Insurance (NIH), and the NIH would cover the whole expanse of adjuvant chemotherapy. Theoretically, all breast cancer patients could receive their condign chemotherapy regardless of their social economic status. The optimal initiation timing of adjuvant chemotherapy is undiscovered, and the effect of delay initiation is still under contestation. In this study, we try to identify the relationship between initiation time of chemotherapy and survival outcome, and different breast cancer subtypes would be analyzed separately. We also evaluate many associated factors that may delay chemotherapy initiation or survival status.**Material and Methods:**In this observational, populational-based study using Taiwan national breast cancer registry database, we studied 110,784 patients diagnosed with Stage I~III breast cancer between January 1, 2006 and Deccember 31, 2016. Time to chemotherapy(TCC) was defined as the days between surgery and the initial dose of adjuvant chemotherapy. We categorized patients into initiate chemotherapy within 30 days, 31~60 days, 61~90 days, and more than 91 days. The patient demography, tumor biology, lymph node status, type of breast surgery, receiving reconstructive surgery or not, radiation therapy, immunohistochemistry data (estrogen receptor, progesterone receptor, and human epidermal growth factor 2[HER2]), and we categorized patients according to different breast cancer subtypes. Univariate analysis with Kaplan-Meier method is used to evaluate TTC influence, and log-rank test is used to compare differences between groups. Multivariate logistic regression model is used to identify important factors associated with delayed chemotherapy initiation and survival.**Preliminary Results:**Totally 72840 patients were enrolled in this study, and the median age at initial diagnosis was 52.4 years old. Delayed wound healing and breast reconstruction are the main factors associated with delated TTC. Comparing with TTC<30 days group, TTC of 31~60 days group showed no difference in disease-free survival and overall survival, while TTC of 61~91 days group had a trend of lower disease-free survival (p=0.12). TTC more than 91 days had worse disease-free survival (HR=1.16, 95%CI=1.03~1.38) and overall survival (HR=1.23, 95%CI=1.08~1.52). We assumed initiate first chemotherapy more than 90 days as delated TTC as generally accepted in previous publications. In subgroup analysis, delayed TTC caused worse disease-free survival especially in triple negative group (HR=1.42, 95%CI=1.21~1.68) and HER2 group (HR=1.38, 95%CI=1.22~1.55).**Conclusion:**For breast cancer patients who assumed to receive adjuvant systemic chemotherapy, delayed in initiation
of chemotherapy (more than 90 days) may result in worse outcome, especially in triple negative breast cancer and HER2 group. Besides the above preliminary result, other multivariate analysis and intergroup comparison are still ongoing. More information will reveal in SABCS 2020.

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# Trop-2 inactivation of E-cadherin drives triple negative breast cancer relapse

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Hundreds of proteins/genes have been linked to the metastatic phenotype. However, consistent markers of tumour aggressiveness and metastatic potential in breast cancer patients were not identified, not even including proteomic analysis and large-scale genome sequencing.Metastasis-associated genes were predicted to include not only drivers of the metastatic phenotype, but also secondary events, together with adaptive, counterbalancing changes. Thus, to identify candidates with a required role in metastatic diffusion, we looked for genes that were concordantly dysregulated across orthogonal cancer metastasis settings. This led us to identify Trop-2 as uniquely upregulated and associated to metastasis in experimental models of breast cancer, as well as in other solid tumors. We identified functional inactivation of E-cadherin by Trop-2 as the main motor of metastatic diffusion of such metastatic systems. Trop-2 binding to E-cadherin inactivated its cell-cell adhesion function, through release from the cytoskeleton, for activation of β-catenin transcriptional activity. This led to anti-apoptotic signaling, increased cell migration capacity and enhanced cancer cell survival. We showed that this mechanism led to metastatic diffusion of xenotransplants growing in immunosuppressed mice. An E-cadherin-inactivation metastasis program was then shown to be recapitulated in breast cancer patients, as well as in other solid tumors, over 24 independent case series, encompassing 13,042 primary tumours. Aggressive triple-negative breast cancers were shown to be driven toward global relapse by Trop-2 overexpression, through E-cadherin inactivation and activation of β-catenin transcriptional activity. No disease recurrence was observed in control cases over +12 years of follow-up. These finding lead to a novel paradigm of a Trop-2-driven, E-cadherin-inactivation program as a main metastasis driver in solid tumors. This may open far-reaching perspectives in diagnostic procedures and anti-cancer therapies.

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# Molecular subtyping by BluePrint improves prediction of treatment responses and survival outcomes in patients with discordant clinical and genomic classification

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**Background**: The risk of distant recurrence gene signature, MammaPrint (MP), together with the molecular subtyping gene signature, BluePrint (BP), stratifies breast tumors into Luminal A, Luminal B, HER2, and Basal subtypes, independent of immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH) expression. In the Neoadjuvant Breast Registry Symphony Trial (NBRST), MP and BP identified patients likely to respond to neoadjuvant treatment with higher accuracy compared to conventional methods. Here, we report 5-year follow up (FU) data in breast cancer (BC) patients from the NBRST registry with discordant clinical and genomic subtyping.**Methods**: This prospective study enrolled 1072 early-stage BC patients from 2009-2014 who received MP and BP testing. Patients received neoadjuvant therapy following standard of care and consented to 5 years post-surgery FU. IHC determined hormone receptor (HR) status, including ER and PR, and IHC and/or FISH determined HER2 status. Median FU for distant metastasis free survival (DMFS) and overall survival (OS) was 4.6 and 5 years, respectively. Differences in DMFS and OS was assessed by Kaplan Meier analysis and log-rank test.**Results**: Overall, BP reclassified 22% of tumors into different molecular subtypes compared to IHC/FISH (Table). BP reclassified 17% of ER+HER2- tumors as BP Basal, with higher pathological complete response (pCR) rates compared to ER+/BP Luminal tumors (36% vs. 4%). ER+/BP Basal patients had similar pCR rates as triple negative BC (TNBC)/BP Basal patients (36% vs. 37%) following neoadjuvant treatment, and pCR correlated with improved survival outcomes. The 5-year DMFS and OS probabilities were lower in ER+/BP Basal patients compared to TNBC/BP Basal patients and were substantially lower compared to ER+/BP Luminal patients ($P < 0.001$). There were 106 HR-HER2+ patients, of whom BP reclassified 23.6% to Basal and 2.8% as Luminal B; the remaining 73.6% were confirmed HER2 by BP. The 5-year DMFS and OS probabilities were worse in HER2+/BP Basal patients compared to HER2+/BP HER2 patients. Of 142 triple positive (TP, ER+PR+HER2+) patients, BP classified 55% as Luminal, 39% as HER2, and 6% as Basal, with higher pCR rates observed in BP Basal and BP HER2 tumors compared to BP Luminal. The 5-year DMFS and OS probabilities were substantially lower in TP/BP Basal patients compared to TP/BP HER2 and TP/BP Luminal patients ($P < 0.05$ and $P < 0.04$). Of clinical HER2+ patients (HR+ or HR-) that received pertuzumab, patients that reclassified as BP Basal had worse OS compared to BP HER2 patients ($P < 0.04$).**Conclusion**: ER+HER2- and HER2+ patients that reclassified as BP Basal are more likely to achieve pCR and have improved survival, demonstrating the clinical utility of BP in the neoadjuvant setting. These patients may benefit from optimized chemotherapy used for TNBC, including novel emerging treatments such as PD-1 and PARP1 inhibitors, in addition to HER2-targeted therapy. Furthermore, HER2+ tumors that were confirmed HER2 by BP may have high response rates to regimens containing TDM-1. Lastly, BP identified a subgroup of triple positive BC patients, who reclassified as BP Luminal, that may avoid overtreatment. Overall, molecular subtyping using MP and BP is more accurate in stratifying patients and predicting treatment responses and 5-year disease outcomes than conventional methods and thus, facilitates successful treatment decisions.

| Clinical subtype | Frequency of BP classification | BluePrint subtype | pCR% | 5-yr DMFS (95% CI) | 5-yr OS (95% CI) |
|---|---|---|---|---|---|
| **TNBC (n=236)** | 0.42% (1/236) | Luminal A | 100% (1/1) | N/A | N/A |
| | 2.54% (6/236) | Luminal B | 16.67% (1/6) | N/A | N/A |
| | 1.27% (3/236) | HER2 | 33.33% (1/3) | N/A | N/A |
| | 95.76% (226/236) | Basal | 36.73% (83/226) | 100% (pCR) | 100% (pCR) |
| | | | | 60.5% (50.5-69.1) (non-PCR) | 64.3%(52.1-71.2) (non-PCR) |
| **ER+HER2- (n=520)** | 28.84% (152/520) | Luminal A | 1.97% (3/152) | 91.1% (84.0-95.2) | 94.6% (88.3-97.6) |
| | 52.37% (276/520) | Luminal B | 5.43% (15/276) | 75.2% (69.0-80.4) | 84.5% (79.0-88.7) |
| | 1.33% (7/520) | HER2 | 14.29% (1/7) | N/A | N/A |
| | 17.46% (92/520) | Basal | 35.9% (33/92) | 84.1% (67.8-92.5) (pCR) | 86.3% (70.1-94.1) (pCR) |
| | | | | 54.6% (42.0-65.5) (non-pCR) | 57% (43.7-68.2) (non-pCR) |
| **HR-HER2+ (n=106)** | 2.83% (3/106) | Luminal B | 66.67% (2/3) | 100% | 100% |
| | 73.59% (78/106) | HER2 | 69% (54/78) | 82.8% (69.9-90.5) | 88.6% (76.0-94.8) |
| | 23.58% (25/106) | Basal | 40% (10/25) | 79.0% (52.5-91.7) | 79.0% (52.5-91.7) |
| **Triple Positive (n=142)** | 12.68% (18/142) | Luminal A | 22.22% (4/18) | 88.8% (76.5-94.8) | 94.5% (83.8-98.2) |
| | 42.25% (60/142) | Luminal B | 11.67% (7/60) | | |
| | 38.73% (55/142) | HER2 | 44.44% (24/55) | 87.5% (72.0-94.7) | 97.9% (83.8-98.2) |
| | 6.34% (9/142) | Basal | 55.56%(5/9) | 62.5% (22.9-86.1) | 70.0% (22.5-91.8) |
| **HER2+ (HR+ or HR-)treated with pertuzumab (n=105)** | 28.6%(30/105) | Luminal | 37% (11/30) | 84.7% (63.8-94.1) | 92.2%(71.8-98.0) |
| | 57%(60/105) | HER2 | 82% (49/60) | 91.4% (78.3-96.8) | 92.9%(79.2-97.7) |
| | 14%(15/105) | Basal | 40% (6/15) | 66.0%(31.1-86.3) | 64.0% (29.1-85.1) |

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# Computational drug repositioning for the identification of new agents to sensitize drug-resistant breast tumors across treatment arms and molecular subtypes

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Introduction: One of the principal limiting factors to achieving cures in patients with cancer is drug resistance. Drug repositioning is the application of FDA-approved drug compounds for novel indications beyond the scope of the drug's original intended use. This approach offers advantages over traditional drug development by reducing development costs and providing shorter paths to approval, as drug safety has already been established during the drug's original regulatory process. One approach for computational drug repositioning involves generating a disease gene expression signature and then identifying a drug that can reverse this disease signature. In this study, we extracted drug resistance signatures from the I-SPY 2 TRIAL by comparing gene expression profiles of responder and non-responder patients stratified by treatment and molecular subtype. We then applied our drug repositioning pipeline to predict compounds that can reverse the gene expression profiles of these drug resistance signatures. We hypothesize that reversing these drug resistance signatures will resensitize tumors to treatment and improve patient outcome.
Methods: We first generated the drug resistance signatures by performing differential expression between responders (RCB 0/I) and non-responders (RCB III) within treatment arms and molecular subtypes. An optimal log fold-change cutoff was selected for each signature by identifying the cutoff that best separates the responder and non-responder samples using k-means clustering. We then applied our drug repositioning pipeline to identify compounds that significantly reverse these signatures using the drug perturbation profiles generated in a breast cancer cell line in the Connectivity Map v2 dataset. Briefly, the pipeline uses a non- parametric, rank-based pattern-matching strategy based on the Kolmogorov-Smirnov (KS) statistic to assess the enrichment of resistance genes in a ranked drug gene expression list. Significance of each prediction is estimated from a null distribution of scores generated from random gene signatures.
Results: We found that few individual genes are shared among the resistance signatures across the treatment arms and molecular subtypes, with the most common genes present in only 5/17 of the treatment arm and molecular subtype groups. At the pathway-level, however, we found that immune-related pathways are generally enriched among the responders and estrogen-response pathways are generally enriched among the non-responders. Although most of our drug predictions are unique to treatment arms and molecular subtypes, our drug repositioning pipeline identified the selective estrogen receptor degrader (SERD) fulvestrant as a compound that can potentially reverse resistance across a majority of the treatment arms and molecular subtypes.
Conclusion: We applied our drug repositioning pipeline to identify novel agents to sensitize drug-resistant tumors in the I-SPY 2+ clinical trial and identified a SERD, fulvestrant, as a potential candidate for multiple molecular subtypes and treatment arms.

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# Tailored axillary surgery to omit axillary lymph node dissection independently from the use of neoadjuvant chemotherapy in patients with clinically node-positive breast cancer: Pre-specified subproject within TAXIS (SAKK 23/16 / IBCSG 57-18 / ABCSG-53 / GBG 101)

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**Introduction**: We developed tailored axillary surgery (TAS) to selectively remove positive nodes and omit axillary lymph node dissection (ALND) in patients with clinically node-positive breast cancer irrespective of the use of neoadjuvant chemotherapy. In this study, we evaluate the performance of this novel surgical concept that tailors the extent of axillary surgery to the extent of axillary disease. **Methods**: A prospective study was pre-specified to assess the performance of TAS in the international multicenter phase-III TAXIS trial randomizing patients with clinically node-positive breast cancer to undergo ALND or axillary radiation after TAS. TAS consists of selective removal of all palpably suspicious findings and the SLNs followed by specimen radiography to document removal of the clip placed in the sampled node. Imaging-guided localization is encouraged to increase the chances of clip removal. Only patients with confirmed nodal disease at the time of surgery can be randomized in TAXIS; the first 200 randomized patients were analyzed together with the ones achieving nodal pCR in this study. ClinicalTrials.gov Identifier: NCT03513614. **Results**: A total of 296 patients with a median age of 56.5 years (range: 25-88 years) were included at 28 breast centers from four European countries, 125 (42.3%) of whom underwent NACT and 75 (25.3%) of whom had nodal pCR. Subtype was hormone receptor (HR) positive (+) and human epidermal growth factor receptor 2 (HER2) negative (-) in 194 (65.5%), HR+/HER2+ in 40 (13.5%), HR-/HER2+ in 17 (5.7%) and HR-/HER2- in 39 (13.2%) patients. Breast-conserving surgery was performed in 178 patients (60%) and mastectomy in 117 (40%). Imaging-guided localization was attempted in 258 patients (87.2%) and was successful in 243 (82.1%). TAS removed a median of two (interquartile range [IQR] 0-3) palpably suspicious lesions and two (IQR 1-3) SLNs, thereby successfully removing the clip in 279 (94.3%) patients. There were no significant differences by use of imaging-guided localization (94.6% with vs 92.1% without, p=0.47) or type of clip (p=0.19), but a trend toward lower rate of clip removal after NACT (91.2% with vs 96.5% without NACT, p=0.075). Palpable disease was left behind after TAS in two (2.1%) patients and no SLN was detected in three (3.1%). In the 200 randomized patients with confirmed nodal disease at the time of surgery, lymph node metastases were palpable at the time of initial diagnosis in 102 (51%) patients and detectable only by imaging in 98 (49%). The median number of lymph nodes removed by TAS was four (IQR 2-8), two (IQR 1-4) of which were positive. Completion ALND following TAS removed additional positive nodes in 71 of 100 (71%) patients in the control group (20% with one additional node, 9% with 2, 8% with 3, 6% with 4, and 28% with >4). The median number of additional lymph nodes removed by ALND was 14 (IQR 10-18), two (IQR 0-6) of which were positive. Of the 200 randomized patients, one in the TAS group received a radiotherapy boost and one in the ALND group returned to the operating room for residual suspicious findings on imaging. **Discussion**: The present results suggest that TAS has the potential to become the new axillary surgery standard in patients with clinically node-positive breast cancer. TAS was successfully performed in the vast majority of patients, with no further improvement by imaging-guided localization, which makes the procedure feasible at most breast centers. TAS selectively removed positive lymph nodes and was much less radical than ALND, but ALND removed additional positive nodes in more than two thirds of patients. Disease-free survival and quality of life will be assessed in the randomized trial.

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Prognostic role of distant disease-free interval from completion of adjuvant trastuzumab in HER2-positive early breast cancer: Analysis from the ALTTO (BIG 2-06) trial

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**Background:** In HER2-positive breast cancer patients, timing from the end of (neo)adjuvant trastuzumab (T)-based therapy to diagnosis of metastatic breast cancer is the key factor in determining the optimal first-line treatment. There is currently lack of clear evidence to support the possible prognostic role of this interval and 12 months has been mostly empirically used. The present analysis aimed to investigate patterns of relapse, first-line choice and survival outcomes of patients with HER2-positive early breast cancer who relapsed after adjuvant T-based therapy depending on T-free interval (TFI, i.e. timing from end of adjuvant T to diagnosis of distant metastases).
**Methods:** In ALTTO, HER2-positive early breast cancer patients were randomized to 1 year of either T alone, lapatinib (L) alone, their sequence (T-->L) or their combination (T+L). This exploratory analysis included only pts in the T or T+L arms who experienced a distant disease-free survival (DDFS) event. Two cohorts of patients were defined depending on TFI: group A (TFI of <12 months) and group B (>12 months). Baseline characteristics, patterns of relapse, first-line choice and overall survival (OS) were compared. OS was defined as time between date of DDFS event to death; age at diagnosis, tumor size and hormone receptor status were the variables included in the final multivariate models.
**Results:** Out of 8,381 patients included in ALTTO, 404 patients in the T and T+L arms developed a DDFS event, of whom 201 occurred ≤12 months (group A) and 203 >12 months (group B) after the end of adjuvant T. Patients in group A were older (p=0.013), had larger tumors (p=0.004) and more frequently hormone receptor-negative disease (p<0.001). No significant difference in patterns of first DDFS event was observed (p=0.073); however, a numerically higher number of patients in group A compared to group B developed brain metastasis (26% vs. 15%). First-line anti-HER2 therapy was received by 57% of the patients. Choice of first-line anti-HER2 therapy was different between the two groups (p=0.022): the majority of patients received T in both groups (61% vs. 65% in groups A and B, respectively), while more patients in group A received L (25% vs. 11%) and less received pertuzumab (8% vs. 17%). OS survival was significantly shorter in group A compared to group B: median OS was 18.4 and 29.3 months in groups A and B, respectively (adjusted HR 0.69; 95% CI 0.54-0.89; p=0.004). Similar results were observed after the exclusion of patients treated with first-line pertuzumab-based therapy (n=29): median OS was 18.2 and 26.8 months in groups A and B, respectively (adjusted HR 0.66; 95% CI 0.51-0.86; p=0.002). Better outcomes in terms of OS for patients in group B was observed across all analyzed subgroups with no interaction according to hormone receptor status (p=0.814) nor type of adjuvant anti-HER2 treatment (p=0.233): hormone receptor-positive (adjusted HR 0.69; 95% CI 0.48-0.99), hormone receptor-negative (adjusted HR 0.68; 95% CI 0.48-0.98), T+L arm (adjusted HR 0.55; 95% CI 0.38-0.80) and T arm (adjusted HR 0.80; 95% CI 0.55-1.17).
**Conclusions:** In the ALTTO trial, HER2-positive early breast cancer patients who experienced shorter TFI (i.e. ≤12 months vs. >12 months) following adjuvant T-based therapy had inferior OS after the diagnosis of distant recurrence. Given its prognostic value, TFI can help to individualize clinical recommendations and to design future trials in the metastatic setting for patients relapsing after prior exposure to anti-HER2 therapy for early disease.

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# Comprehensive genomic and transcriptomic profiling of molecular subtypes reveal ancestral differences in the activity of signaling pathways between patients with African and European ancestry

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**Background:** Breast cancer demonstrates heterogeneity in biological features, and the therapeutic strategy depends on tumor subtype. African-Ancestry (AA) patients experience a disproportionally high rate of triple negative breast cancer (TNBC) and worse outcomes than European-Ancestry (EA) patients. However, the biological drivers causing this disparity between ancestral populations are not deeply understood. To address the issue, we performed genomic and transcriptomic sequencing of breast tumors for comparison between AA and EA patients according to breast cancer molecular subtypes. **Materials and Methods:** The study included 221 AA and 341 EA patients. Collected samples underwent the Tempus xT next-generation sequencing panel. Following DNA-panel and whole-transcriptome RNA-sequencing, we compared gene mutation rates, homologous recombination deficiency (HRD) scores, degree of immune infiltration and tumor mutational burden (TMB) between ethnicities and molecular subtypes. Additionally, differences between the activity of relevant signaling pathways were evaluated from RNA-sequencing data. **Results:** Relative to EA TNBC, AA TNBC tumors exhibited higher mutation rates in *TP53* (94% vs 86%), *KMT2C* (17% vs 9%), *APOB* (19% vs 10%), *BRCA2* (11% vs 5%), *EP300* (8% vs 2%), *NOTCH1* (12% vs 4%), and *EGFR* (11% vs 4%). Conversely, AA TNBC tumors had relatively lower rates of *PIK3CA* (10% vs 18%), *RB1* (8% vs 15%), and *NF1* (5% vs 11%) mutations. Among patients with HR+/HER2- breast cancer, AA tumors had higher mutation rates in *CCND1* (23% vs 10%) and *FGF3* (16% vs 10%) than EA tumors, but lower rates in *TP53* (32% vs 39%). HRD scores were higher in TNBC and HR-/HER2+ tumors compared with the other subtypes ($P<0.001$). However, there was no significant difference between the HRD scores of AA and EA tumors within TNBC or HR-/HER2+ populations. The highest percentage of immune infiltration was observed in HR-/HER2+ tumors ($P=0.036$), with no difference between AA or EA groups. TMB did not differ across ancestries or subtypes. Although immune pathways were generally more active in TNBC compared to the other subtypes, there was no difference in pathway-specific immune activation between ethnicities. The G2M and E2F pathways were significantly more active in TNBC (P<2e-16 for both), in particular more active in AA than EA tumors (G2M, P=0.035; E2F, P=0.037). On the other hand, PI3K, ROS, and xenobiotic metabolism (XM) pathways were significantly less active in TNBC compared to the other subtypes (PI3K, P=2.4e-5; ROS, P=0.014; and XM, P<2e-16). Furthermore, these pathways were significantly less active in AA than EA tumors across all subtypes (PI3K, P=0.026; ROS, P=0.00035; and XM, P=0.00041) and within TNBC (PI3K P=0.012, ROS P=0.014, and XM P=0.00018). **Conclusion:** These data demonstrate significant differences in breast tumor heterogeneity and mutation spectrum in TNBC and HR+/HER2- breast cancers between AA and EA patients. Ancestral differences were also observed in the activity of relevant signaling pathways for TNBC. Overall, the results identify previously unexplored pathways and molecular phenotypes of aggressive disease, providing opportunities for development of more effective biomarker informed treatment of breast cancer in diverse populations.

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The optimal living and survivorship program: Piloting a novel cancer survivorship care model

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**Background:** Multiple national agencies define cancer survivorship as beginning at the time of cancer diagnosis. However, traditional care models typically deliver “survivorship care” months or years after diagnosis, which can lead to disruption in care and “transition anxiety”. We hypothesized that an approach centered around wellbeing could be applied across the cancer continuum (starting at diagnosis) and serve as a novel survivorship care model.
**Methods**: We developed the Optimal Living and Survivorship Program, a novel telehealth platform that is designed to better engage cancer survivors by providing multidisciplinary and individualized lifestyle management during and after cancer therapy. Our multilevel approach relies on three key components: 1) a digitized centralized model that provides automated and coordinated multidisciplinary care; 2) an individualized Wellness Plan (WP); and 3) enrollment at the time of cancer diagnosis in order to mitigate the experience of post-treatment transition. Participants complete a digital wellness questionnaire (WQ) consisting of validated instruments that provide risk assessment for a broad range of lifestyle and psychosocial factors prior to the first medical oncology consult, receive a validated algorithm-based WP reviewed by a Wellness Coordinator, and meet with a specially trained Wellness Advanced Practice Provider (WAPP) via tele-medicine. The WP consists of individualized topic-specific educational materials (e.g., webinars, videos) and referrals to indicated supportive services (e.g., nutrition, exercise physiology, financial counseling, integrative medicine). The WAPP will ultimately assume care of the patient in the post-treatment (“survivorship”) phase. We piloted this approach in patients diagnosed with breast cancer beginning in November 2019. The primary outcome is feasibility defined by completion of the WQ. Secondary outcomes include participation in the WAPP visits, attendance at referral appointments, and quality of life (QOL).
**Results:** As a result of COVID-19, the pilot was paused in February 2020. Data collected from November 2019 through February 2020 reveal a total of 67 eligible patients with newly diagnosed breast cancer were approached, with 65 (97%) enrolled in the program. All participants completed the WQ and all received a WP with indicated supportive referrals and educational resources. All participants engaged partially or fully with WP recommendations. Participants were screened at high risk for an average of 3.8 unmet needs, and 98% were at high risk for 2 or more needs at the time of diagnosis. Exercise was identified as the highest unmet need (83%). There was 76% adherence with referral to the program’s Exercise Physiologist. Other commonly identified areas of needs were nutrition (59%) and sleep quality (51%). WAPP tele-medicine visits began in June 2020 and are ongoing; visit completion rates and interventions will be presented. Qualitative data regarding patient experience and QOL will be obtained via focused interviews and feedback will be categorized in thematic domains.
**Conclusions:** In this pilot, the majority of patients with newly diagnosed breast cancer enrolled in the program, completed a WQ in advance of their initial medical oncology visit, and engaged with the WP. Our findings suggest that this early introduction to survivorship care is feasible. Earlier patient engagement and incorporation of wellness and supportive services from time of diagnosis may significantly improve our ability to address multifactorial needs during and after cancer therapy.

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# Deep-learning based prediction of homologous recombination deficiency (hrd) status from histological features in breast cancer; a research study

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BackgroundHomologous recombination deficiency (HRD), originally described in tumors from patients with germline mutations in *BRCA1/2* genes, renders cells sensitive to poly-ADP ribose polymerase inhibitors (PARPi) (1), but can be caused by mutations in other genes and is prevalent across multiple cancer types (2). HRD status is of clinical interest because it can indicate patient eligibility for treatment with PARPi. Currently, HRD status is determined by sequencing to identify BRCA mutations or genomic instability, but this has a high rate of failure (3). In this research study, we apply a deep-learning based computational approach to directly infer HRD status from digitized images of hematoxylin and eosin (H&E) stained histology samples in breast cancer tumors.  MethodsDigitized whole slide images (WSI) of 931 H&E stained, formalin-fixed and paraffin-embedded (FFPE) breast adenocarcinoma (BRCA) tumor biopsies from the cancer genome atlas (TCGA) were used to train machine learning (ML) models to identify patients that are HRD based on human-interpretable features (HIFs) and end-to-end (E2E) modeling. To train the models, samples were split into training and validation sets designated either HRD or homologous recombination proficient (HRP) based on a previously generated aggregate HRD score (calculated from regions of loss of heterozygosity, large scale genomic instability, and telomeric allelic imbalance) by genomic analysis of the PanCancerAtlas (2). We applied an untuned HRD score threshold of 45 to assign class labels resulting in 142/931 (15.3%) HRD cases.
Board certified pathologists (N=93) annotated tissue regions and cellular foci on the PathAI research platform yielding 65,477 annotations. ML models based on convolutional neural networks were trained to recognize breast cancer cells, lymphocytes, macrophages, plasma cells, fibroblasts, and tissue compartments including cancer epithelium, cancer stroma and necrosis within the H&E stained breast cancer samples.
Two pipelines constructed H&E histology-based classifiers of HRD status. A weakly-supervised “end-to-end” model using ResNets extracted features from small image patches with an attention module to aggregate across patches and directly predict HRD status. The HIF-based approach used the tissue segmentation and cell identification classifiers to quantify histological features in the WSI. From the labeled images, we extracted 600 HIFs that capture complex relationships between cell and tissue types. HIFs and patient clinical covariates were applied as input to a Sparse Group Lasso model to predict the HRD status of the associated patients.ResultsML models predicted HRD status from H&E stained WSI. The area under the receiver operating characteristics curve (AUROC) was 0.87 for the HIF model and 0.80 for the E2E model. Both classifiers achieved high sensitivity for HRD status (0.86) with more moderate precision (F1 score HIF: 0.80 and E2E: 0.72).  Our HIF with clinical covariates model revealed morphological features that were significantly associated with HRD compared with HRP. HRD samples were enriched for areas of necrosis, stromal fibroblasts, and tumor infiltrating lymphocytes ($p < 0.001$, Mann-Whitney U test).
Conclusions
Computational models built with the PathAI research platform identified HRD positive patients directly from routinely collected H&E stained WSIs and identified a histological basis for how mutational signatures impact the tumor microenvironment. Disclaimer: The PathAI platform and HRD model are not intended for diagnostic purposes.
1 Farmer et al., 2005. Nature 14;434(7035):917-212 Knijnenburg et al., 2018. Cell Rep 23, 239–2543 Hoppe et al., 2018. JNCI 110(7): djy0854 Coudray et al., 2018 Nat Med 24:1559-15675 Kather et al., 2019. Nat Med 25: 1054–1056pages

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Hotspot *ESR1* mutations rewire cell-cell adhesome to facilitate breast cancer metastasis

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Background: Estrogen receptor alpha (ER/*ESR1*) mutations are found in 20-40% of endocrine resistant ER+ metastatic breast cancers, and they are associated with worse outcome. Preclinical studies have shown that they cause ligand-independent growth, resistance to endocrine therapy, and there is growing evidence for a role in metastasis. It is not known how *ESR1* mutant cancer cells cause metastases and whether such a mechanism may indicate novel therapeutic options. Methods: ddPCR was used to detect hotspot *ESR1* mutations. Transcriptome data were derived from cell line models and clinical samples. For *in vitro* phenotypic characterization, Y537S and D538G genome-edited MCF7 and T47D cell models from four different labs were used. Cell-cell adhesive properties were assessed using calcein-labelled adhesion, spontaneous cell aggregation and microfluidic aggregation assays. Altered expression of cell-cell adhesion genes detected in RNA seq data was validated via qRT-PCR, immunoblot and immune staining. Functional contributions of desmosome and gap junctions were tested by blocking peptide and carbenoxolone respectively. Mutant ER cistromes were profiled using ChIP-sequencing. Tail vein injection was performed on nude mice to evaluate metastasis *in vivo*. Mouse lung micro-metastatic foci were quantified using human-specific CK19 staining. Circulating tumor cells (CTCs) clustering propensity *in vivo* was assessed via intracardiac injection of *ESR1* WT and mutant cells into nude mice following CTC microfilter capture. CTCs enumeration from breast cancer patients' blood samples was performed using CellSearch™ system. Results: We identified a significant enrichment of *ESR1* mutations in distant (12/48) vs local (0/27) recurrences, confirming the strong association of mutant ER with metastasis. Transcriptomic analysis revealed altered cell-to-cell interaction pathways in *ESR1* mutant tumors compared to ESR1 WT tumors, suggesting a previously undescribed role of *ESR1* mutations in reprogramming cell-cell adhesome. *ESR1* mutant cells grown in suspension culture revealed more compact multicellular spheroids compared to WT cells. This observation was confirmed under both static and microfluidic conditions, indicative of increased cell-cell interactions. The effect was more pronounced in MCF7 compared to T47D cells, and it correlated with increased expression of multiple desmosome and gap junction pathway genes, which were also significantly enriched in *ESR1* mutant tumors. Pharmacological blockade of desmosome and gap junctions significantly rescued enhanced cell-cell adhesion in *ESR1* mutant cells. Mechanistically, our ER ChIP-seq did not identify any gained mutant ER binding sites in proximity to cell-cell adhesion gene loci, indicating indirect regulation by mutant ER. Consistent with this, expression of Connexin 43, one of the top upregulated gap junction components, was induced by cFOS found to be highly upregulated in *ESR1* mutant cells. Tail vein injection of *ESR1*-mutant cells derived more distant macro- (MCF7) and micro- (T47D) metastases. Given increasing evidence for role of cell-cell attachment in CTC phenotypes, we tested CTC formation for *ESR1* WT and mutant cells. *In vivo* studies showed MCF7 Y537S *ESR1* mutant cells formed larger multi-cellular CTC clusters with increased compactness compared to WT CTCs. These preclinical data translated to clinical observation, where we observed an enrichment of CTC clusters in patients with *ESR1* mutant-metastatic breast cancers. Conclusion: Hotspot *ESR1* mutations induce expression of multiple desmosome and gap junction genes and confer increased cell-cell adhesion, which facilitate breast cancer metastasis via increased CTCs clustering propensity. These findings might guide approaches to test potential repurpose of drugs targeting gap junction in ER mutant tumors.

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# Impact of tucatinib on health-related quality of life in patients with HER2+ metastatic breast cancer with stable and active brain metastases

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**Background** Patients (pts) with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer (MBC) who have brain metastases (BM) have limited treatment options and lower health-related quality of life (HRQoL) compared with pts without BM (Hurvitz 2019). HER2CLIMB is a randomized trial (2:1) of tucatinib vs. placebo in combination with trastuzumab and capecitabine in pts with HER2+ MBC that included pts with stable and active brain metastases (NCT02614794). In HER2CLIMB, the addition of tucatinib to trastuzumab + capecitabine demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) in pts with HER2+ MBC and in those with stable and active BM, with importantly, a tolerable and manageable safety profile (Murthy 2020). An evaluation of the impact of tucatinib on HRQoL in pts with stable and active BM is presented here. **Methods** HRQoL data were available from 330 of 612 pts, including 163 pts with BMs. HRQoL was assessed using the EQ-5D-5L tool which includes a visual analog scale (EQ-VAS) and a descriptive system (EQ-5D) comprising 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Data were collected at Cycle 1 Day 1, Cycles 3-9 (every 2 cycles; 21-day cycles), Cycle 12 and beyond (every 3 cycles), and at the 30-day follow-up. The EQ-5D-5L scores were summarized by cycle for each treatment arm. Time to deterioration, defined as a ≥7-point change from baseline on the EQ-VAS, was estimated by the Kaplan-Meier approach. The median time to deterioration (and 95% CIs) were computed for each arm. **Results** In total, 163 pts with stable and active BM were included in this HRQoL analysis, 107 pts on the tucatinib arm and 56 pts on the placebo arm. Compared to the placebo arm, pts on the tucatinib arm had an approximately 49% reduction in the risk of deterioration (hazard ratio: 0.51; 95% CI: 0.28, 0.93); the median time to deterioration has not been reached in the tucatinib arm with available follow-up and was 5.5 months (95% CI; 4.2, -) in the placebo arm. Decline in all domains of the EQ-5D-5L and the EQ-VAS scores were seen once pts discontinued therapy, particularly on the 'usual activities' domain. Additional available QoL data will be presented. **Conclusions** Pts with MBC and BM treated with tucatinib in combination with trastuzumab + capecitabine demonstrated significantly longer and clinically meaningful time to deterioration of HRQoL. HRQoL was maintained throughout the treatment course, allowing them to receive full benefit of the therapeutic approach and resulting in statistically significant and clinically meaningful improvement in OS. **References** Hurvitz SA, O'Shaugnessy J, Mason G, et al. Central Nervous System Metastasis in Patients with HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from SystHERs. Clin Cancer Res. 2019;25(8):2433-2441.Murthy RK, Loi S, Okines A, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020;382(7):597-609.

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# A picture worth a thousand words - “classic” inflammatory breast cancer (IBC) appearance associated with overall survival

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Background: IBC is considered a clinical diagnosis characterized by rapid onset of diffuse skin changes in the setting of a breast cancer diagnosis. A wide variety of visual changes are accurately diagnosed as IBC. Here, we sought to determine whether the most subjectively “classic” appearing presentation (swollen, involved breast with nipple inversion and diffuse skin change) was associated with worse outcomes.
Method: We reviewed the images and charts of patients from the prospective IBC registry from the MD Anderson IBC Clinic. Breast medical photographs were reviewed by a non-expert and the visual presentation was scored as classic (as above), not classic, and in between. Comparative analyses were used to assess differences between patient groups using Chi-squared test, or Fisher’s exact test for categorical variables. Wilcoxon rank sum test was used for continuous measures. We used the Kaplan Meier estimator and the log-rank test to investigate association between scoring and survival distributions. Cox proportional hazard regression was employed to assess the impact of important covariates on the overall survival.
Results: We analyzed 245 IBC patients with median age 55 (range, 26-81), M0 vs. M1 status (157 and 88 patients, respectively), 68 TNBC vs. 177 non-TNBC patients. The classic presentation was significantly associated with smoking, post-menopausal status, and metastatic disease at presentation ($P = 0.002$, 0.018, and 0.004, respectively). Presentation was significantly associated with OS in univariate analysis ($P < 0.001$). 10 year overall survival was 57% vs. 33% for classic (score 3) versus non-classic or in between presentation. The multivariable Cox regression model adjusting for clinical staging ($P<0.001$) and TNBC status ($P<0.001$) demonstrated classic presentation score was significantly associated with poorer OS time (HR 2.4, CI 1.6-3.6, $p<0.001$).
Conclusions: A visual inspection of presentation photograph for “classic” appearance, obvious swelling, skin change, and nipple inversion, independently predicted poorer OS in IBC. Further work is warranted to understand the differences in classic and non-classic presentations, and the relationship between smoking and breast cancer presentation.

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**Publication Number:** PD9-04

# Identification of biomarkers associated with therapeutic resistance: Quantitative protein/phosphoprotein analysis of ~750 patients across 8 arms of the neoadjuvant I-SPY 2 TRIAL for high-risk early stage breast cancer

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**Background:** The goal of I-SPY 2 is to rapidly test novel therapies in addition to standard of care in high-risk breast cancer patients. It has resulted in increasing response rates, where pCR rates in TNBC and HR-HER2+ subsets have reached ~60% and ~75%, respectively. Yet, there remains a sizeable subset of non-responders, especially among HR+ patients. Identification of ‘universal’ resistance mechanisms may guide rational selection of agents to improve these patient's outcomes. Thus, we analyzed reverse phase protein array (RPPA) based quantitative protein/phosphoprotein data across arms to assess whether there are common mechanisms rendering these cancers resistant to all agent classes tested to date. **Methods:** 736 patients (260 HR+HER2-, 252 TN, 142 HR+HER2-, and 82 HR-HER2+; over 8 arms: 194 Ctr, 105 neratinib (N), 63 veliparib/carboplatin (VC), 128 AMG386 (anti-ANG1/2), 87 MK2206 (anti-AKT), 43 TH/pertuzumab (P), 49 TDM1/P, and 67 pembrolizumab (Pembro)) with pCR and RPPA data at the pre-treatment time point were considered for this analysis. 141 RPPA endpoints representing key cancer pathways were assessed for association with pCR using logistic regression modeling, with HR, HER2 and treatment arm as covariates (likelihood ratio test; $p<0.05$). Analysis was also performed in HR/HER2 subsets and within treatment arms. Markers were analyzed individually; multiple comparison correction (Benjamini-Hochberg) was applied to p-values. Our analysis is exploratory, and does not adjust for other biomarkers outside this study. **Results:** Prior to FDR correction, high levels of Cyclin D1, a cell cycle protein implicated in estrogen-mediated DNA damage repair, associate with non-pCR in the population as a whole and within all subtypes except for the HR-HER2+ subset; an association that retains significance after FDR correction overall as well as in HER2- and HR+HER2- subsets. Within individual arms, high Cyclin D1 predicted non-response in VC, control, and AMG386; and trends toward association in Pembro and N. In addition, high quantitative ER and phospho-androgen receptor (pAR; S650) associate with non-pCR in the population as a whole and in the HR+HER2- subset. For both ER and pAR the strongest association with non-pCR was in the Pembro arm. Candidates for universal sensitivity signals include immune proteins JAK-STAT (pSTAT5 (Y694) and pSTAT1 (Y701)) overall; and pERBB2/pEGFR for HER2+ patients. **Conclusions:** High levels of Cyclin D1, but not other cell cycle proteins, predict non-response to chemo-/targeted-therapy across arms and subtypes, suggesting that agents specifically targeting Cyclin D1 may increase chemo-sensitivity. ER/phospho-AR as global resistance signals suggest inclusion of anti-AR agents in combination therapy, and the need for new endocrine-based approaches.

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# Classification of triple negative breast cancer (TNBC) by DNA damage immune response (DDIR) signature and homologous recombination deficiency (HRD) status: Analysis of SWOG S9313 adjuvant trial

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**Introduction/Aims**: DDIR signature, HRD, and stromal tumor infiltrating lymphocytes (sTIL) have each been associated with favorable outcomes in early stage TNBC. We assessed the overlap between these markers and created prognostic categories based on their combined use in a prospective trial of TNBC patients uniformly treated with adjuvant doxorubicin (A) and cyclophosphamide (C) on the SWOG S9313 trial. **Methods**: SWOG S9313 trial accrued 3,125 women with early stage breast cancer to two alternative dose schedules of AC, with no difference in outcomes between the two arms. 425 centrally determined TNBC cases from S9313 were identified. DDIR signature (score ≥ 0.3681 = DDIR+, Almac Diagnostic Services), HRD status (score ≥ 42 = HRD+, Myriad Genetics), and sTIL were assessed. Gene expression data (Xcel™ array) was subjected to clara$^{T}$ V3.0.0 biological signature analysis (Almac Diagnostic Services), and co-expression cluster analysis was used to identify signatures associated with DDIR and HRD status. The impact of dual classification by DDIR and HRD status (**Group 1**: DDIR+/HRD+, **Group 2**: DDIR+/HRD-, **Group 3**: DDIR-/HRD+, **Group 4**: DDIR-/HRD-) on disease free survival (DFS) and overall survival (OS) was examined using Cox regression with adjustment for randomized treatment assignment and nodal status. **Results**: For the 425 patients, median age was 45 years, 33% were node-positive, and 5-year DFS and OS were 74% and 82%, respectively. DDIR and HRD status was available for 89% each, sTIL% was available for 99%, and all three markers were available for 77% (328/425) of patients. 60% were DDIR+ and 65% HRD+. Among DDIR- tumors, 58% were HRD+. sTIL% was associated with DDIR status (*P*<0.0001) but not with HRD status (*P*=0.75). The proportion of patients in each group, median sTIL%, and 5-year DFS and OS for each group are outlined in Table 1. DFS and OS were similar for Groups 1, 2, and 3 but significantly lower for Group 4. As expected, cluster analysis showed that immune response signatures dominated Groups 1 and 2 regardless of HRD status. Group 3 tumors were characterized by over-representation of genomic instability signatures, a paucity of immune-related signatures, and low sTIL infiltration. Despite this immune-depleted phenotype, the 5-year OS for Group 3 was similar to that of the immune-enriched DDIR+ groups. Signatures associated with epithelial-mesenchymal transition, mast cell infiltration, and xenobiotic metabolism were over-represented in Group 4. **Conclusions**: Forty percent of patients with early stage TNBC demonstrate immune-deplete (DDIR-) phenotype, and within this phenotype, more than half demonstrate HRD+ status. HRD+ status within the immune-deplete phenotype predicts for better DFS and OS with adjuvant AC, probably due to underlying genomic instability and increased sensitivity to DNA damaging chemotherapy. Sixty percent of early stage TNBC patients demonstrate an immune-enriched (DDIR+) phenotype, and this phenotype is associated with improved survival with adjuvant AC chemotherapy regardless of HRD status. These findings provide important insights for patient selection and stratification in ongoing and future trials assessing DNA damaging therapy (e.g. PARPi, anthracyclines, platinum agents), immunotherapy, and their combinations in TNBC.

Table 1

| | **Immune-Enriched Groups** | | **Immune-Deplete Groups** | |
|---|---|---|---|---|
| | **Group 1 DDIR+/HRD+** N=137 (42%) | **Group 2 DDIR+/HRD-** N=59 (18%) | **Group 3 DDIR-/HRD+** N=77 (23%) | **Group 4 DDIR-/HRD-** N=55 (17%) |
| **5-year DFS** | 82% | 74% | 74% | 56% |
| P=0.001 (Group 1 vs 4); P=0.006 (Group 2 vs 4); P=0.016 (Group 3 vs 4); P=NS (Groups 1 vs 2, 1 vs 3, and 2 vs 3) | | | | |
| **5-year OS** | 88% | 86% | 83% | 69% |
| P=0.001 (Group 1 vs 4); P=0.003 (Group 2 vs 4); P=0.026 (Group 3 vs 4); P=NS (Group 1 vs 2, 1 vs 3, and 2 vs 3) | | | | |
| **Median sTIL (%)** | 20% | 20% | 5% | 5% |
| P<0.0001 (Group 1 vs 3); P<0.0001 (Group 2 vs 3); P=NS (Group 1 vs 2, 3 vs 4) | | | | |

**2020 San Antonio Breast Cancer Symposium®**

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Rintodestrant (G1T48), an oral selective estrogen receptor degrader in ER+/HER2- locally advanced or metastatic breast cancer: Updated phase 1 results and dose selection

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**Background**: Rintodestrant (G1T48) is a potent oral selective estrogen receptor degrader (SERD) that competitively binds to the estrogen receptor (ER) and blocks ER signaling in tumors resistant to other endocrine therapies. Preliminary results from Part 1 dose escalation showed robust target engagement on $^{18}$F-fluoroestradiol positron emission tomography (FES-PET), a favorable safety profile, and encouraging antitumor activity in patients with heavily pretreated ER+/HER2- advanced breast cancer (ABC), including those with *ESR1* mutations (Dees et al., ESMO 2019 [abstract #3587]). Here, we present updated results from dose escalation and expansion (Parts 1 and 2). **Methods**: This Phase 1, first-in-human, open-label study evaluated rintodestrant monotherapy in women with ER+/HER2- ABC after progression on endocrine therapy. Part 1 was a 3+3 dose escalation (200-1000 mg once daily [QD]); Part 2 expanded 600 and 1000 mg QD; and Part 3 was added to assess rintodestrant with palbociclib in patients in earlier lines in the advanced setting. Primary objectives included dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, and recommended Phase 2 dose. Secondary objectives included pharmacokinetics and antitumor activity (RECIST v1.1). Exploratory objectives included pharmacodynamic inhibition of ER target engagement (FES-PET), mutation profiling (cell-free DNA [cfDNA]), and change in ER expression from baseline to on-treatment tumor biopsies. **Results**: As of May 13, 2020, 67 patients (Part 1: n = 26; Part 2: n = 41) were treated, with a median age of 61 years (range 34-83) and ECOG PS of 0 (49%) or 1 (51%). Median number of prior lines in the advanced setting was 2 (range 0-9), including prior fulvestrant (64%), CDK4/6 inhibitor (69%), mTOR inhibitor (22%), and/or chemotherapy (46%). Median number of prior lines of endocrine therapy in the advanced setting was 2 (range 0-5), with 61% of patients having received ≥2 lines. Treatment-related adverse events (TRAEs) were reported in 70% of patients. The most common TRAEs in ≥10% of patients included hot flush (24%), fatigue (21%), nausea (19%), diarrhea (18%), and vomiting (10%), mostly grade 1 or 2. No DLTs were reported and MTD was not reached. Dose reduction due to TRAEs occurred in 1 patient (1%), with elevated transaminases (grade 3 ALT and grade 2 AST) at 600 mg. Serious TRAEs occurred in 2 patients at 1000 mg (grade 5 cerebral hemorrhage in the setting of low molecular weight heparin and grade 2 upper abdominal pain). Two patients (3%) discontinued treatment due to TRAEs. Overall, the frequency of patients with TRAEs at 800 mg was comparable with that at 600 mg (57% vs 63%) and less than that at 1000 mg (81%). Of 67 patients, 16 were on study treatment for ≥24 weeks and 3 (n = 1 at 600 mg; n = 2 at 1000 mg, including 1 with *ESR1* mutation) had a confirmed partial response (clinical benefit rate [CBR]: 28%). FES-PET standard uptake values decreased at week 4 with a mean reduction of 87% (±8%) at doses ≥ 600 mg. Of 59 patients tested for baseline cfDNA, 41% harbored ≥1 *ESR1* mutation, with a similar CBR in both groups (33% in *ESR1* mutant and 29% in *ESR1* wild-type). Seven of 9 patients had a decrease in ER immunohistochemistry H-score at both 600 and 1000 mg (median [range]: -27.8% [-33.8%, -3.4%]), irrespective of *ESR1* mutation status. Based on safety, efficacy, and ER degradation, 800 mg was selected as the optimal dose for further study. **Conclusions**: Rintodestrant continues to demonstrate an excellent safety/tolerability profile across all doses, with promising antitumor activity in patients with heavily pretreated ER+/HER2- ABC, including those with tumors harboring *ESR1* mutations. Part 3 of this study, evaluating rintodestrant 800 mg QD with palbociclib in a more endocrine-sensitive population, is ongoing (NCT03455270).

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# Health maintenance and breast cancer screening during the COVID-19 pandemic

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**Background:** WISDOM is a large (target enrollment>40,000) healthy women preference-tolerant, pragmatic study comparing traditional annual screening to personalized risk-based breast screening. Cancer screening, routine health care, and elective procedures were disrupted due to attempts to manage resources during the COVID-19 pandemic. Understanding of the impact on COVID-19 on trial participants is important to gain a broader understanding of the effect of the pandemic on healthcare activities. **Methods**: Women aged 40-74 years with no history of breast cancer or DCIS, and no previous double mastectomy can join the WISDOM (NCT02620852) study online at wisdomstudy.org. A total of 28,600 women have consented to participate. As part of the trial, each patient completes a baseline and interval surveys through a Salesforce platform. In May, the study IRB was amended to add a COVID specific survey with questions related to participants COVID risk perceptions, coexisting conditions, and receipt of healthcare services in the 2 months prior to the survey. An initial survey was sent May 2020, with follow-up surveys planned every 2 months. In addition, national surveys on a population-based cross section of individuals across the nation will be performed in parallel. Data was collected, de-identified, and then analyzed using basic descriptive analysis, chi-2 analysis, and logit regression. **Results**: A total of 7,523 individuals in WISDOM responded to the survey (response rate 27%). Of those that responded, the average age at the time of the survey was 59 (range 40-79). The population was 87% Caucasian, 6% Hispanic, and 4% African-American. Only 3.6% of the sample felt they had COVID-19 either by symptoms or through testing. However, 10.0% felt they were at higher risk compared to similar individuals their age to get COVID-19. Of the sample, 29% had some form of high-risk coexisting condition that put them at higher risk for COVID-19. In terms of healthcare utilization in the prior 2 months, 43% had a routine medical visit cancelled by their primary care provider or health system, whereas 26% cancelled an appointment themselves. In terms of breast cancer screening, 16% had their screening visit either cancelled or delayed. Individuals who believed they were at higher risk (and more likely to have shorter interval screening recommendations on this trial) had a higher Odds Ratio (1.66) for a screening cancellation ($p<0.001$). Those individuals who held the belief that COVID-19 was no more dangerous than the seasonal flu were more likely to have medical visits and routine care in the preceding 2 months than those that did not share that belief. (OR 1.18, $p=0.032$). Individuals were significantly more worried about COVID-19 than developing breast cancer (43% moderate to severely worried about COVID compared to 8.2% for breast cancer). Those worried about COVID were more likely to have screening cancellation (OR 1.18, $P<0.001$) and those more worried about breast cancer were less likely to have a screening cancellation (OR. 0.83, $P<0.001$). **Conclusions**: Health maintenance, prevention, and specifically breast cancer screening are important, but these health activities have been significantly disrupted due to the COVID-19 pandemic. Given that the pandemic will likely continue for many months until there is either a vaccine, treatment, or herd immunity, it will be important to define the drivers and messages (healthcare and screening) to ensure patients receive proper health maintenance and prevention to reduce the risks associated with other diseases that are not COVID-19. The preliminary data presented as part of this abstract submission are the early results of an effort to develop a predictive model and targeted strategies for communication and intervention for cancer screening during the course of the COVID-19 pandemic.

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# Evaluating serum thymidine kinase 1 in hormone receptor positive metastatic breast cancer patients receiving first line endocrine therapy in the SWOG S0226 trial

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**Background:** Endocrine therapies (ETs) are effective in hormone receptor positive metastatic breast cancer (MBC), but resistance is a major clinical problem. Thymidine Kinase 1 (TK1) plays a key role in DNA synthesis and is a marker of cellular proliferation. Serum (sTK1) activity is associated with poor prognosis in MBC patients treated with chemotherapy. SWOG S0226 trial demonstrated that anastrazole (A) + fulvestrant (F) is more effective than A alone in post-menopausal women with hormone receptor positive MBC, specifically those without prior adjuvant tamoxifen (Mehta et al NEJM 2019). We hypothesized that baseline (BL) and serial sTK1 levels are prognostic and demonstrate differential activity of A+F vs. A. **Methods:** sTK1 activity was assessed in 1,726 archived S0226 serum samples (BL, cycle 2, 3, 4, and 7) using DiviTum® assay (100% evaluation rate). Pre-specified cutoff of ≥200 DiviTum Unit per liter (Du/L) was considered high. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier, log-rank tests and Cox regression. **Results:** Serum samples at BL were available in 432/694 (62%) patients. Outcomes on this subset were comparable to those on the full trial. Median sTK1 at BL was 135 Du/L. sTK1 was elevated in 171 (40%) patients. Overall, patients with high vs. low BL sTK1 had significantly worse PFS [hazard ratio (HR)=1.76; 95% CI (1.43-2.16); P<0.0001; median PFS 11.2 vs.17.3 months]. In patients with no prior adjuvant tamoxifen and high sTK1, PFS was significantly better for those treated with A+F vs. A alone [HR=0.64; 95% CI (0.43-0.95); P=0.027; median PFS 13.6 vs. 8.7 months], whereas PFS did not differ between A+F vs. A alone for those with low sTK1 (P=0.34). Differences in OS for high vs. low sTKI were even more pronounced [HR=2.38; 95% CI (1.91-2.98); p<0.0001; median OS 30 vs. 58 months]. For high sTK1, OS was significantly better for those treated with A+F vs. A alone who did not have prior adjuvant tamoxifen [HR=0.58; 95% CI (0.38-0.87); P=0.0087; 46 vs. 21 months], whereas for low sTK1 there was no difference by therapy (p=0.44). During serial monitoring, patients with high sTK1 had significantly worse subsequent PFS and OS than those with low sTK1 (at cycle 2: PFS HR=1.70, P<0.0001, OS HR=2.51, P<0.0001). **Conclusions:** High sTK1 at BL and at subsequent time points is associated with worse prognosis in hormone receptor positive MBC patients starting 1st line ET. Patients with low sTK1 at BL may do relatively well on single agent and may not need combination ET. We speculate that patients with low sTK1 need only ET monotherapy and may not benefit from the addition of CDK4/6 or mTOR inhibitors. However, further evaluation of the predictive potential of sTK1 will need prospective clinical trials.
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Antitumor activity of Z-endoxifen (ENDX) is mediated via PKCβ1-dependent ERα loss and cell cycle arrest in ERα-positive breast cancer

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**Background:** The tamoxifen (TAM) metabolite, ENDX, demonstrated promising antitumor activity in endocrine resistant breast cancer (BC) in both phase I and phase II settings. Furthermore, ENDX resulted in superior *in vivo* antitumor activity compared to TAM and letrozole in aromatase-expressing aromatase inhibitor-sensitive and resistant MCF7AC1 models. Recently, we identified protein kinase C beta 1 (PKCβ1), which regulates cell proliferation and tumorigenic transformation, as a novel target of ENDX. ENDX-bound PKCβ1 at concentrations achieved in phase I/II ENDX studies (100-300 nM). In contrast, TAM binding to PKCβ1 occurred at concentrations 7-10 folds higher (2 μM) than achievable with TAM 20 mg/day dosing. However, the clinical relevance of targeting PKCβ1 kinase activity is unclear, since drugs that target PKCβ1 (enzastaurin) have been ineffective in BC and other solid tumors. Therefore, we sought to understand how ENDX altered PKCβ1 and to further compare and contrast ENDXs effects to that of PKCβ1 kinase inhibition in ERα+ BC. **Methods:** The effects of PKCβ1 silencing and ENDX treatment on gene expression was analyzed by RNAseq in MCF7AC1 cells. The impact of PKCβ1-silencing on cell cycle was evaluated by flow cytometry. Protein expression of cell cycle regulators in PKCβ1 and ENDX-treated MCF7AC1 and T47D cells were compared to TAM and enzastaurin *in vitro* and to letrozole, TAM or control *in vivo*. The effects of PKCβ1 and drugs on growth were analyzed by cell proliferation assays. *PRKCB* gene amplification was assessed in primary tumors using TCGA data and in metastatic tumors using whole-exome sequencing data from patients enrolled in the PROMISE study (NCT 03281902). **Results:** RNAseq analysis revealed E2F targets and G2M checkpoints as the top hallmark genesets significantly downregulated in both PKCβ1-silenced and ENDX-treated MCF7AC1 cells. Flow cytometry demonstrated that PKCβ1 silencing increased G1 and reduced S phases of the cell cycle. Western blot analyses of PKCβ1-silenced MCF7AC1 and T47D cells displayed reduced protein levels of the cell cycle regulators Cyclin D1, Retinoblastoma (Rb), phospho-Rb$^{S807/811}$, CDK4, Chk1 and E2F1 that regulate G1/S transition. While short term ENDX (48 hours) treatment did not alter PKCβ1 levels, prolonged *in vitro* ENDX treatment profoundly reduced PKCβ1 protein levels and the aforementioned cell cycle regulators, faithfully replicating PKCβ1 silencing effects. In contrast, enzastaurin had no impact on proliferation or cell cycle proteins in either model. Consistent with this finding, ENDX, but not TAM or letrozole, reduced protein levels of ERα and cell cycle regulators *in vivo*. Overexpression of PKCβ1 induced TAM, but not ENDX, resistance and had little impact on responsiveness to enzastaurin. While *PRKCB* gene amplification was uncommon in newly diagnosed ERα+/HER2- BC (5%, TCGA), *PRKCB* was amplified in 40% of metastatic ERα+/HER2- BC (PROMISE study). **Conclusion:** We have confirmed the relevance of a new ENDX target, PKCβ1, in ERα+/HER2- BC. While targeting PKCβ1 kinase activity elicited no anticancer effects in ERα+ cells, PKCβ1 downregulation, either by siRNA or ENDX, resulted in profound ERα turnover, reduced protein levels of essential cell cycle mediators and profoundly inhibited cell proliferation. Furthermore, PKCβ1 protein expression is associated with TAM, but not ENDX, resistance, a finding whose clinical relevance is further magnified by identification of *PRKCB* amplification in metastatic ERα+ BC, confirming its potential importance in progression. Efforts are currently underway to elucidate the mechanistic basis for ENDX-induced PKCβ1 and ERα degradation and the contribution of these effects to the superior antitumor activity of ENDX in ERα+ BC.

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# The impact of sleep on weight loss in overweight or obese breast cancer survivors

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**BACKGROUND:** Sleep disturbance, common in cancer survivors, is associated with obesity, eating behaviors and metabolism, and may impact weight loss treatment outcomes. Weight loss promotion in breast cancer survivors is important because it can potentially decrease cancer recurrence. We have previously demonstrated the efficacy of a behavioral weight loss (BWL) intervention for overweight/obese breast cancer survivors in the POWER-remote breast cancer trial. In the current study we aimed to evaluate the impact of baseline sleep on weight outcomes at 6 and 12 months. We hypothesized that participants with poor sleep at baseline will lose significantly less weight. **METHODS:** Women with a history of stage 0-III breast cancer, who completed local therapy and chemotherapy, with a body mass index ≥25 kg/m$^2$ were randomized to a self-directed approach or the 12-month POWER-remote intervention, a BWL intervention consisting of telephone-based coaching, online educational materials and tracking of diet, physical activity and weight. Participants completed demographic questionnaires at baseline, and patient-reported outcomes (PROs) at baseline, 6 and 12 months, including the 6-item NIH PROMIS Adult Sleep Disturbance Version 1.0 Short Form, assessing sleep quality, depth, and restoration over the last week. Weight was measured at baseline, 6 and 12 months and % total weight loss (%TWL) was calculated from baseline weight. Those with poor sleep were defined as having a sleep T-score ≥55, and associations between sleep scores and change in weight at 6 and 12 months were made using a linear regression model, while adjusting for baseline weight. Fisher's exact test was also used to compare the number of patients who had 5% weight-loss between sleep groups.
**RESULTS:** A total of 48 women with early stage breast cancer received BWL. Those with poor sleep in the BWL group (n= 16) lost significantly less weight than those with normal sleep in the BWL group (n=32) at both 6 (-4.06% vs -6.77% TWL, p>0.05) and 12 months (-3.87% vs -7.54% TWL, p>0.05), respectively. Similar findings were seen in poor sleepers in the BWL group and attaining 5% weight loss at 6 (p>0.05) and 12 months (p>0.05). There were no significant differences in weight loss outcomes among those in usual care.
**CONCLUSION:** Breast cancer survivors receiving the weight loss intervention who reported normal sleep at baseline had double the weight loss than those with sleep disturbance at 12 months (-7.54% vs -3.87%). While this is not statistically significant, it is clinically significant and leaves room for further study. These results suggest that sleep may affect weight loss. Updated data, including comparison with control group and analyses by weight loss irrespective of arm, will be reported at the conference. Further studies are need to evaluate the association between baseline sleep and weight loss, and determine if interventions that detect and treat underlying sleep disturbance may augment behavioral interventions for weight loss.
**FUNDING**: Breast Cancer Research Foundation, Cigarette Restitution Fund
Table 1: Weight Loss Summary in BWL group based on Sleep Disturbance

| **Variables** | **Poor sleep (T-score >55)** | **Normal sleep (T-Score <55)** | **Total** |
|---|---|---|---|
| **Sample Size** | **N = 16** | **N = 32** | **N = 48** |
| Baseline Weight - Mean (SD) | 202.1 (32.26) | 182.64 (27.73) | |
| Weight Loss 6mo. (lbs) - Mean (SD) | -8.5 (10.02) | -11.58 (11.03) | |
| Weight Loss 12mo. (lbs) - Mean (SD) | -7.92 (14.61) | -12.63 (13.72) | |
| Percent change in weight from BL to 6mo. - Mean (SD) | -4.06 (4.83) | -6.77 (6.45) | p>0.05 |
| Percent change in weight from BL to 12mo. - Mean (SD) | -3.87 (7.29) | -7.54 (7.91) | p>0.05 |

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**Publication Number:** PS3-04

Breast tumor targeted fluorescence guidance for intraoperative margin assessment

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**BACKGROUND:** A majority of the 270,000 women diagnosed with breast cancer in the United States annually are candidates for breast conserving surgery (lumpectomy), however, up to 30% of patients require reoperation due to positive margins. The ideal resolution is to make residual in-breast disease visible at the time of surgery. The goal of this research is to develop a systemically administered fluorescent molecular imaging agent that is targeted to breast tumors for intraoperative margin assessment using fluorescence guided surgery (FGS). **METHODS**: To identify targetable cell-surface markers for use in FGS, gene expression profiling of publicly available Affymetrix mRNA microarray data from patients with invasive ductal or invasive lobular carcinoma tumors (n=34) and surrounding normal breast tissues (n=32) was performed. Protein expression of select targets was determined by immunohistochemistry (IHC) staining of patient tissue specimens. A humanized CEACAM6 (carcinoembryonic cell adhesion molecule 6) specific antibody fragment (scFv-Fc [IgG4]) was conjugated to the near-infrared IRDye800CW fluorescent dye (LiCor) by NHS-ester linkage to create CEACAM6-800. The conjugate was characterized for *in vitro* specificity by immunocytochemistry (ICC) and live cell uptake studies. As proof-of-principle, the conjugate (15 µg) was intravenously injected into nude mice bearing orthotopic human MCF-7 breast cancer mammary fat pad (MFP) xenograft tumors with endogenous expression of CEACAM6. FGS was performed using the “SurgVision” clinical imaging platform (approved for clinical use in Europe) at 24 h post-injection.**RESULTS:** We identified 263 genes with higher mRNA expression in tumor relative to normal. From this list, we selected 9 genes for confirmation of protein expression by IHC. Of the 9 targets, only CEACAM6 had no protein expression in normal breast tissues and robust expression in ~50% of tumors. ICC staining using the CEACAM6-800 conjugate and multiple human ductal carcinoma tumor cell lines confirmed the cell surface localization of CEACAM6. In live-cell uptake studies, CEACAM6-800 accumulated on the cell surface as early as 10 min after addition to the media and was internalized after 90 min. Blocking studies demonstrated specificity. In the proof-of-principal FGS study, we observed high fluorescence in MCF-7 MFP tumors relative to background and the tumors and their residuals were completely removed in the first attempt. **CONCLUSION:** We have confirmed CEACAM6 protein as a cell-surface adhesion receptor target for breast cancer FGS. The CEACAM6-800, fluorescent-dye to antibody-fragment conjugate was prepared and tested *in vitro* for sub-cellular localization and specific uptake. *In vivo* studies demonstrated specific uptake into MFP tumors and FGS for tumor resection. We are currently performing studies to determine the *in vivo* pharmacokinetics of CEACAM6-800 uptake and clearance in tumor and normal tissues and pre-clinical post-surgery survival using our pre-clinical models. These studies will enable future translational studies.

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**Publication Number:** PD5-04

# DCIS biosignature reclassified patients who met RTOG 9804 or ECOG-ACRIN E5194 ‘low-risk’ clinicopathologic criteria into an elevated invasive risk group who benefited significantly from radiation therapy

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**Background:** The goal of therapy for DCIS is to prevent invasive breast cancer. Randomized clinical trials for DCIS demonstrated that patients benefited from adjuvant radiation therapy (RT) after breast conserving surgery (BCS). However, treatment selection for patients with DCIS remains a challenge. Studies evaluating ‘low-risk’ clinicopathologic features have not identified a group of patients who do not benefit significantly from RT after BCS. Recently, a biosignature, DCISionRT (PreludeDx, Laguna Hills, CA), has been validated in multiple cohorts. The test provides a continuous 10-year breast event risk for patients treated with and without RT after BCS. In this study, we examined the utility of the biosignature to identify patients who met RTOG 9804 or ECOG 5194 ‘low-risk’ criteria but remained at elevated invasive risk after BCS and benefited from RT.
**Methods:** The analysis was performed in a combined cohort made up of four studies. FFPE tissue samples and patient outcomes were obtained from Uppsala University Hospital and Västmanland County Hospital, Sweden (UUH) between 1986 and 2004, the University of Massachusetts, Worcester (UMass) from 1999 to 2008, from Kaiser Permanente Northwest (KPNW) from 1990-2007, and from the SweDCIS trial cohort (1987-2000). Patients were treated with or without RT after BCS. Treatment decisions were neither randomized nor strictly rules-based, except for the randomized SweDCIS trial for RT. Individual patient outcome and biosignature results were analyzed independently at University of South Florida. Hazard ratios (HR) were determined using Cox proportional hazards analyses, and 10-year risks were assessed with survival analysis.
**Results:** Complete biomarker and clinical data was available for 660 women meeting a ‘low-risk’ clinico-pathologic criteria like ECOG 5194 grade 1 or 2 and for 535 women meeting RTOG 9804 like criteria. In this subset, there were 49 invasive breast cancer events for ECOG 5194 and 38 for RTOG 9804 within 10 years of diagnosis. In the biosignature low risk group there was no significant reduction from RT (p>0.15), where the 10-year absolute invasive benefit from RT varied from 1% to 2% for patients meeting RTOG 9804 or ECOG 5194, Table 1. However, in the biosignature elevated risk group, RT significantly reduced invasive cancer risk (p<.0022) for RTOG9804 or ECOG 5194 Grade 1 or 2 criteria. The 10-year absolute invasive benefit from RT was 15% for RTOG 9804, 12% for ECOG 5194 Grade 1 and 2. This corresponded to a 10-year invasive relative risk reduction of 84% for RTOG 9804, 74% for ECOG 5194 Grade 1 or 2. The number needed to treat (NNT) in the biosignature low risk group was > 100 for RTOG 9804 like criteria, while the NNT was 7 in the biosignature elevated risk group.
**Conclusions:** The DCIS biosignature identified patients from four cohorts that met ‘low-risk’ clinicopathologic criteria like RTOG 9804 or ECOG 5194 grade 1 or 2, and had elevated 10-year risk after BCS but had a substantial 84% relative benefit from RT. In contrast, the biosignature also identified a low risk group of patients with who had minimal (1-2%) risk reduction from RT. In comparison with traditional clinicopathologic features used to make RT recommendations, the DCISionRT score was dramatically associated with RT therapy benefit.

Biosignature low risk group (DS<=3)

| | patients, n | events, n | 10-year invasive risk difference, % | 10-year Invasive Cancer Risk, % | |
|---|---|---|---|---|---|
| | +/- RT | +/- RT | no RT - RT | No RT | RT |
| RTOG9804 | 296 | 23 | 0.6 | 6.9 | 6.3 |
| ECOG 5194 (Grade 1-2) | 344 | 26 | 1.4 | 7.6 | 6.2 |

Biosignature elevated risk group (DS>3)

| | patients, n | events, n | 10-year invasive risk difference, % | 10-year Invasive Cancer Risk, % | |
|---|---|---|---|---|---|
| | +/- RT | +/- RT | No RT - RT | No RT | RT |
| RTOG9804 | 239 | 15 | 15.0 | 17.9 | 2.9 |
| ECOG 5194 (Grade 1-2) | 316 | 23 | 11.8 | 15.9 | 4.2 |

(p>0.15)

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# Trastuzumab deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy: A randomized, phase 3 trial (DESTINY-Breast05)

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**Background**
Preoperative chemotherapy in combination with trastuzumab and pertuzumab is a preferred regimen for treating patients (pts) with HER2-positive, invasive, early breast cancer (BC). Pts who have received such treatment but still have residual invasive disease in the breast or lymph nodes at surgery are at greater risk for disease recurrence or death than those with a pathological complete response. The antibody-drug conjugate (ADC) T-DM1 was recently approved as a postneoadjuvant treatment for pts with residual invasive disease (in the breast and/or axillary nodes) after optimal neoadjuvant chemotherapy and trastuzumab (or trastuzumab with pertuzumab). T-DXd is a potent HER2-targeted ADC with a humanized HER2 antibody attached to a membrane-permeable topoisomerase I inhibitor payload by a cleavable tetrapeptide-based linker and a drug-to-antibody ratio of ≈ 8. Recently, T-DXd was approved for the treatment of adult pts with HER2-positive, unresectable or metastatic BC who have received ≥ 2 prior anti-HER2–based regimens in the metastatic setting (US) or had prior chemotherapy and are refractory to or intolerant of standard treatments (Japan). These approvals were based on a phase 2 study in which T-DXd demonstrated an objective response rate (ORR) of 60.9% (112/184 pts) and duration of response of 14.8 months in pts with HER2-positive (IHC 3+ or ISH+), unresectable or metastatic BC previously treated with T-DM1 (Modi et al. *N Engl J Med.* 2020;382:610-621). Here, we describe a randomized phase 3 trial evaluating T-DXd vs T-DM1 as postneoadjuvant treatment for high-risk pts with HER2-positive primary BC who have residual invasive disease following neoadjuvant therapy.

**Study Description**
DESTINY-Breast05 is a multicenter, open-label, randomized, phase 3 trial comparing the efficacy and safety of T-DXd with those of T-DM1 in pts with HER2-positive (IHC 3+ or ISH+, centrally confirmed on pretreatment biopsy), invasive BC with pathological evidence of residual invasive disease in the breast or axillary lymph nodes after neoadjuvant therapy. Additionally, pts must be at higher risk for recurrence, having either inoperable (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0) or operable BC at presentation (clinical stages T1-3, N0-1, M0) with axillary node-positive disease after optimal neoadjuvant chemotherapy and anti-HER2 treatment. The trial is recruiting pts from ≈ 400 sites globally. Approximately 1600 pts will be randomized (1:1) to T-DXd or T-DM1. Randomization is stratified by operative status, hormone receptor status, pathological nodal status following neoadjuvant therapy, and type of HER2-targeted neoadjuvant therapy (single vs dual). T-DXd 5.4 mg/kg or T-DM1 3.6 mg/kg will be administered intravenously once every 3 weeks for 14 cycles. Invasive disease-free survival based on investigator assessment is the primary efficacy endpoint; disease-free survival is the key secondary efficacy endpoint. Other secondary endpoints are overall survival, distant recurrence-free interval, and brain metastasis-free interval. Safety assessments include serious and treatment-emergent adverse events, physical examinations, vital signs, on-study chest imaging (to screen for pneumonitis), and clinical laboratory parameters. The pharmacokinetics of T-DXd, biomarkers, and health-related quality of life will also be evaluated. Long-term follow-up will continue after the primary analysis every 6 months until death, withdrawal of consent, loss to follow-up, or trial closure.

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**Publication Number:** PD10-04

Prognostic significance of germline BRCA mutations in patients with HER2-positive breast cancer. Epidemiological analysis in primary BRCA screens

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**Background:** HER2-amplified breast cancers are rare amongst BRCA mutation carriers. No data exist regarding clinico-histological characteristics and prognosis of this subgroup of patients. **Materials and Methods:** Using a retrospective matched cohort design, we collected data from 728 women who were diagnosed with breast cancer from January 2006 to December 2016 and were screened for germline BRCA mutations. Clinical and histological characteristics of the primary tumor, time to relapse, and survival were analyzed by BRCA and HER2 status. **Results:** One hundred and twenty HER2-positive, BRCA mutated cases were evaluated with respect to three control groups: HER2-positive, BRCA wild-type (n=136); HER2-negative, BRCA-mutated (n=226); HER2-negative, BRCA wild-type (n=246). Breast cancers with hormone receptor-negative status or high histologic grade (odds ratio=1.7; 95% confidence interval [CI]: 1.0-2.9) were more likely HER2-positive, with no restriction by BRCA mutation status. Disease-free and overall survival for HER2-positive, BRCA mutated cases were lower than those for the other subgroups. An interaction between BRCA mutations and HER2-positive status was found for poorer overall survival after adjusting for prognostic variables (HR = 3.4; 95% CI: 1.3-16.7). **Conclusions:** Germline BRCA mutations confer worse prognosis in patients with HER2-positive breast cancer. Ongoing trials testing novel therapeutic approaches (e.g. anti-HER2 therapies combined with PARP inhibitors) are warranted.

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**Publication Number:** PS7-04

Population-based estimates of breast cancer risk for germline pathogenic variants identified by gene-panel testing: An Australian perspective

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*BRA-STRAP* is an Australia-wide study of breast cancer predisposition that brings together gene-panel data from 30,000 adult Australian women of all ages, across the breast cancer risk spectrum, with and without a diagnosis of breast cancer. The "*BRA-STRAP* panel" includes 24 genes* that are involved in, or putatively associated with, predisposition to breast and/or ovarian cancer. Despite insufficient evidence for clinical translation for some of these genes, all 24 are commonly included on panel tests for breast cancer predisposition.

We present findings from the population-based case-control sub-study of *BRA-STRAP*, which involved 1451 women diagnosed with breast cancer and 857 age-matched controls participating in the Australian Breast Cancer Family Registry (ABCFR), and 6101 healthy, elderly Australian women enrolled in the *ASPREE* study. These analyses focus on rare genetic variants predicted to lead to loss of function and/or classified as pathogenic/likely pathogenic (P/LP) in ClinVar. Odds ratios (ORs) for their associations with breast cancer were estimated by aggregating genetic variants for each gene.

For the women diagnosed with breast cancer, the median age at diagnosis (inter-quartile range, IQR) was 40.0 (14.0) years and the overall frequency of P/LP variant carriers across all genes was 156/1451 (10.8%). The median age (IQR) of the ABCFR and *ASPREE* controls were 39.4 (14.9) and 73.9 (5.8) years, respectively. The frequencies of P/LP variant carriers were 33/857 (3.9%) and 268/6101 (4.4%) in the ABCFR and *ASPREE* controls, respectively. We combined both control datasets and, after adjusting for age and other potential confounders, the ORs associated with P/LP variants in *BRCA1* and *BRCA2* were 4.1 [95% confidence interval (CI): 1.8-10.2] and 2.9 [95% CI: 1.5-6], respectively. We also found that the OR for P/LP variants in *ATM* was 4.0 [95% CI: 1.5-10.4] and the OR for P/LP variants in *PALB2* was 2.2 [95% CI: 0.75-5.7] although this did not reach statistical significance.

These results contribute to international efforts to refine the breast cancer risk estimates for genetic variants identified from population-based screening of unselected women using genes that are included on panel tests and thought to be potentially breast cancer predisposition genes.The case-control-family design of the ABCFR will also allow us to estimate the age specific cumulative risk (penetrance) of these genetic variants, which is important for genetic counselling and the clinical management of carrier families.

**ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, FANCM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, RECQL, STK11* and *TP53*

**Publication Number:** PD2-05

# Randomized phaseII trial to evaluate alisertib alone or combined with fulvestrant for advanced, endocrine-resistant breast cancer (TBCRC 041)

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Background: In ER+ breast cancer (BC) models, Aurora A kinase (AURKA) activation is associated with expansion of $CD44^{+}/CD24^{low/-}$ tumor initiating cells, down-regulation of ERα, and endocrine therapy resistance. Alisertib, a selective AURKA inhibitor, can restore ERα expression and endocrine sensitivity. Early phase studies evaluating alisertib alone or with fulvestrant for ER+ metastatic BC (MBC) demonstrated a favorable safety profile and promising antitumor activity [Haddad, Breast Cancer Res Treat. 2018]. A phase II trial was conducted to determine if the addition of fulvestrant to alisertib improved objective response rate (ORR) and to assess clinical activity of alisertib alone or with fulvestrant in patients (pts) with prior fulvestrant and CDK 4/6 inhibitor (CDK 4/6i). Methods: Pts were randomized 1:1 to Arm A, alisertib (50 mg PO BID Days 1-3, 8-10, 15-17 q 28 days) or Arm B, alisertib with fulvestrant (500 mg IM Day 1, 15 for Cycle 1 and q 28 days thereafter). Eligibility included postmenopausal women, history of ER+ BC, prior fulvestrant, ≤ 2 prior chemotherapy lines, and measurable disease. Stratification factors included prior CDK4/6i, ER level (<10%, ≥10%), and primary/secondary endocrine resistance. Pts on Arm A could cross over to Arm B at progression. With 45 pts per arm, a one sided alpha=0.15 sequential binomial test would have an 85% chance of detecting an increase of ≥ 20% in the ORR of ArmB when the true ORR for Arm A is ≤ 20%. ORR was defined as a partial response (PR) + complete response (CR) by RECIST v.1.1 criteria. Secondary endpoints include progression free survival (PFS), 24-week clinical benefit rate (CBR = CR + PR + absence of progression for> 6 cycles), overall survival, duration of response (DoR), and safety. Blood and tumor specimens were collected at baseline, end of Cycle 1, and progression. Results: Pts enrolled July 2017 - November 2019 with 118 pre-registered, 96 registered, and 90 evaluable for the primary endpoint (Arm A: 45, Arm B: 45). Median age was 60 (range 33, 85). Nearly all received prior fulvestrant (n=89, 98.9%), aromatase inhibitor (n=83, 92.2%), and CDK4/6i (n=88, 97.8%). Most had secondary endocrine resistance (n=71, 78.9%). Pre-registration biopsy for ER was positive in 84 pts (86.7%) and negative in 6 pts (13.3%). More pts on Arm B had prior everolimus (A: 35.6%, B: 57.8%) and prior chemotherapy (A: 44.4%, B: 55.6%) for MBC. The ORR for alisertib and fulvestrant was 20.0% (90% CI: 10.9-32.3%), not significantly greater than alisertib alone 17.8% (90% CI: 9.2-29.8%). The 24-week CBR for Arm A was 42.2% (90% CI: 29.7-55.6%; n=19, including 7 PR) and Arm B was 31.1% (90% CI: 19.9-44.3%; n=14, including 8 PR). As of July 1, 2020, the median DoR was not reached in either arm. The median PFS time was 5.6 months (95% CI: 3.9 - 9.3) for Arm A and 5.1 months (95%CI: 3.8 - 7.6) for Arm B. Seventeen pts (18.9%) remain on treatment (A: 12, B: 5) having received at least 11 cycles (range up to 32+ cycles). At least one dose reduction was required for pts (A: 19, B: 18), most commonly due to neutropenia. The most common severe (grade ≥3) adverse events included neutropenia (n=19, 42.2% in each arm), anemia (A: 15.6%, B: 8.8%), and fatigue (n=5, 11.1% Arm B only). Pts discontinued therapy due to disease progression equally in each arm (n=28, 62.2%), however more pts on Arm B (n=12) than Arm A (n=5) discontinued therapy due to toxicity, refusal or other reasons. Conclusion: While the addition of fulvestrant to alisertib did not improve ORR, promising clinical activity with alisertib monotherapy was observed overall and notably for pts with endocrine and CDK 4/6i-resistant MBC. More severe toxicities and treatment discontinuation were observed in pts receiving combination therapy. Correlative blood (CTC/cfDNA) and tissue (AURKA, ERα, and stemness biomarkers) studies are underway.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** GS2-04

# A randomized phase III study of radiation doses and fractionation schedules in non-low risk ductal carcinoma in situ (DCIS) of the breast (BIG 3-07/TROG 07.01)

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**Background:** Wholebreast irradiation (WBI) after breast conserving surgery for DCIS reduces therisk of local recurrence including invasive recurrence. The objective of BIG3-07/TROG 07.01 is to test radiation dose escalation to the tumor bed (tumorbed boost) and fractionation sensitivity of whole breast irradiation (WBI) inpatients with non-low risk DCIS treated with breast conserving therapy.
**Methods:** BIG3-07/TROG 07.01 is an international, multicenter, randomized, controlled, phase 3 trial. Eligible women were ≥18 years ofage with completely resected non-low risk DCIS defined as age <50 years orage ≥50 years plus at least one of the risk factors for local recurrence (palpable tumor,multifocal disease, tumor size ≥ 1.5cm, intermediate or high nuclear grade, central necrosis, comedo histologyand/or surgical margin <10 mm). Patients were randomized to have tumor bedboost (16 Gy in 8 daily fractions) or no boost following conventional WBI (50Gy in 25 daily fractions) or hypofractionated WBI (42.5 Gy in 16 dailyfractions) in one of three randomization categories selected by centers priorto study activation. Randomization A was a 4-arm randomization of no boost vs. boostfollowing conventional WBI vs. hypofractionated WBI. Patients in RandomizationB and Randomization C were assigned no boost or boost following conventional WBIand hypofractionated WBI, respectively. The primary endpoint was time to localrecurrence, analyzed by intention to treat. The trial was designed to detect a3% difference in 5-year free-from- local recurrence rates between the no boostand boost groups (93% vs 96%; hazard ratio, 0.56) with 90% power and 2-sidedalpha level of 5%. The primary effect of boost was assessed on all randomizedpatients. The secondary effect of WBI dose-fractionation and the interactionbetween boost and WBI dose-fractionation were assessed on patients in RandomizationA and additionally on all patients.
**Results:** BetweenJune 2007 and June 2014, 1608 patients were randomized to have no boost (805patients) or boost (803 patients) after WBI. Conventional WBI was given in 831 patients(no boost in 416 patients; boost in 415 patients). Hypofractionated WBI wasgiven in 777 patients (no boost in 389 patients; boost in 388 patients). Adjuvantendocrine therapy was planned in 106 patients (13%) in the no boost group and105 patients (13%) in the boost group. Median follow-up was 6.6 years. The 5-yearfree-from- local recurrence rates were 93% in the no boost group and 97% in theboost group (hazard ratio, 0.47; 95% confidence interval [CI], 0.31 to 0.72;P<0.001). Forty-four percent and 45% of LRs were invasive in the no boostgroup and boost group, respectively. The effect of boost did not vary significantlyby age, tumor size, nuclear grade, surgical margin or endocrine therapy. Therewere no significant differences in the 5-year free-from- local recurrence ratesbetween the conventional WBI group and hypofractionated WBI group inRandomization A (94% vs. 94%, P=0.84) and in all randomized patients (95% vs.95%, P=0.89). The test for interaction between boost and dose-fractionation wasnot significant in Randomization A or in all randomized patients (both P=0.89).The rates of grade ≥2 breastpain (12% vs. 16%, P=0.84) and skin and subcutaneous tissue fibrosis (6% vs.15%, P=0.14) did not differ significantly between the groups.
**Conclusions:** Inwomen with non-low risk DCIS treatedwith breast conserving surgery, the addition of tumor bed boost followingconventional or hypofractionated WBI reduced local recurrence rates. There wasno difference in local recurrence rates between conventional WBI andhypofractionated WBI. (Registered with ClinicalTrials.gov, NCT00470236.)

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**Publication Number:** GS4-04

Endocrine therapy alone in patients with intermediate or high-risk luminal early breast cancer (0-3 lymph nodes), recurrence score <26 and Ki67 response after preoperative endocrine therapy: First efficacy results from the ADAPT HR+/HER2- trial (n=4,690)

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**Background:** In hormone receptor (HR) positive/HER2-negative node-negative early breast cancer (EBC) , patients (pts) with Recurrence Score™ (RS) <26 (postmenopausal) and <16 (premenopausal) have an excellent prognosis and do not benefit from additional chemotherapy. However, prognostic impact of RS results in node-positive disease and the importance of Ki67 decrease after short preoperative endocrine therapy (ET) in the context of genomic signatures remain unclear. Here, we present for the first time outcome data from the large prospective phase III ADAPT HR+/HER- trial combining both static (RS result on baseline core biopsy) and dynamic (Ki67 response) biomarkers to optimize the adjuvant therapy approach in luminal EBC. **Methods:** Pts with clinically high-risk EBC (cT2-4 OR clinically node-positive OR G3 OR Ki67≥15% HR+/HER2-) were treated by 3 (+/-1) weeks of standard ET (mostly aromatase inhibitors in postmenopausal and tamoxifen in premenopausal pts) before surgery or sequentially core biopsy. Pts with RS 0-11 OR 12-25 AND post-endocrine central Ki67≤10% were treated by ET alone at investigator choice (Part 1). All pts with high-risk disease (RS>25 or RS 12-25 with postendocrine Ki67>10% or c/pN2-3) were treated by chemotherapy within a phase III chemotherapy protocol (Part 2). Primary objective (Part 1) was non-inferiority of 5-year invasive disease-free survival (iDFS) in a minimum of 1760 patients with RS 12-25 and ET-response vs. RS 0-11. Secondary endpoints included overall survival (OS), distant DFS, and translational research. **Results:** 5323 pts were registered and 4690 finally allocated to ET (n=2355) or CT (n=2335) within ADAPT HR+/HER2-. About 1/3 of pts were premenopausal; about 40% had node-positive disease. Efficacy results will be available in October 2020.

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# Including a 21-gene assay recurrence score in multivariable predictive model generation improves prediction of local recurrence after breast conserving surgery for ductal carcinoma-in-situ

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**Introduction** Accurate prediction of local recurrence (LR) after breast conserving surgery (BCS) for ductal carcinoma-in-situ (DCIS) is crucial to personalize recommendations for adjuvant radiotherapy (RT). The 21-gene recurrence score (RS) predicts for distant metastases for woman with invasive breast cancer. We hypothesised that the RS could improve prediction of LR after BCS for DCIS. **Methods** We performed a population-based analysis of 1226 woman aged ≤74 treated with BCS ± RT for pure DCIS. Expert pathology review was obtained for all cases, as was the RS. Treatment and outcomes were obtained by deterministic linkage to administrative databases and chart review. Clinico-pathologic features obtained included: age, tumor size, nuclear grade, presence of comedonecrosis, multifocality, margins, and adjuvant radiation. The outcome assessed was local recurrence by 10 years from diagnosis of DCIS. The LR prediction model was developed using multivariable Cox regression, where a non-parametric approach was implemented to estimate the baseline hazard function. The proportional hazards assumption was assessed and time-interaction terms were included with each covariate in the model. Models were ranked based on c-statistic, log-likelihood estimate, and Akaike information criterion (AIC). Backward selection was used to obtain the final reduced model with time-interaction terms. Calibration for the best model was examined by grouping predicted 10-year risk of LR into deciles and plotting against observed 10-year risk of LR based on mean Kaplan-Meier estimates. Internal validation was performed by bootstrapping. **Results** Of the 1226 woman included, 514 were treated with BCS alone and 712 received adjuvant RT. Median follow up from time of treatment was 16 years (interquartile range (IQR): 14-18). The median age was 56 years (IQR: 49-64). Margins were negative in 90.5% of cases. Tumor size was ≤1cm in 430 (35.1%), 1-2.5cm in 633 (51.6%), and >2.5cm in 163 (13.3%). The median RS was 15 (IQR: 8-30) and the mean RS was 21.37 (SD 18.93). The best predictive model included the RS and had a c-statistic of 0.68 as well as the lowest AIC. This model included the following variables: RS, age, tumor size, nuclear grade, margin status, comedonecrosis (≤30% vs higher), multifocality, and treatment (BCS vs BCS+RT); it also included the following interaction terms: treatment and time, RS and time, comedonecrosis and time, and treatment and tumor size. Due to the non-linear relationship between certain characteristics and the risk of LR, quadratic terms for RS and age were also included. This model was well calibrated overall, especially in the lower risk range around the 10% risk threshold. It was also well calibrated in this risk range in the subset of woman who were treated with BCS alone. **Conclusion** The best performing model generated to predict LR after BCS for DCIS includes the RS. Work is ongoing to compare RS and the 12-gene DCIS score in terms of prediction of LR, as well as prediction of invasive LR specifically. This work can help guide future clinical de-escalation trials by better identifying woman with truly low risk of LR after BCS for DCIS.

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FGFR1 associates with gene promoters and regulates gene transcription: Implications for endocrine resistance in ER+/FGFR1-amplified breast cancer

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**Background:** *FGFR1* amplification occurs in ~ 15% of ER+ breast cancers. In these tumors, nuclear FGFR1 has been shown to interact with DNA, but its role in transcriptional regulation is unclear. Thus, we investigated the genomic role of FGFR1 in ER+/*FGFR1*-amplified breast cancer. **Results:** FGFR1 ChIP-Seq detected 4,412 DNA binding sites in CAMA1 ER+/*FGFR1*-amplified breast cancer cells cultured in estrogen-free conditions. Of these binding sites, 67% were enriched at promoter regions. ChIP-qPCR confirmed FGFR1 binding to several promoter regions in a second ER+/*FGFR1*-amplified cell line, MDA-MB-134, and a patient derived xenograft, HCI-011. To determine the nuclear FGFR1 interactome, we performed FLAG immunoprecipitation of mixed nuclear and chromatin fractions of CAMA1 cells transduced with a 3XFLAG-FGFR1 plasmid, followed by mass spectrometry (MS) of FLAG antibody pulldowns. MS revealed RNA Polymerase II subunits among the top nuclear FGFR1 interacting proteins. FGFR1 mainly bound Pol II phosphorylated on Ser5 (Pol II S5P), a marker of transcription initiation, in CAMA1, MDA-MB-134 and HCI-011 cell extracts. Pol II S5P ChIP-Seq revealed that 2,867/4,412 (65%) FGFR1 peaks were shared with Pol II S5P. ChIP-Seq also showed that 95% of FGFR1 peaks overlapped with both H3K4me3 and H3K27ac, markers of active transcription. Consistent with these results, RNA-Seq of CAMA1 cells showed that expression of FGFR1-bound genes was markedly higher than non FGFR1-bound genes ($p<0.0001$), suggesting that FGFR1 binds to actively transcribed genes. In addition to Pol II, MS detected FOXA1 among FGFR1 interacting proteins. ChIP-Seq analysis revealed FOXA1 enriched at FGFR1-bound loci. siRNA-mediated FOXA1 knockdown reduced FGFR1 distribution to several genomic loci in CAMA1 cells, as measured by FGFR1 ChIP-Seq, suggesting that FOXA1 mediates FGFR1 recruitment to chromatin. We next transduced MCF-7 cells with an FGFR1(SP-)(NLS) plasmid, where the NLS sequence forces nuclear import of the resulting protein. To determine the role of FGFR1 on transcriptional regulation, we used Binding and Expression Target Analysis (BETA), integrating FGFR1 ChIP-Seq and RNA-Seq results from $MCF7^{FGFR1(SP-)(NLS)}$ vs $MCF7^{EV}$ cells. This analysis predicted a direct role for genomic-bound FGFR1 in activating gene expression ($p$=8.01e-6). $MCF7^{FGFR1(SP-)(NLS)}$ cells were markedly less sensitive to fulvestrant compared to control cells. Gene Set Enrichment Analysis (GSEA) of the 1,009 genes upregulated in $MCF7^{FGFR1(SP-)(NLS)}$ cells and bound by FGFR1 at a genomic level revealed a strong enrichment of estrogen response early ($q$=2.2e-44) and late ($q$=6.4e-33) genes, suggesting that nuclear FGFR1 induces an ERα-associated transcriptional profile that may contribute to endocrine resistance. Finally, an expression signature associated with nuclear FGFR1 correlated with endocrine resistance in three cohorts of patients with ER+ breast cancer treated with aromatase inhibitors. We next studied the effect of growth factor stimulation on FGFR1 transcriptional function. Stimulation with FGF2 enhanced nuclear FGFR1 import in CAMA1 cells, as well as FGFR1-Pol II S5P association. Notably, these effects were not abrogated by treatment with the FGFR1 inhibitor erdafitinib. ChIP-Seq revealed that erdafitinib did not impair the FGFR1 genomic distribution. These results do not support a causal link between the FGFR1 activated TK and the receptor's activity in the nucleus. **Conclusions:** We have demonstrated a role for nuclear FGFR1 in transcriptional regulation in breast cancer. FGFR1-induced gene expression contributes to endocrine resistance and is not affected by FGFR TKIs. These findings provide a rationale for developing treatment strategies to inhibit nuclear FGFR1 in ER+/*FGFR1*-amplified breast cancer.

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**Publication Number:** GS3-06

# Biomarker evaluation in the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer

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**Background:** Trophoblast cell-surface antigen-2 (Trop-2) is highly expressed in many epithelial tumors, including triple-negative breast cancer (TNBC). Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to SN-38, an active metabolite of irinotecan, via a unique hydrolyzable linker that allows for SN-38 release intracellularly and in the tumor microenvironment (bystander effect). Preclinical studies have shown a great range of efficacy with SG in mice bearing tumors with low, moderate, and high Trop-2 expression levels. We report subgroup analyses by Trop-2 expression from ASCENT, a randomized, phase 3 confirmatory study of SG versus standard-of-care chemotherapy in patients with metastatic TNBC (mTNBC). **Methods:** In the global, multicenter, open-label, phase 3 ASCENT study (NCT02574455), 529 patients with mTNBC refractory to or relapsing after at least 2 prior chemotherapies were randomized 1:1 to receive SG (10 mg/kg intravenously on days 1 and 8 every 21 days) or single-agent treatment of physician's choice (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) measured by central independent review per RECIST v1.1. Secondary endpoints included objective response rate (ORR) per RECIST v1.1, duration of response, overall survival (OS), and safety. Exploratory endpoints included biomarker assessments, including Trop-2 and *BRCA1/2*. Trop-2 expression was assessed using a validated immunohistochemistry assay. **Results:** Subgroup analyses by biomarker expression including Trop-2 and *BRCA1/2* were performed, and outcomes by PFS, OS, ORR, and safety results will be reported. **Conclusions:** These analyses will provide further insights into the relationship of Trop-2 expression and the activity of SG in previously treated patients with mTNBC.

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Mismatch repair deficiency predicts response to HER2 blockade in HER2-negative breast cancer

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Estrogen receptor positive ($ER^+$) breast cancer is a leading cause of cancer-related death globally. Resistance to standard of care endocrine treatment occurs in at least 30% of $ER^+$ breast cancer patients resulting in ~40,000 deaths every year in the US alone. Preclinical studies strongly implicate activation of growth factor receptor, HER2 in endocrine treatment resistance of $ER^+$ breast cancer that is $HER2^-$ at diagnosis. However, clinical trials of pan-HER inhibitors in $ER^+/HER2^-$ patients have disappointed, likely due to a lack of predictive biomarkers. Here we demonstrate that loss of *MLH1*, a principal mismatch repair gene, causally activates HER2 in $ER^+/HER2^-$ breast cancer upon endocrine treatment. Additionally, we show that HER2 activation is indispensable for endocrine treatment resistant growth of MLH1-defective cells *in vitro* and *in vivo*. Consequently, inhibiting HER2 restores sensitivity to endocrine treatment in multiple experimental models including patient-derived xenograft tumors. Patient data from multiple clinical datasets (TCGA, METABRIC, Alliance (Z1031) and E-GEOD-28826) supports an association between MLH1 loss, HER2 upregulation, and sensitivity to trastuzumab in endocrine treatment-resistant $ER^+/HER2^-$ patients. These results provide strong evidence that MLH1 could serve as a first-in-class predictive marker of sensitivity to combinatorial treatment with endocrine drugs and HER2 inhibitors in endocrine treatment-resistant $ER^+/HER2^-$ breast cancer patients. Implications of this study extend beyond breast cancer to Lynch Syndrome cancers.

**Publication Number:** PD3-05

# The DAPHNE trial: A feasibility study of chemotherapy de-escalation based on response to neoadjuvant paclitaxel-HP (THP) in HER2-positive breast cancer

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**Background:** De-escalation of adjuvant therapy following pathologic complete response (pCR) to an abbreviated neoadjuvant regimen in HER2-positive (HER2+) breast cancer is the focus of a recently initiated national trial. However the feasibility of this approach, and its appeal to patients (pts) and providers, has not been formally investigated. **Methods:** We conducted a single arm pilot trial to determine the feasibility of de-escalated adjuvant therapy (HP-only) in patients with pCR following neoadjuvant THP. Eligible pts had clinical anatomic stage II-III treatment-naïve HER2+ breast cancer. All pts received weekly paclitaxel x12 doses, and HP every 3 weeks x4 doses (up to 6 doses allowed in case of surgical delay). The primary objective was to assess adherence to protocol-specified antibody doublet therapy (HP-only, without cytotoxic chemotherapy) in the adjuvant setting among pts with pCR (ypT0/isN0) following neoadjuvant THP; the primary endpoint was receipt of adjuvant cytotoxic chemotherapy, assessed 3 months post-operatively. Trastuzumab emtansine (T-DM1) was not considered cytotoxic chemotherapy. Among pts with pCR to THP, de-escalation would be deemed infeasible if the true rate of adherence to HP-only were ≤80%. With sample size of 100 pts, the study was designed to have >90% power to reject the null if the true rate of adherence were ≥95% (Binomial exact test; one-sided alpha=0.05). Questionnaires were administered and records were reviewed to assess pts' and physicians' decision-making about adjuvant systemic therapy following pCR and non-pCR. **Results:** 98 pts received at least one dose of THP on study. Median age was 50 yrs (range 24-78), pts were 99% female, 86% had stage II/14% stage III tumors, 32% ER/PR negative. No pts progressed during neoadjuvant THP. Five pts had incomplete clinical response following THP and received AC prior to surgery. They were classified as non-pCR and censored from further analyses. At the time of analysis, 93 pts were evaluable for response to neoadjuvant therapy (1 pt withdrew from study early; 4 pts had not reached surgery by the data cutoff). Overall pCR rate was 55% (51/93 pts); 10%, 28%, and 2% of pts had RCB I, II, and III responses, respectively (this excluded patients who received AC preoperatively). Of 51 pts who had pCR to THP, 40 had verified data available regarding adjuvant chemotherapy receipt at data cutoff. 39/40 pts (97.5%, 95% CI 86.8-99.9%) who had pCR did not receive adjuvant cytotoxic chemotherapy, meeting the trial's prespecified threshold for declaring this a feasible approach (primary endpoint), though data remain pending for 11 pts with pCR and will be available at presentation. Of 30 pts who did not experience pCR to THP and had adjuvant chemotherapy status verified at data cutoff, 14/30 pts received adjuvant cytotoxic chemotherapy, and 16/30 pts did not receive adjuvant chemotherapy. The most common reasons cited by pts for non-receipt of adjuvant cytotoxic chemotherapy, despite residual disease at surgery, were (N=21): plan for adjuvant T-DM1 alone (67% of pts), good response to preop chemo (38% of pts), and plan for adjuvant hormonal therapy (24% of pts). The most common reason cited by treating physicians for non-administration of adjuvant chemotherapy, despite residual disease at surgery, was plan for adjuvant T-DM1 (17/21 (81%) physicians). With brief follow-up (median 10.2 mos), there were no breast cancer recurrences. **Conclusions:** De-escalation of adjuvant cytotoxic chemotherapy among pts who experience pCR in early stage HER2+ breast cancer appears to be an acceptable approach for both pts and physicians, though data are not yet complete and will be updated at the time of presentation. The long-term efficacy of this approach will be determined in the ongoing national CompassHER2-pCR trial.

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Racial differences in breast cancer immune microenvironments

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**Background:** Black women suffer 40% higher mortality from breast cancer (BC) compared to non-Hispanic white women, and the underlying causes of these disparities remain uncertain. Growing evidence supports the importance of the immune microenvironment in BC survival, but immune response differences by race are poorly understood. We sought to characterize the immune microenvironment of BC to evaluate how phenotypes of immune response vary across race and tumor intrinsic subtype to impact clinical outcomes. **Methods:** We leveraged the Carolina Breast Cancer Study (CBCS), a large population-based study that oversampled young (≤50) and black women with invasive breast cancer and collected tumor tissue on >95% of participants. We curated a 48-gene panel representative of 13 individual immune cell types, and performed NanoString gene expression profiling on tissue from 1957 BC patients, including 1033 (53%) Black and 924 (47%) Non-Black women. Consensus clustering was used to identify phenotypes of immune response, and individual immune cell scores were calculated as the median expression of cell-type markers. Immune phenotypes and cell-type scores were compared against validated protein markers and H&E-based quantification of TILs from corresponding tissue microarrays (TMAs). We estimated associations of immune classes with BC intrinsic subtype, ROR-PT scores (calculated as low, medium and high), age and race using relative frequency differences (RFDs), adjusting for age and tumor stage. Cell type scores were compared by race using Welch's t-tests and adjusted for multiple comparisons with the Benjamani-Hochberg procedure. **Results:** We identified three BC immune phenotypes primarily defined by features related to an Adaptive-enriched, Innate-enriched, or a Quiet immune microenvironment. These expression-based groups correlated with histological evidence of immune cells from corresponding TMAs. Similarly, expression-based cell scores correlated strongly with protein-based quantification of immune cells from corresponding TMAs (e.g. B-cell score vs. CD19 immunofluorescence, rho=0.75; ICOS RNA counts vs. protein; Rho=0.76). Both Adaptive-enriched and Innate-enriched tumors were associated with high ROR-PT scores [RFD for Adaptive-enriched vs. Quiet: 24.1% (95% CI 19.3-28.8); Innate-enriched vs. Quiet RFD: 13.1 (95% CI 9.1-17); frequencies: 37.2%, 26.2% and 10% for Adaptive, Innate and Quiet, respectively], the basal-like intrinsic subtype [RFD for Adaptive-enriched vs. Quiet: 19.4% (95% CI 14.3-24.6); Innate-enriched vs. Quiet RFD: 9.8 (95% CI 5.6-14.1); frequencies: 43.4%, 27.4% and 8.9% respectively] and Black race [RFD for Adaptive-enriched vs. Quiet: 16.1% (95% CI 10.3-21.9); Innate-enriched vs. Quiet RFD: 9.5 (95% CI 3.9-15); frequencies 60.5%, 53.5% and 42.5% respectively]. After adjusting for tumor subtype, the Adaptive-enriched class remained associated with Black race (RFD for Adaptive-Enriched vs Quiet: 7.5% (95% CI 1.4-13.6). Conversely, tumors in the immune-quiet group were primarily non-basal (90%) with low ROR-PT scores (86.7%). Within the Adaptive-enriched class, Black women displayed decreased CD8 T cell scores (p=0.05) but increased T-reg cell scores (p=0.02) relative to Non-Black women. **Conclusion:** Immune response appears to be intricately related to race and tumor subtype, with black women having strong associations with adaptive-enriched and innate-enriched immune microenvironments. Differences in CD8 T cell and Treg expression suggest that even within broad classes of immune response, racial differences in specific cell-type distributions exist. Immune response differences may be targetable to improve treatment response, and therefore it is important to identify race- and subtype-specific differences in immune microenvironments.

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# Axillary recurrence is a rare event in node-positive patients. treated with sentinel node biopsy alone after neoadjuvant chemotherapy: Results of a prospective study

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**Background:** Four prospective multi-institutional trials have demonstrated that clinically node-positive patients (cN1) who receive neoadjuvant therapy (NAC) and convert to cN0 can be reliably staged with sentinel lymph node biopsy (SLNB) with false-negative rates (FNRs) of < 10%, when ≥ 3 SLNs are retrieved. Since study patients all had axillary lymph node dissection (ALND), the rate of axillary recurrence after SLNB alone is unknown. Of concern is the possibility that residual chemotherapy-resistant axillary disease could lead to higher recurrence rates than seen in the primary surgery setting for cN0 patients where SLN FNRs of 5-10% result in axillary recurrence in < 1% of cases. Here we report regional recurrence rates in a prospectively defined cohort of cN1 patients receiving NAC, followed by a negative SLNB using a standardized technique, and no further axillary surgery. **Methods:** From 06/2014 to 02/2019, patients with cT1-3 biopsy-proven cN1 breast cancer who received NAC and converted to cN0 by physical exam were prospectively managed with SLNB with dual tracer mapping and omission of ALND if ≥ 3 SLNs were pathologically negative. Nodes were not routinely clipped, and retrieval of clipped metastatic nodes was not required. Pathologically negative SLNs were defined as the absence of any metastases including isolated tumor cells. **Results:** Of 610 cN1 patients treated with NAC, 555 (91%) converted to cN0 and had SLNB; 234 (42%) had ≥ 3 negative SLNs and were treated with SLNB alone. Median patient age was 49 years and median tumor size at presentation was 3 cm; 61% were HER2+ and 18% triple negative. Most (91%) received doxorubicin-based NAC and 88% received adjuvant radiotherapy (RT), with 80% (n = 164) of RT patients receiving nodal RT (Table). At a median follow-up of 35 months, there was only 1 (0.4%) axillary recurrence for the entire cohort, synchronous with a breast recurrence, in a patient who refused RT. Among patients who received RT (n = 205), there were no axillary recurrences. The 4-year rate of distant recurrence for all patients was 6.1% (95% CI, 3.4-10.7%) and 4-year overall survival was 93.9% (95% CI, 87.6-97.1%). **Conclusion:** In cN1 patients treated with NAC, rates of axillary recurrence in patients with ≥ 3 pathologically negative SLNs treated with SLNB alone were low, without routine nodal clipping. Although further follow-up is needed, multiple studies have shown that nodal recurrence is an early event, particularly in HER2+ and triple negative patients, who comprised the majority of the population. Our findings support omitting ALND in cN1 patients after NAC when the SLNs are negative using an optimal SLNB technique.

Table. Patient Population

| | **Overall cohort (n = 234)** |
|---|---|
| **Age, years (median, IQR)** | 49 (40, 58) |
| **Tumor size at presentation, cm (median, IQR)** | 3.0 (2.2, 5.0) |
| **Number SLNs retrieved (median, IQR)** | 4 (3, 5) |
| **Palpable nodes at presentation (n, %)** | 179 (76%) |
| **Histology** | |
| Ductal | 211 (90%) |
| Lobular and mixed | 7 (3%) |
| Micropapillary and mixed | 10 (4%) |
| Other | 3 (1%) |
| Occult | 3 (1%) |
| **Differentiation** | |
| Well | 1 (0.5%) |
| Moderate | 36 (15%) |
| Poor | 196 (84%) |
| Unknown | 1 (0.5%) |
| **Receptor Status** | |
| HR+/HER2- | 47 (20%) |
| HR+/HER2+ | 80 (34%) |
| HR-/HER2+ | 64 (27%) |
| HR-/HER2- | 43 (18%) |
| **Breast Surgery** | |
| BCS | 118 (50%) |
| Mastectomy | 116 (50%) |
| **Breast pCRY** | |
| Yes | 161 (70%) |
| No | 70 (30%) |
| **NAC regimen** | |
| AC-T | 197 (84%) |
| AC-T + carbo | 15 (6.4%) |
| TC | 8 (3.4%) |
| Other | 14 (6%) |
| **Neoadjuvant anti-HER2 treatment** | |
| HP (dual-therapy) | 144 (100%) |
| **Adjuvant RT** | |
| Yes | 205 (88%) |
| No* | 29 (12%) |
| Y3 patients had occult primary breast cancer and were not included in breast pCR calculation; *6/29 patients who did not receive RT enrolled in NSABP B-51 | |

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Phase 1/2 clinical trial of a topical submicron particle paclitaxel (SOR007) for the treatment of cutaneous metastases

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**Background**: Cutaneous Metastases (CM) are an infrequent presentation of advanced solid tumors and are usually associated with symptoms of pain, pruritus, and secondary infections, all of which negatively affect quality of life and result in additional morbidity. Systemic chemotherapy, advanced wound care, topical agents, cryo-, electro-, photodynamic-, laser and intralesional therapies have been limited by inconsistent efficacy, inconvenience, or toxicity. In this open-label phase 1/2 clinical trial, submicron particle paclitaxel in an anhydrous base (SOR007) was evaluated for topical treatment of CM from breast cancer (n=21), leiomyosarcoma (n=1) and Paget's disease (n=1). Previously, *in vitro*, *in vivo,* and clinical studies demonstrated penetration of paclitaxel into the dermis with the silicone-based anhydrous producing subtoxic plasma levels in GLP toxicology studies and early clinical trials.
**Trial Design**: The phase 1/2 open label trial evaluated 3 doses of SOR007 (0.15%, 1.0%, 2.0%). Approximately 0.5 grams (1 FTU) of SOR007 per 50 cm2 treatment area was applied BID during a 3+3 dose-rising phase for 28 days (n=10) or a dose-expansion phase at 2% strength BID for 28 days (n=2) or 56 days (n=11) unless discontinuation became necessary due to clinical course of the underlying disease.
**Results:** At least one eligible lesion was treated per subject and classified per RECIST 1.1. In the 28-day application group, 10 subjects were treated and in the 56-day application group, 11 subjects were treated. Lesion response is summarized in the table below for data to date. Lesion response was evaluated within 2 weeks of last treatment day in most subjects.
**Conclusions:** SOR007 was safe when applied to CM lesions. SOR007 resulted in decreased lesion progression or reduced lesion area in the majority of CM subjects. These clinical benefits became more consistent and pronounced at 2% strength with longer treatment suggesting a dose/duration response. Lesion pain reduction is also suggested from the study. Additional clinical research with more subjects and longer treatment periods is in the early planning stage.

Lesion Response

| | Lesion response by **SUBJECT** | Lesion response by **SUBJECT** | Lesion response by **INDIVIDUAL LESION** | Lesion response by **INDIVIDUAL LESION** |
|---|---|---|---|---|
| | Dose-rising 0.15%, 1%, 2% & Dose expansion 2% BID x 28 days | Dose-expansion 2% BID x 56 days | Dose-rising 0.15%, 1%, 2% & Dose expansion 2% BID x 28 days | Dose-expansion 2% BID x 56 days |
| N (subjects or lesions) | 8 | 11 | 18 | 23 |
| Complete Response | 0% (0/8) | 9.1% (1/11) | 5.5% (1/18) | 26% (6/23) |
| Objective Response Rate | 13% (1/8) | 45% (5/11) | 17% (3/18) | 43% (10/23) |
| No lesion progression in evaluable subjects | 63% (5/8) | 82% (9/11) | 61% (11/18) | 83% (19/23) |

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Value of [$^{18}$F]-FES-PET to solve clinical dilemmas in breast cancer patients: A retrospective study

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**Introduction:** Breast cancer (BC) is a heterogeneous disease, in which estrogen receptor (ER) expression plays an important role in the majority of breast tumors. A clinical dilemma may arise when a metastasis biopsy to determine the ER status cannot be performed safely or when ER heterogeneity is suspected between tumor lesions. Whole-body ER imaging, such as 16α-[$^{18}$F]-fluoro-17β-estradiol ([$^{18}$F]-FES) positron emission tomography (PET), may have additional value in these situations. However, the role of this imaging technique in routine clinical practice remains to be further determined. Therefore, we assessed the value of [$^{18}$F]-FES-PET in a large retrospective set of patients, by evaluating if the physicians' clinical dilemma that remained after standard workup was solved by the [$^{18}$F]-FES-PET scan. **Methods:** In this single center study, [$^{18}$F]-FES-PET scans, performed in patients with (suspected) ER+ metastatic BC with remaining clinical dilemma after standard workup (such as computed tomography, [$^{18}$F]-fluorodeoxyglucose ([$^{18}$F]-FDG)-PET, bone scintigraphy, magnetic resonance imaging, or biopsy), performed at the UMCG between November 2009 and January 2019, were included. A whole-body [$^{18}$F]-FES-PET scan was performed 60 min after ~200 MBq of [$^{18}$F]-FES was injected intravenously. ER antagonists had to be discontinued at least 5 weeks before [$^{18}$F]-FES-PET. Primary endpoint was the percentage of cases in which the referring physician's clinical dilemma was solved based on the [$^{18}$F]-FES-PET results. The dilemma was considered solved if 1) the [$^{18}$F]-FES-PET provided a solution for the clinical dilemma (for example an extra metastatic site to biopsy), or 2) a treatment decision (to change or continue) was made based on the [$^{18}$F]-FES-PET result. If the physician had doubts about the diagnosis after the [$^{18}$F]-FES-PET examination, and additional workup was necessary for treatment decision-making, the dilemma was considered not solved. Secondary endpoints were type of clinical dilemma, and rate of [$^{18}$F]-FES positive or negative PET scans (visual interpretation), related to frequency of solved dilemmas. **Results:** One hundred [$^{18}$F]-FES-PET scans were performed in 83 patients. Clinical dilemma types were: 1) inability to determine extent of (suspected) metastatic disease with standard workup ($n$=52), 2) unclear disease ER status ($n$=31), and 3) inability to determine which primary tumor caused metastases ($n$=17). Dilemmas were solved by [$^{18}$F]-FES-PET in 87/100 cases (87%). In these 87 cases, treatment was changed in 52 cases, and continued in 35 cases. The frequency of solved dilemmas was not related to the type of clinical dilemma. In contrast, the frequency of solved dilemmas was related to whether scans were [$^{18}$F]-FES positive or negative. Out of the 63 [$^{18}$F]-FES positive scans, the clinical dilemma was solved in 61 cases (97%); in 26 out of the 37 [$^{18}$F]-FES negative scans (70%) the dilemma was solved ($p$<0.001). **Conclusion:** In this real life study of BC patients with a clinical dilemma after standard workup, we showed that [$^{18}$F]-FES-PET solved the dilemma in the large majority of cases. Relevant treatment decisions were made based on the scan, particularly in ER+ disease. This indicates that the [$^{18}$F]-FES-PET can be of value to solve clinical dilemmas in BC patients. Ultimately, this can support optimal treatment in these patients and potentially improve outcome. Prospective trials are currently ongoing to further assess this.

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# A phase 2 study of oral paclitaxel and encequidar (oPac+E) in the treatment of cutnaeous angiosarcoma: The breast angiosarcoma subgroup

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**Background** Cutaneous angiosarcomas are highly aggressive malignant tumors with poor prognosis. Currently there is no FDA-approved treatment. oPac+E is a combination of oral paclitaxel and a novel oral P-glycoprotein inhibitor, Encequidar. **Materials and Methods:** This is a phase-2 study evaluating the activity, safety and tolerability of oPac 205mg/m$^2$ + E 12.9 mg once daily for 3 consecutive days weekly for patients with unresectable cutaneous angiosarcoma. Tumour response was evaluated every 6 weeks using RECIST and photography. **Results:** From Aug-2018 to May-2020, 7 of 26 enrolled patients (pts) had breast cutaneous angiosarcoma. All had previous breast cancer, mastectomy and radiotherapy and/or adjuvant chemotherapy, no prior taxane for angiosacoma and no metastatic disease. Median age was 66 yrs (range 49-76). Best objective response rates were: complete response (CR) 43% (3/7 pts), partial response (PR) 14% (1/7 pts), stable disease (SD) 43% (3/7 pts), progressive disease (PD) 0%. Furthermore, 3 pts (43%) who had inoperable lesions were deemed operable after Oraxol treatment and received curative intent surgical resection. Median progression free survival (PFS) was 17 weeks. oPac+E was generally well tolerated. Grade-3 treatment related adverse events (AEs) occurred in 5 pts: diarrhea=1, fatigue=2, neutropenia =1, dyspnea=1, dehydration=1, pneumonitis=1. Grade-4 AE were neutropenia in 2 pts. Grade-2 paraesthesia=1. All pts fully recovered. Dose reductions were needed in 3 subjects. No patients discontinued treatment due to AEs. To date no patients died. **Conclusions:** oPac+E may provide an effective oral treatment for radiation-associated breast angiosarcoma, with a high clinical benefit rate (CR + PR+ SD=100%), durable response and enabled resection of unresectable tumors. It is generally well tolerated even in elderly patients; with low incidence of neuropathy. It may allow patients to avoid hospital IV chemotherapy visits and the option of home treatment.

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# Neoadjuvant chemotherapy (NCT) response in postmenopausal women with clinical stage II or III estrogen receptor positive (ER+) and HER2 negative (HER2-) breast cancer (BC) resistant to endocrine therapy (ET) in the ALTERNATE trial (Alliance A011106)

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**Background:** Ki67 values >10% 2-4 weeks (wks) after starting neoadjuvant ET (NET) indicates persistent cell proliferation, resistance to ET, and is associated with increased risk of recurrence. The ACOSOG Z1031 trial suggested that these tumors are also relatively chemotherapy (chemo) resistant with a low pathologic complete response (pCR) rate to NCT. The ALTERNATE trial (NCT01953588) is a randomized study of neoadjuvant anastrozole (ANA), fulvestrant (FUL), or ANA + FUL in postmenopausal patients (pt) with newly diagnosed clinical stage II or III ER+ (Allred score 6-8)/HER2- BC. Ki67 >10% at wk 4 or 12 after starting NET triggered triage to NCT of physician choice or weekly paclitaxel. Pts who refused protocol-directed therapy, were not candidates for NCT, or decided to undergo immediate surgery are being followed per protocol. Here we report the rates of pCR and residual cancer burden (RCB) following NCT for pts triaged to NCT due to Ki67 >10% at wk 4 or 12. **Results:** Of the 1,299 eligible pts randomized to receive ANA, FUL, or ANA + FUL, 286 (22%) had Ki67 >10% at wk 4 or 12. 168 of these 286 pts (58.7%) chose to switch to NCT, 32 went to surgery (11.2%), and 86 discontinued further protocol-directed therapy (30.1%). Among the 168 pts who underwent NCT, the presenting clinical T stages were cT2 (n=113; 67.26%), cT3 (n=47; 27.98%) and cT4 (n=8; 4.76%) and N stages were cN0 (n=82; 48.8%), cN1 (n=75; 44.6%), cN2/3 (n=9; 5.4%) and cNx (n=2; 1.2%). Central ER testing was performed on pre-treatment biopsies and confirmed ER Allred score 6-8 in 155 of 168 (92.2%) pts, with the rest being ER Allred score 4-5 (n=5; 3%), ER- (Allred score 0) (n=2; 1.2%), or not tested (n=6; 3.6%). Most (n=139; 82.7%) were ER+/PR+, while 17.3% (n=29) were ER+/PR-, and tumor grades were G1 (n=10; 6%), G2 (n=99; 58.9%), G3 (n=54; 32.1%), not reported (n=5; 3%). Baseline Ki67 levels prior to NET were >10% in 94% (n=158), ≤10% in 3% (n=5), and not done in 3% (n=5). NCT regimens administered included doxorubicin/cyclophosphamide (AC) followed by paclitaxel (T) (n=60; 35.71%); weekly paclitaxel (n=56; 33.33%), docetaxel/cyclophosphamide (TC) (n=33; 19.65%), other doxorubicin and/or taxane containing regimen (n=17; 10.12%), and cyclophosphamide/methotrexate/fluorouracil (CMF) (n=2; 1.19%). 35 (20.8%) pts did not complete planned course of NCT due to toxicity (n=27) or refusal (n=8). 154 NCT pts underwent surgery (mastectomy in 40.3%, and breast conserving surgery in 59.7%). The path ypT stages were Tis/0 (n=10; 6.5%), T1 (n=62; 40.3%), T2 (n=61; 39.6%), and T3/4 (n=21; 13.6%), and the ypN stages were N0 (n=66; 42.9%), N1 (n=57; 37%), N2/3 (n=30; 19.5%), and Nx (n=1; 0.6%). Among the 168 pts who started on NCT (intent to treat population), there were 8 pCRs (no invasive disease in the breast or lymph nodes) (4.8%; 95% CI: 2.1% to 9.2%). Residual Cancer Burden (RCB) categories include RCB 0 (n=8; 4.8%), RCB 1 (n=15; 8.9%), RCB 2 (n=82; 48.8%), RCB 3 (n=42; 25.0%), and not determined (n=21; 12.5%). Correlations of baseline pt and tumor characteristics with pathology response to NCT will also be presented. **Conclusion:** In pts with NET-resistant ER+/HER2- BC, salvage NCT is not likely to induce a complete or near complete response. More effective treatments are needed for this high-risk ER+/HER2- pt population. **Support:** U10CA180821, U10CA180882, U24CA196171, UG1CA189856, U10CA180868 (NRG); NCI BIQSFP, BCRF, Genentech, AstraZeneca. https://acknowledgments.alliancefound.org. Clinical Trials.gov Identifier: NCT01953588

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# Genetic profiling for circulating tumor cell clusters to unveil molecular drivers of metastasis

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**Introduction:** Although CTCs display the same spatial and temporal heterogeneity as the primary tumor, they represent a privileged window to disclose mechanisms of metastases. A portion of CTCs may form clusters that contain two or more CTCs bound together which were reported to have up to 50-fold of potential of forming distant metastasis in MBC as compared to individual CTCs (Aceto N. Cell, 2015) . However, genomic characterization of CTCs-clusters compared to single CTCs remain largely unknown. We previously reported single CTC sequencing for HER2$^+$ CTCs (2020 AACR #3120). Herein, we report a new finding of heterogeneity profiling for CTC-clusters compared to single CTCs, which would be helpful to evaluate the MBC metastasis capability and treatment in clinic. **Methods:** Whole blood sample (7.5ml/each) was collected from stage III/IV MBC patients before therapy. CTC enumeration was performed using the FDA-cleared CellSearch™ System (Menarini) targeting the EpCAM antigen for capturing CTCs which were then stained by Anti-CK-PE, DAPI, anti-CD45-APC and anti-HER2-FITC. The CTC-clusters and single CTCs were isolated using DEPArray™ System (Menarini). DNA was isolated from CTC-clusters and single CTCs by Arcturus™ PicoPure™ DNA Extraction kit. The initial library was prepared by SMARTer® PicoPLEX® Gold Single Cell DNA-Seq Kit, and the exome capture was performed by Twist Human Core Exome EF Multiplex Complete Kit. The sequencing was prepared by NextSeq 500 mid output V2.5 kit and was performed on the NextSeq 500 (Illumina). It was a paired end run, 75×75 bps run with dual indexing. **Results:** We identified 107 CTCs by CellSearch™, including 93 single CTCs, 14 CTC-clusters and 145 WBCs. Autologous CTC-clusters (CK$^+$DAPI$^+$CD45$^-$, Group 1), single CTCs (CK$^+$DAPI$^+$CD45$^-$, Group 2), and leukocytes (CK$^-$DAPI$^+$CD45$^+$, Group 3) were sequenced respectively. The sequencing data was processed following the GATK pipeline and annotated using SnpEff. There were 60,638 counts (6.77%) and 70,334 counts (8.20%) for exon variants in CTC-clusters and single CTCs respectively, 507,595 counts (56.69%) and 486,119 counts (56.69%) for intron variants, 194,026 (21.67%) and 175,819 counts (20.51%) for intergenic variants, 54,174 counts (6.05%) and 50,370 counts (5.87%) for downstream genes, 51,716 counts (5.78%) and 45,915 counts (5.36%) for upstream genes, and 3.04% and 3.37% of others variants in CTC-clusters and single CTCs respectively. Meanwhile, there was 0 count for exon and intron variants found in Group 3. There were 60 and 79 gene variants (SNP and Ins-Del) identified to have the highest impact effect (≥20) on CTC-clusters and single CTC exons respectively, which affect significantly on the functional proteins coding. Among the top 50 high impact gene variants in each group, there were 25 gene alteration sites were similar in Group 1 and 2, including *XYLB, RAN, QPCT, HPGDS, HDAC8, GABBR2, CYP11B2* and *CHKA*. Specific to Group 1, there were 25 gene alterations which were primarily related to cellular proliferation and tumor promotion (*AMD1*), liver drug clearance (*CES1)*, tissue remodeling (*CHI3L1*), immune cytokine signaling (*JAK1*) and metabolism (*ASRGL1*). Meanwhile, there are 25 specific gene alterations in Group 2 compared to Group 1, which were associated with nucleotide-excision repair (*DDB1 and FAN1)* chromosome positioning (*KIF11),* cell growth, differentiation, mitotic cycle, oncogenic transformation (*PTPN3 and MAPK14),* apoptosis (*CASP1*) and cell growth (*CTNNB1)*. **Conclusion:** Genomic characterization of CTC-clusters compared to autologous single CTCs and leukocytes elucidated new specific gene alterations in CTC-clusters associated with most aggressive disease metastasis in MBC, which will help to gain new insights on the molecular mechanisms associated with the metastasis and find new molecularly driven therapies for disease metastasis.

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Subtype-specific MRI models to guide selection of candidates for de-escalation of neoadjuvant therapy

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**Background**: MRI measured functional tumor volume (FTV) can predict pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) as early as 3 weeks after treatment initiation (1), indicating the potential of using MRI to guide treatment de-escalation. We developed MRI based, subtype-specific models for predicting pCR, to be used as part of a de-escalation strategy combining MRI and inter-regimen core biopsy pathology in I-SPY 2. **Methods**: I-SPY 2 patients underwent MRI exams at pre-treatment, early treatment (3 wks), inter-regimen (12 wks), and pre-surgery. pCR was assessed at surgery. FTV was calculated semi-automatically for every MRI (2). Subtype-specific FTV-based MRI prediction models were trained using FTV measurements at baseline, early treatment and inter-regimen timepoints for patients enrolled in I-SPY 2 between May 2010 and November 2016. Breast cancer subtype was defined by hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. The MRI prediction model was then used to predict probability of achieving pCR for each patient at inter-regimen, based on their subtype. The therapy de-escalation strategy focuses on achieving high positive predictive value (PPV, correct identification of patients with pCR) while maximizing sensitivity (proportion of patients with pCR identified by the test). Predicted probability above a specified threshold was considered a positive test for pCR. This study investigated the tradeoff between PPV and sensitivity within subtype groups defined by HR and HER2, and held to constraints set by probability thresholds at the 1$^{st}$, 2nd (median) and 3$^{rd}$ quartile. **Results**: A total of 814 patients were included in the analysis. Median age was 49 (range: 24 - 77) years. The pCR rate was 36% (289/814). Table 1 shows patient number and pCR rate by HR/HER2 subtype. The subtype-specific MRI models consist of the predictors: change of FTV (dFTV) at inter-regimen for HR+/HER2- and HR-/HER2+; dFTV at early treatment for HR+/HER2+; pre-treatment FTV and dFTV at inter-regimen for triple negatives. The highest probability varied by subtype: 0.24 for HR+/HER2-, 0.61 for HR+/HER2+, 0.73 for HR-/HER2+, 0.68 for triple negatives. The maximum PPV was 67% for HR+/HER2- and 100% for all other subtypes. Table 1 shows the tradeoff between PPV and sensitivity by subtype using the 1$^{st}$, median, and 3$^{rd}$ quartile thresholds.
**Conclusions**: Our data demonstrate that PPV and sensitivity vary by breast cancer subtype when the probability threshold generated by MRI model increases from low to high quartile. Results from this study suggest that the probability threshold for recommending treatment de-escalation should be selected carefully based on breast cancer subtype. Imaging results will be combined with core biopsy information obtained at the 12-week timepoint to further improve overall accuracy.

Table 1 Tradeoff between positive predictive value (PPV) and sensitivity at different levels of PPV

| Cohort | N | pCR rate | Probability threshold | | PPV (%) | Sensitivity (%) |
|---|---|---|---|---|---|---|
| HR+/HER2- | 328 | 20% (64/328) | 1$^{st}$ quartile | 0.18 | 24 | 91 |
| | | | 2$^{nd}$ quartile | 0.21 | 28 | 77 |
| | | | 3$^{rd}$ quartile | 0.23 | 35 | 52 |
| HR+/HER2+ | 132 | 39% (51/132) | 1$^{st}$ quartile | 0.27 | 44 | 86 |
| | | | 2$^{nd}$ quartile | 0.40 | 53 | 69 |
| | | | 3$^{rd}$ quartile | 0.51 | 58 | 37 |
| HR-/HER2+ | 71 | 66% (47/71) | 1$^{st}$ quartile | 0.67 | 75 | 85 |
| | | | 2$^{nd}$ quartile | 0.71 | 81 | 62 |
| | | | 3$^{rd}$ quartile | 0.72 | 89 | 34 |
| Triple negative(HR-/HER2-) | 283 | 45% (127/283) | 1$^{st}$ quartile | 0.34 | 54 | 91 |
| | | | 2$^{nd}$ quartile | 0.52 | 62 | 70 |
| | | | 3$^{rd}$ quartile | 0.60 | 73 | 41 |

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Serum thymidine kinase activity in patients with luminal metastatic breast cancer treated with palbociclib and fulvestrant within the PYTHIA trial

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**Background:** The CDK4/6 inhibitor palbociclib (P) plus fulvestrant (F) is approved for the treatment of patients (pts) with luminal metastatic breast cancer (MBC) progressed on prior endocrine therapy (ET). Despite clinical activity, a significant proportion of pts in this setting show primary resistance to P+F, with treatment failure within 3-6 months of initiation. To date there is no validated biomarker to identify such pts. Thymidine kinase 1 is a cancer proliferation marker downstream of the CDK4/6 pathway, whose activity can be measured in serum as a readout of tumour proliferation. Circulating thymidine kinase activity (TKa) is a potential prognostic and monitoring marker in pts treated with ET alone or in combination with P for MBC. However, the prognostic value of early changes in TKa during P+F treatment and its role in identifying pts with primary resistance are not yet defined. Here we prospectively investigated the role of serum TKa measured at different timepoints in pts treated with P+F within the PYTHIA trial (IBCSG 53-14/BIG 14-04; NCT02536742), a downstream trial of the AURORA platform (BIG 14-01; NCT02102165).
**Methods:** PYTHIA is a biomarker discovery phase II trial including pts (Aug ‘16 to Jun ’19) with ET-resistant luminal MBC who received P+F at standard schedule and dose with 3-monthly imaging. Serum samples were collected at baseline (D0; n=122), on-treatment at day 11-16 of cycle 1 (D15; n=108), and during the one week off P before initiating cycle 2 (D28: Day 24-37 of Cycle 1; n=108). TKa was measured with DiviTum®, a refined ELISA-based assay. Complete TKa response (CTR) was defined as TKa below the limit of detection (LOD; 20 Du/L) at D15. Cox models evaluated association of log-transformed TKa measurements with progression-free survival (PFS; from initiation of therapy until progression by RECIST criteria or death). Kaplan-Meier method estimated median, 3 and 6 months (95% CI) PFS in groups of patients defined by dichotomizing TKa as “high” or “low” at the median or by CTR. A sample size of 120 provided 80% power to detect a hazard ratio of 2.0 for biomarker with 30-50% prevalence (two-sided α=0.05) after ≥80 events.
**Results:** A total of 122 pts were enrolled. About half had received one prior line of ET for MBC, and 18% had received one prior line of chemotherapy. 48% had visceral metastases and 31% had bone-only disease. TKa at D0 was not associated with clinical characteristics. Median TKa (mTKa) at D0 was 87 Du/L. Overall, 82 pts experienced progression, with a median PFS (mPFS) of 11 months (95% CI: 8.6 - 16). P+F dramatically suppressed mTKa levels at D15, with 90/108 (83%) pts achieving CTR. At D28, TKa showed some rebound in most pts. At each timepoint, higher TKa was significantly and consistently associated with shorter PFS (each p<0.001). The effect of TKa on PFS remained statistically significant after adjusting for clinical variables. At 6 months, the largest difference between PFS probabilities was observed between patients with CTR versus no CTR at D15.
**Conclusions:** TKa is an independent prognostic biomarker in pts treated with P+F. High baseline TKa and incomplete suppression of TKa during treatment may identify pts with poor prognosis and primary resistance to P+F. TKa may represent a novel biomarker to select pts for alternative treatment modalities. These results warrant further investigation in prospective comparative trials.

| | **Timepoint** | | |
|---|---|---|---|
| | **Baseline (D0)** | **D15[1]** | **D28** |
| **TK median value (Du/L) (range)** | 87 (<20 - 14,510) | <20 (<20 - 7,060) | 52 (<20 - 3,533) |
| **Sample size** | | | |
| *High TKa* | 61 | 18 | 54 |
| *Low TKa* | 61 | 90 | 54 |
| **mPFS (months) (95% CI)** | | | |
| *High TKa* | 7.4 m (5.5 - 8.7) | 4.9 m (2.8 - 5.9) | 8.3 m (5.6 - 11) |
| *Low TKa* | 17.0 m (14 - NR[2]) | 16.0 m (11 - 30) | 19.0 m (17 - NR[2]) |
| **PFS at 3 months(95% CI)** | | | |
| *High Tka* | 79% (43% - 68%) | 61% (42% - 88%) | 78% (67% - 90%) |
| *Low TKa* | 93% (87% - 100%) | 92% (87% - 98%) | 96% (91% - 100%) |
| **PFS at 6 months(95% CI)** | | | |
| *High TKa* | 54% (43% - 68%) | 17% (6% - 47%) | 56% (44% - 71%) |
| *Low TKa* | 88% (81% - 97%) | 85% (78% - 93%) | 92% (86% - 100%) |

[1] For D15 High/Low TKa correspond to no CTR/CTR; [2] NR = not reached

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# Latest findings from the breast cancer cohort in SUMMIT - a phase 2 'basket' trial of neratinib + trastuzumab + fulvestrant for *HER2*-mutant, hormone receptor-positive, metastatic breast cancer

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**Background:** *HER2* mutations are oncogenic in hormone receptor positive (HR+) metastatic breast cancer (MBC), and may confer resistance to prior endocrine therapy but retain sensitivity to neratinib. Neratinib is an oral, irreversible, pan-HER tyrosine kinase inhibitor with clinical activity either as a single agent or in combination with fulvestrant in *HER2*-mutated, *HER2*-non-amplified MBC. Genomic analyses suggest that acquired resistance to neratinib can occur via additional *HER2* alterations, which may alter HER2-pathway signaling. We investigated whether dual HER2-targeted therapy could improve clinical benefit in a cohort of patients with *HER2*-mutant, HR+ MBC treated with neratinib + trastuzumab + fulvestrant (N+T+F) from SUMMIT - a phase 2 basket trial (NCT01953926).
**Methods:** Patients with HR+ MBC with known or suspected pathogenic *HER2* mutation(s) identified by genomic sequencing were eligible to receive N+T+F (oral neratinib 240 mg/day, i.v. trastuzumab 8 mg/kg initially followed by 6 mg/kg every 3 weeks, and i.m. fulvestrant 500 mg on days 1&15 of month 1, then on day 1 every 4 weeks). Loperamide prophylaxis was mandatory during the first 2 treatment cycles. There was no restriction on the number of prior lines of systemic treatment for MBC. Efficacy endpoints: confirmed objective response rate and clinical benefit rate (RECIST v1.1); duration of response; progression-free survival.
**Results:** As of 22-May-2020, 46 patients were enrolled in the N+T+F cohort and received at least 1 dose of study medication (safety population). 14 unique *HER2* allelic variants were identified: 8 kinase domain missense; 1 extracellular domain missense; 2 transmembrane domain missense; 2 exon-20 insertion; 1 exon-19 deletion. The most common *HER2* mutant variant was L755S (n=15, 33%) Median number of prior systemic regimens for metastatic disease was 4 (range 0-10); 34 (74%) patients had received prior fulvestrant, and 31 (67%) patients had received prior cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy. 16 (35%) patients had ductal histology, 29 (63%) had lobular carcinoma, and 1 (2%) had mixed ductal and lobular carcinoma. At this time, 30/46 patients had RECIST measurable disease and are efficacy evaluable (ongoing patients who did not have the opportunity for their first post-baseline tumor assessment were excluded); clinical activity - see Table. Diarrhea was the most commonly reported adverse event (80% any grade) with 15 (33%) patients reporting grade 3 diarrhea (no grade 4 diarrhea). 10 patients (22%) had a neratinib dose reduction due to diarrhea but no patients discontinued treatment due to diarrhea.

| | **RECIST measurable and efficacy evaluable patients (n=30)** |
|---|---|
| Confirmed objective response,[a] n (%) | 12 (40) |
| CR | 0 |
| PR | 12 |
| **ORR, %** (95% CI) | **40** (23-59) |
| Best overall response, n (%) | 18 (60) |
| CR | 0 |
| PR | 18 |
| **Best overall response rate, %** (95% CI) | **60** (41-77) |
| **Median[b] DOR, months** (95% CI) | **8.4** (4.1-NE) |
| Clinical benefit,[c] n (%) | 14 (47) |
| CR or PR | 12 |
| SD ≥24 weeks | 2 |
| **CBR, %** (95% CI) | **47** (28-66) |
| **Median[b] PFS, months** (95% CI) | **8.3** (4.2-12.5) |

[a]ORR is defined as either a CR or a PR that is confirmed no less than 4 weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis; [c]CBR is defined as confirmed CR or PR or SD for ≥24 weeks; CR, complete response; CBR, clinical benefit rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, stable disease.

**Conclusions:** The combination of N+T+F demonstrated encouraging clinical activity in heavily pre-treated *HER2*-mutant, HR+, *HER2*-non-amplified MBC, including patients who had previously received either fulvestrant and/or CDK4/6 inhibitor-based therapies. While the rate of grade 3 diarrhea was higher than that observed with single-agent neratinib in SUMMIT, this was manageable through loperamide prophylaxis, and no patients discontinued study treatment due to diarrhea. SUMMIT has recently been amended to evaluate N+T+F, T+F and F (1:1:1 randomization) and continues to enroll patients.

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# Concordance between patient-reported and physician-documented comorbidities among stage 4 breast cancer patients

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**Background**
Comorbidities in metastatic breast cancer patients (pts) impact treatment decisions, eligibility for clinical trials, and influence prognosis and quality of life (QoL). The aim of this study was to evaluate the concordance between pt-reported and physician-documented (PD) comorbidities in an electronic medical record to (1) reliably document pts' health histories to establish eligibility for clinical trials and novel therapeutics, and, (2) identify comorbidities that may be more comprehensively reported by pts rather than physicians.

**Patients and Methods**
All new pts at UCSF's Breast Care Center (BCC) are administered an electronic intake survey that includes an assessment of pt-reported health history, comorbidities and symptoms. Between November 2016 and March 2020, 305 pts self-reported metastatic breast cancer (described as "breast cancer spread to sites other than breast or axillary lymph nodes"), and 222 consented to use of their clinical data for research. Chart-reviews were conducted for PD comorbidities at their initial BCC clinic visit. Pt and physician concordance was summarized for 54 comorbidities. Cohen's kappa (κ) was used to quantify level of agreement. Concordance was classified using Landis and Koch thresholds with agreement as poor or slight (κ <0.20), fair (κ ≥0.20 to <0.40), moderate (κ ≥0.40 to <0.60), substantial (κ ≥0.60 to <0.80), or almost perfect (κ ≥0.80).

**Results**
Of the 222 pts, 37 pts (17%) incorrectly reported having metastatic breast cancer, 4 (2%) had duplicate surveys, 7 (3%) cancelled appointment and 5 (2%) had metastatic cancer from another primary. Thus, 168 pts with confirmed metastatic disease were included in the analysis (median age, 56 years; age range, 29-86 years; median time from diagnosis of metastatic breast cancer, 0.46 years). Highest PD comorbidities were obesity, hypertension (HTN) and thyroid disease, while highest reported comorbidities by pts were HTN, depression and arthritis. 23 of 54 comorbidities had a moderate to high level of agreement between physician and pt reports (κ□0.40). As shown in Table 1, agreement was high for diabetes (type 1 or 2), HTN and thyroid disease, moderate for asthma/bronchitis and depression, and low for obesity, anxiety, stomach ulcers/gastroesophageal reflux disease (GERD) and arthritis.

Table 1: Concordance between physician-documented and patient-reported comorbidities

| ***Comorbidity*** | **Physician Reported** | **Patient Reported** | **Concordance** | **κ** |
|---|---|---|---|---|
| *Diabetes* | 6% | 5% | 98% | 0.83 |
| *Hypertension* | 24% | 20% | 93% | 0.79 |
| *Thyroid Disease* | 20% | 18% | 92% | 0.74 |
| *Insulin dependent Diabetes* | 1% | 1% | 99% | 0.66 |
| *Depression* | 11% | 20% | 87% | 0.51 |
| *Asthma/bronchitis* | 12% | 15% | 89% | 0.51 |
| *Stomach ulcers/ GERD* | 11% | 18% | 84% | 0.36 |
| *Obesity* | 34% | 15% | 75% | 0.36 |
| *Heart disease/heart valve disease* | 7% | 4% | 93% | 0.32 |
| *Anxiety* | 10% | 18% | 83% | 0.30 |
| *Non-insulin dependent diabetes* | 3% | 1% | 97% | 0.27 |
| *Arthritis* | 9% | 20% | 78% | 0.14 |

**Conclusion**
In this review of data collected as part of routine care at an academic medical center, rates of comorbidities were relatively low, and there is substantial variance in the concordance of comorbidity reporting between pt and physicians. Pt-reported comorbidity data may help physicians more comprehensively document conditions such as depression, anxiety, arthritis and stomach ulcers/GERD, which in some cases may be subjective in nature but may significantly impact a pt's quality of life and performance status. However, pts may underreport conditions such as obesity and heart disease, and inaccurately report other conditions such as non-insulin dependent diabetes. Recognition of depression, anxiety and GERD as comorbidities is important since some medications for these conditions may be contraindicated in some clinical trials.
Understanding this concordance data may inform how we collect pt reported data to optimize understanding of a pt's global health condition.

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# Trends in breast-conserving surgery in Mexico after the implementation of a public health insurance system

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**Introduction** Although temporal trends in breast conserving surgery (BCS) have been described for developed countries like the United States (US), there is a lack of information regarding the uptake of breast conservation in developing regions of the world. In developing countries, the implementation of breast conservation might be hindered by the availability of radiation therapy, lack of training among surgeons, or concerns regarding compliance with follow-up care and surveillance. In 2006, the Mexican government created *Seguro Popular*, which provided coverage for breast cancer care for all Mexican women, thus potentially mitigating the difficulties with obtaining care after BCS and improving access to multidisciplinary care. We undertook an overview of ten years of breast cancer surgery at our Mexican cancer center following the implementation of *Seguro Popular*, and explored changes in surgical technique over time. **Methods** A retrospective cohort analysis was conducted using the National Cancer Institute of Mexico (INCAN) database from 2006 to 2016. All patients with a diagnosis of breast cancer seen during that period were included. Patients who received surgery for breast cancer where then grouped together based on the type of surgery (mastectomy versus BCS). The effect of the year of diagnosis and of clinical stage at the time of presentation was evaluated. Logistic regression was used to model temporal trends in use of BCS over mastectomy for three 3-year periods (2006-2009, 2010-2012, and 2013-2016). **Results** The patient cohort consisted of 5289 women from the INCAN database, of which 4519 received some form of local surgical treatment. Sixty-one percent (n = 2764) had locally advanced disease (stages IIB-IIIC) at the time of presentation, and a quarter (n = 1156) had ≥60 days between diagnosis and receipt of surgical treatment. Eighty percent of the patients in the entire cohort (n = 3611) were treated with mastectomy, while 20% (n = 908) received BCS. For the 2006-2009 period, out of 1596 total surgeries, 9.9% were BCS (n = 158). The proportion of BCS increased for each of the other two studied periods, being 18.5% for the 2010-2012 period (n = 276/1490), and 33.1% for the 2013-2016 period (n = 474/1433) ($p<0.01$ for trend). While the increase in BCS was significant for all stages, it was most pronounced for women with early-stage disease (Stages I-IIA), going from 17% in 2006-2009 to 52% in 2013-2016 ($p<0.01$), than in those with locally-advanced disease (6.5 to 18%, $p<0.01$). **Conclusions** In the ten years after the start of the *Seguro Popular* public insurance program, the proportion of BCS at a Mexican cancer center increased significantly, particularly for women with early-stage disease. The rates seen at INCAN for the period between 2013-2106 resemble those reported by the US National Cancer Database, in which approximately 61% of women with stage I-II breast cancer and 20% of women with stage III disease receive BCS. Potential reasons for the increase in the uptake of BCS include improved access to adjuvant radiation therapy, improved access to systemic treatment, and higher adherence to follow-up care after the start of *Seguro Popular*, as well as improvements in surgical training. In addition, changes in BCS may also be related to improvements in the implementation of multidisciplinary teams over time, which may lead to a more homogeneous and comprehensive care. Our results show that improving access to care for patients living in developing countries positively impacts the uptake of BCS for women with breast cancer.

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Hypofractionated volumetric modulated arc therapy for breast cancer: A propensity-score-weighted comparison of radiation-related toxicity according to fractionation and modality

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**Background:** Recent trials support a shorter, hypofractionated regimen (HF-RT) for breast cancer. Based on START-B trial, 3-week schedules of hypofractionated-RT (HF, 40 Gy/15 fractions) has been adopted as the one of standard of cares. We studied the clinical benefit of combining volumetric modulated arc therapy (VMAT) and HF-RT in the incidence of radiation-related toxicities.**Methods:** We retrospectively reviewed 4209 patients treated with three-dimensional conventional fractionation (CF-3D, mostly 50·4 Gy/28 fractions) and 1540 patients treated with HF-RT (768 received HF-3D and 772 received HF-VMAT, mostly 40 Gy/15 fractions) between 2005 and 2017 at a tertiary academic center. A total of 2229 patients (38.8%) received regional node irradiation (RNI): 1642 (39.0%), 167 (21.7%), and 420 (54.4%) patients received RNI in the CF-3D, HF-3D, and HF-VMAT, respectively. VMAT was used to HF patients either to minimize cardiac dose in regional RT for unfavorable/challenging cardio-thoracic anatomy (n = 420) or to shorten the treatment time by using 3.2 Gy of simultaneous integrated boost (SIB) in 15 fractions for breast conservation (n = 352). Physician-reported events during/within 3 months after RT were defined as acute/subacute toxicity. Late toxicities included radiation pneumonitis, lymphedema, hypothyroidism, and cardiotoxicity. Propensity scores were calculated via logistic regression then inverse probability of treatment weighting analysis was performed for pairwise comparison.**Result:** The rate of grade 2+ acute/subacute toxicities were the highest in patients treated with CF-3D (15.0%, 2.6%, and 1.6% in patients treated with CF-3D, HF-3D, and HF-VMAT, respectively; p < 0.001). HF-VMAT significantly reduced grade 2+ acute/subacute toxicities compared to CF-3D (odds ratio [OR] 0.11, p < 0.001) and HF-3D (OR 0.45, p = 0.010). The 3-year cumulative rate of late toxicities was 18·0% (20·1%, 10·9%, and 13·4% in patients treated with CF-3D, HF-3D, and HF-VMAT, respectively; p < 0·001). The sensitivity analysis showed that the benefit of HF-VMAT was greater in the regional RT group. The local recurrence rate did not differ among the groups (p > 0·05).**Conclusion:** HF was associated with decreased toxicities than CF in this real-world inverse probability of treatment weighting analysis cohort. HF-VMAT further decreased acute and late toxicity than HF-3D or CF-3D, especially in women underwent RNI, although prospective long-term follow-up is needed. The shortening of overall treatment time by SIB-VMAT in HF may be of value.

Table. **Pairwise comparisons of outcomes by treatment group after propensity score weighting**

| Outcome | CF-3D vs. HF-3D (reference: CF-3D) | | CF-3D vs. HF-VMAT (reference: CF-3D) | | HF-3D vs. HF-VMAT (reference: HF-3D) | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Acute or subacute toxicity with any grade ≥2 | 0.20 (0.15-0.27) | <.0001 | 0.11 (0.08-0.17) | <.0001 | 0.45 (0.24- 0.83) | 0.0101 |
| | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| Late toxicity | 0.79 (0.69-0.90) | 0.0006 | 0.58 (0.50-0.68) | <.0001 | 0.79 (0.60-1.03) | 0.0838 |
| Radiation pneumonitis | 1.54 (1.16-2.04) | 0.0029 | 0.27 (0.15-0.48) | <.0001 | 0.14 (0.06-0.29) | <.0001 |
| Lymphedema | 0.96 (0.81-1.14) | 0.6540 | 0.85 (0.71-1.03) | 0.0947 | 0.98 (0.71-1.35) | 0.9279 |
| Hypothyroidism | 0.25 (0.15-0.42) | <.0001 | 0.16 (0.08-0.32) | <.0001 | 1.67 (0.40-6.67) | 0.4886 |
| Cardiotoxicity | 0.56 (0.38-0.83) | 0.0039 | 0.38 (0.23-0.66) | 0.0005 | 0.76 (0.32-1.79) | 0.5369 |
| Locoregional recurrence | 0.93 (1.28-1.79) | 0.1309 | 1.15 (0.79-1.67) | 0.4700 | 0.74 (0.39-1.41) | 0.3543 |

*Abbreviations*: CF, Conventional fractionation; 3D, three-dimensional conformal radiation therapy; HF, Hypofractionation; VMAT, Volumetric-modulated arc therapy; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

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# Using blueprint to elucidate the molecular heterogeneity of triple negative breast cancers

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**Background**: Triple negative breast cancers (TNBC) are more aggressive, have a worse prognosis, and few targeted therapies compared to other BC subtypes. TNBC is molecularly heterogeneous, with at least 4 distinct subtypes: basal-like immune-activated (BLIA), basal-like immunosuppressed (BLIS), luminal androgen receptor (LAR), and mesenchymal (MES). The molecular subtyping gene signature, BluePrint (BP), classifies breast tumors into Luminal, HER2, or Basal subtype based on the assessment of downstream signaling pathways and independently of IHC expression. Compared to IHC-defined TNBC, a higher frequency of BLIS or BLIA subtypes and fewer LAR or MES tumors were reported in BP-defined Basal tumors. To advance our understanding of TNBC heterogeneity, we evaluated the relationship between gene expression signatures, TNBC subtype and BluePrint, in IHC-defined TNBC.
**Methods**: The FLEX registry (NCT03053193) is an ongoing, prospective study evaluating primary tumors from stage I-III BC patients who receive the risk of distant recurrence gene signature, MammaPrint (MP), and BP testing and consent to clinically annotated full transcriptome data collection. This analysis includes 204 IHC-defined TNBC patients. TNBC subtypes BLIA, BLIS, LAR, and MES were derived using an adjusted version of the Burstein centroid signature. BP classified patient samples into Luminal, HER2, and Basal subtypes. A proportion of tumors may exhibit a secondary but less pronounced activated pathway or BP subtype. Therefore, each BP subtype was divided into single activated or mixed subtype based on BP indices.
**Results**: Of 204 TNBC tumors, 84% were classified as Basal by BP, most of which were BLIS (65%), followed by BLIA (22%), with a low frequency of MES (8%) and LAR (5%) subtypes (Table). Approximately 14% of TNBCs were reclassified as Luminal by BP, most of which were LAR (76%), whereas 24% were MES. Clustering analysis revealed similar gene expression profiles between Basal-BLIS and Basal-BLIA tumors. Interestingly, the transcriptional profile of Basal-MES and Basal-LAR tumors were similar to Luminal-MES and Luminal-LAR tumors. BP Basal indices distinguished between different TNBC subtypes. The Basal pathway was predominantly activated in 90% of BP Basals (single activated tumors), most of which were either BLIS or BLIA (96%), whereas 10% of BP Basals were mixed subtype and more likely to classify as LAR (53%) or MES (35%). Approximately 25% of the BP Basal gene signature overlapped with the TNBC subtype gene signature. Expression of 18 and 12 genes out of 28 genes that make up the BP basal signature were significantly different in Basal-BLIA/BLIS compared to LAR or MES, respectively ($P < 0.05$). *PRR15* and *CAPN13* were significantly differentially expressed between LAR and MES within Basals.
**Conclusion**: BP reclassified a subgroup of TNBC tumors to Luminal, explaining the discrepancy in the distribution of TNBC subtypes between IHC-defined TNBC and BP Basal tumors. Furthermore, BP indices distinguished between single activated and mixed subtypes, which correlated with different TNBC subtypes. These data suggest that molecular classification by BP adds further precision in classifying TNBC patients and sheds new light on the heterogeneity of these tumors. These findings have clinical implications in stratifying patients and identifying successful targeted treatment options. Future studies are warranted to investigate treatment response and prognosis in these molecular subgroups.

| | **Basal** | **Luminal** | **HER2** | **Total** |
|---|---|---|---|---|
| BLIA | 37 | 0 | 0 | 37 |
| BLIS | 111 | 0 | 0 | 111 |
| LAR | 10 | 22 | 3 | 35 |
| MES | 14 | 7 | 0 | 21 |
| **Total** | **172 (84.3%)** | **29 (14.2%)** | **3 (1.5%)** | **204 (100%)** |

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# Fertility preservation in young women with breast cancer: Impact on treatment and outcomes

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**Background.** The American Society of Clinical Oncology guidelines recommend timely referral to reproductive endocrinology and infertility (REI) specialists for young women diagnosed with breast cancer. There is a paucity of data evaluating the impact of FP on oncologic outcomes and timely initiation of chemotherapy.
**Methods.** This retrospective review included all women age ≤ 45y diagnosed with stage I-III unilateral breast cancers at Memorial Sloan Kettering Cancer Center between 2009-2015 who received chemotherapy and consulted with an REI specialist. Factors associated with the decision to undergo FP were analyzed. Survival curves were constructed using the Kaplan-Meier method.
**Results.** A total of 172 women were identified. Median age was 34y (interquartile range 31-37). The majority of women were single (n = 99, 58.1%) and nulliparous (n = 134, 77.9%). Most women underwent FP (n = 121, 70.3%). Tumor characteristics and treatments were similar between women who underwent FP and those who declined (Table 1). While white race was associated with decision to pursue FP, this association did not persist on multivariable analysis (MVA). Young age (p = 0.003), nulliparity (p = 0.001), referral from Breast Surgery (p = 0.009), and private insurance (p < 0.001) were independent predictors of FP on MVA. Timing of chemotherapy (adjuvant vs neoadjuvant) was not associated with decision to undergo FP. FP was not associated with breast cancer treatment delays.
A total of 25.5% (n = 44) of women had a biological child following breast cancer treatment (Table 2). Women who underwent FP were more likely to have a biological child after breast cancer treatment. Race and insurance type were also associated with having a biological child after treatment, with white women and women with private insurance being more likely to have a biological child. MVA revealed that undergoing FP, being married, and being white were independent predictors of having a biological child.
The 5-year overall survival (OS) was 97.5% (95% CI: 93.5-99.1%) and the 5-year recurrence-free survival (RFS) was 91.4% (95% CI: 85.9%-94.8%) with a median follow-up of 70 months (range 4-127). Five-year overall survival (OS) and recurrence-free survival (RFS) were similar between women who underwent FP and those who declined (OS: FP 98.2%, 95% CI 92.9%-99.5% vs 95.9%, 95% CI 84.6-98.9%, p = 0.20 and RFS: FP 92.1%, 95% CI: 85.4-95.8% vs declined 89.7%, 95% CI 76.9-95.6%, p = 0.42). Disease stage, race, and pregnancy were not associated with differences in OS or RFS. Private insurance was associated with improved OS but not with improved RFS.
**Conclusions.** Most women underwent FP. Women pursued FP at high rates independent of the timing of chemotherapy and oncologic factors. These findings indicate that timely consultation with REI specialists is the key factor in completing FP, and highlight opportunities for improved education and counseling regarding FP. They also identify FP as a possible area of racial disparities within breast cancer care, and serve as a reminder of the complex interplay between socioeconomic factors, reproductive choices, and pregnancy outcomes.

Table 1. Factors associated with decision to pursue cryopreservation

| **Factors** | | **Declined Cryopreservation (n = 51)** | **Cryopreservation (n = 121)** | ***p* value** |
|---|---|---|---|---|
| **Median Age, years (IQR)** | | 37 (32-40) | 33 (30-37) | < 0.001 |
| **Race** | White | 26 (56.5%) | 86 (78.2%) | 0.015 |
| | Black | 10 (21.7%) | 7 (6.3%) | |
| | Asian | 9 (19.6%) | 15 (13.6%) | |
| | Other | 1 (2.2%) | 2 (1.8%) | |
| | Unknown | 5 | 11 | |
| **Insurance Type** | Private | 39 (76.5%) | 114 (94.2%) | < 0.001 |
| | Government | 11 (21.6%) | 4 (3.3%) | |
| | Uninsured | 1 (2.0%) | 3 (2.5%) | |
| **Single** | | 29 (56.9%) | 70 (57.9%) | > 0.99 |
| **Nulligravid** | | 21 (41.2%) | 80 (66.1%) | 0.004 |
| **Nulliparous** | | 31 (60.8%) | 103 (85.1%) | < 0.001 |
| **Referring Service** | Breast Surgery | 24 (47.1%) | 87 (71.9%) | 0.004 |
| | Breast Medicine | 26 (51.0%) | 33 (27.3%) | |
| | Genetics/GYN | 1 (2.0%) | 1 (0.8%) | |
| **Tumor Grade** | I | 2 (4.0%) | 2 (1.7%) | 0.52 |
| | II | 7 (14.0%) | 14 (11.8%) | |
| | III | 41 (82.0%) | 103 (86.6%) | |
| | Unknown | 1 | 2 | |
| **Receptor Profile** | ER/PR+ HER2- | 31 (60.8%) | 64 (52.9%) | 0.74 |
| | ER/PR+ HER2+ | 8 (15.7%) | 27 (22.3%) | |
| | ER/PR- HER2+ | 2 (3.9%) | 4 (3.3%) | |
| | Triple Negative | 10 (19.6%) | 26 (21.5%) | |
| **Stage** | I | 12 (23.5%) | 44 (36.4%) | 0.074 |
| | II | 27 (52.9%) | 63 (52.1%) | |
| | III | 12 (23.5%) | 14 (11.6%) | |
| **Breast Surgery** | Lumpectomy | 19 (37%) | 38 (31.4%) | 0.57 |
| | Mastectomy | 32 (63%) | 83 (68.6%) | |
| **Systemic Therapy** | Adjuvant Chemotherapy | 43 (84.3%) | 104 (86.0%) | 0.97 |

| | | | | |
|---|---|---|---|---|
| | Median Time from Surgery to Chemotherapy, weeks (range) | 7 (4-19) | 7 (2-18) | 0.9 |
| | Delay > 12 Weeks to Chemotherapy | 2 (4.7%) | 3 (2.9%) | 0.63 |
| | Neoadjuvant Chemotherapy | 8 (15.7%) | 17 (14.0%) | 0.97 |
| | Median Time from Diagnosis to NAC, weeks (range) | 3 (1-8) | 3 (2-12) | 0.29 |
| | Delay > 6 weeks to chemotherapy start | 1 (12.5%) | 2 (11.8%) | > 0.99 |
| | Endocrine Therapy | 41 (80.4%) | 92 (76.0%) | 0.67 |
| **Radiation Therapy** | Adjuvant Whole Breast Radiation Therapy | 16 (31.4%) | 38 (31.4%) | 0.99 |
| | PMRT | 16 (31.4%) | 43 (35.5%) | 0.73 |
| *IQR* interquartile range, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor. "Unknowns" were not included in percentage calculations or in univariate analysis. | | | | |

Table 2. Factors associated with having a biological child after breast cancer treatment

| **Factors** | | **Had a biological child (n = 44)** | **Did not have a biological child (n = 128)** | ***p* value** |
|---|---|---|---|---|
| **Completed fertility preservation** | | 40 (90.9%) | 81 (63.3%) | 0.001 |
| **Race** | White | 36 (90.0%) | 76 (65.5%) | 0.029 |
| | Black | 1 (2.5%) | 16 (13.8%) | |
| | Asian | 3 (7.5%) | 21 (18.1%) | |
| | Other | 0 | 3 (2.6%) | |
| | Unknown | 4 | 12 | |
| **Insurance Type** | Private | 40 (90.9%) | 113 (88.3%) | 0.020 |
| | Government | 1 (2.3%) | 14 (10.9%) | |
| | Uninsured | 3 (6.8%) | 1 (0.8%) | |
| **Married** | | 30 (68.2%) | 43 (33.6%) | < 0.001 |
| **Nulligravid** | | 24 (54.5%) | 77 (60.2%) | 0.64 |
| **Nulliparous** | | 32 (72.7%) | 102 (79.7%) | 0.45 |
| **Referring Service** | Breast Surgery | 33 (75.0%) | 48 (37.5%) | 0.22 |
| | Breast Medicine | 11 (25.0%) | 78 (60.9%) | |
| | Genetics/GYN | 0 | 2 (1.6%) | |
| **Tumor Factors** | | | | |
| **Tumor Grade** | I | 1 (2.4%) | 3 (2.3%) | > 0.99 |
| | II | 5 (11.9%) | 16 (12.6%) | |
| | III | 36 (85.7%) | 108 (85.0%) | |
| | Unknown | 2 | 1 | |
| **Stage** | I | 19 (43.2%) | 37 (28.9%) | 0.21 |
| | II | 19 (43.2%) | 71 (55.5%) | |
| | III | 6 (13.6%) | 20 (15.6%) | |
| **Breast Cancer Treatment** | | | | |
| **Mastectomy** | | 32 (72.7%) | 83 (64.8%) | 0.44 |
| **ALND** | | 15 (34.1%) | 51 (39.8%) | 0.62 |
| **Systemic Therapy** | Adjuvant Chemotherapy | 39 (88.6%) | 108 (84.4%) | 0.66 |
| | Neoadjuvant Chemotherapy | 5 (11.4%) | 20 (15.6%) | |
| **Radiation Therapy** | | 26 (59.1%) | 87 (68.0%) | 0.38 |
| *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *DCIS* ductal carcinoma in situ, *ER* estrogen receptor. "Unknowns" were not included in percentage calculations or in univariate analysis. | | | | |

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**Publication Number:** PD15-05

# Sipa1 effects rock pathway in human breast cancer linking to HGF mediated changes in tight junction functions controlling metastasis

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**Background:** SIPA1 (Signal-induced proliferation-associated gene 1) is a mitogen-inducible gene encoding a GTPase-activating protein for Rap1 and Rap2 and has been suggested to be involved in metastatic progression. We have previously shown SIPA1 may regulate barrier function in breast cancer cells as part of hepatocyte growth factor-determined changes and that this may be via a number of regulatory pathways, most likely via the ROCK pathway. Our aim with this current work was to definitively identify which pathway is involved. **Methods:** After knockdown of SIPA1 in MDA-MB-231 cells, they were treated to a number of inhibitors to proteins involved in pathways involved in TJ barrier function (ROCK, N-WASP, ARPs, WAVEs, MAPK, ERK, PLC-gamma). Following the identification of suitable inhibitor a large scale *in vivo* study was carried out using a tumour model of SIPA1 knockdown versus WT control was treated with/without inhibitors and immunohistochemistry (IHC) used to assess changes in tumour growth, architecture and protein expression. We also assessed the expression of SIPA-1 in a cohort of human breast cancer tissues using IHC. **Results:** After knockdown of SIPA1 in MDA-MB-231 cells, we subjected cells to a number of inhibitors to proteins involved in pathways involved barrier function (ROCK, N-WASP, ARPs, WAVEs, MAPK, ERK, PLC-gamma). Analysis of behaviour showed that knockdown cells no longer responded to the ROCK inhibitor (ROCKi Y-27632, $p<0.05$, $n=10$). *In vivo* tumour samples were assessed for expression of ROCKI, expression of phospho-ROCK, and any differences when treated with ROCKi. Control tissues showed good levels of all three proteins (SIPA1, ROCKI and phosphor-ROCK). Knockdown tissues exhibited significantly lower levels of ROCK and phosphor-ROCK ($p<0.01$, $n=12$). In control tumours, phosphor-ROCK was increased after treatment with ROCKi; conversely, in SIPA1 knockdown tumours, phosphor-ROCK was decreased after treatment with ROCKi ($p<0.05$). In SIPA1 knockdown tissues, ROCK and phosphor-ROCK was diffuse in staining pattern when compared to the control where the staining was located at the cell membrane. **Conclusion:** Our results confirm our hypothesis that SIPA1 is involved in the control of TJ in breast cancer and that this is through the ROCK pathway. Moreover, these results demonstrate that this may be due to the effect that SIPA1 has on cellular ratios of ROCK to phosphor-ROCK in breast cancer.

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Genome-wide association study identifies *UACA* as a modulator of breast cancer chemoresistance and survival

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Prior studies suggest a strong genetic influence on breast cancer prognosis. Six genome-wide association studies (GWAS) on breast cancer prognosis have been published to date. However, none of the reported loci was replicated across studies and only two passed genome-wide significance ($P < 5 \times 10^{-8}$). In the Pathways Study, a prospective cohort of breast cancer survivors begun in Kaiser Permanente Northern California (KPNC) in 2006, we carried out a GWAS of overall survival (OS) in 3,973 patients. Trans-ethnic meta-GWAS identified an association with OS of a locus on chromosome 15 that almost reached genome-wide significance ($P = 9.42 \times 10^{-8}$). This locus spanned the *UACA* gene, a key regulator of tumor suppressor Par-4. We found that receipt of chemotherapy modified the effect of the *UACA* locus on OS ($P_{interaction} = 2.4 \times 10^{-4}$). This observation led us to hypothesize that the *UACA* locus effect on OS may be specific to Par-4 dependent chemotherapies, which include anti-HER2 therapy and doxorubicin. We stratified patients into two groups, those who received Par-4 dependent chemotherapy agents versus other patients. In separate trans-ethnic meta-GWAS, the *UACA* locus was significantly associated with OS in patients taking Par-4 dependent chemotherapies ($P = 1.27 \times 10^{-9}$), while no association was observed in the other patients ($P = 0.21$). To evaluate whether the *UACA* gene may be responsible for this association, we performed a transcriptome-wide association study (TWAS) of OS in White patients taking Par-4 dependent chemotherapies. Higher *UACA* gene expression was significantly associated with OS ($P = 4.68 \times 10^{-7}$), the only gene reaching transcriptome-wide significance ($P < 4.34 \times 10^{-6}$). These results suggest that higher *UACA* expression may inhibit Par-4 induced apoptosis and lead to stronger chemoresistance and worse survival. We attempted to validate our findings in the independent KPNC Genetic Epidemiology Research on Aging (GERA) cohort. The GERA cohort included only 168 White patients with incident breast cancer after DNA collection who received Par-4 dependent chemotherapies. We found a non-significant association (hazard ratio (HR) = 1.46, $P = 0.66$) consistent with Pathways Study findings. However, the GERA cohort also included 1,983 prevalent breast cancer patients with biospecimen collection after diagnosis. In this group, the risk allele frequency in breast cancer survivors receiving Par-4 dependent chemotherapies was significantly lower than that in the White population ($P = 5.50 \times 10^{-3}$) while the risk allele frequency in the those not receiving these chemotherapies was similar to the population ($P = 0.07$). This is consistent with Pathways Study observations that the *UACA* locus risk allele significantly increased risk of mortality in patients taking Par-4 dependent chemotherapies. A higher mortality in breast cancer survivors carrying the risk allele would result in decreased risk allele frequency. We further validated our findings in Shanghai Breast Cancer Survival Study (SBCSS)and Shanghai Breast Cancer Study, which were conducted from 1996 to 2006 in urban Shanghai and recruited 5,575 breast cancer patients. In this independent Asian breast cancer population, the *UACA* locus was modestly associated with OS in the overall population (HR = 1.18, $P = 0.012$), and more significantly in 1,289 SBCSS patients who received anthracyclines (HR = 1.66, $P = 1.55 \times 10^{-4}$). This is the first human study suggesting the Par-4 pathway affects breast cancer patient survival with *UACA* a key modulator of treatment outcomes by anti-Her2 therapy and doxorubicin. Our findings suggest a path toward new predictive pharmacogenetic markers for personalized medicine targeting the Par-4 pathway for breast cancer treatment.

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**Publication Number:** PS8-05

Randomized controlled trial of decision support tools for patients and providers to increase breast cancer chemoprevention

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**Background:** Breast cancer chemoprevention with selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) have been shown in randomized controlled trials to reduce breast cancer incidence by 50-65% among high-risk women. However, chemoprevention is still underutilized with fewer than 5% of high-risk women offered chemoprevention agreeing to take the medications. Reasons for low chemoprevention uptake include inadequate knowledge about chemoprevention among patients and healthcare providers, concerns about side effects, competing comorbidities, and time constraints during the clinical encounter. To address these barriers to chemoprevention uptake, we developed decision support tools for patients and providers. **Methods:** We conducted a randomized controlled trial of standard educational materials alone or combined with web-based decision support tools, *RealRisks* and *BNAV*, among 300 high-risk women and 50 healthcare providers, respectively. Patient eligibility criteria included: 1) women, age 35-75 years; 2) high-risk for breast cancer, defined as a 5-year invasive breast cancer risk ≥1.67% according to the Gail model or history of lobular carcinoma *in situ* (LCIS); 3) no prior use of a SERM or AI; 4) No personal history of breast cancer; 5) Access to the internet. Providers included primary care providers, such as internists, family practitioners, gynecologists, and nurse practitioners, and specialists, such as breast surgeons and medical oncologists. The *RealRisks* decision aid (DA) is available in English and Spanish and includes interactive modules to communicate personalized breast cancer risk and the risks and benefits of chemoprevention. The *BNAV* tool includes self-paced learning modules on breast cancer risk factors and chemoprevention and was made available to all providers through the electronic health record (EHR) dashboard. The primary endpoint was chemoprevention uptake at 6 months as assessed via the EHR. Secondary outcomes included validated measures of perceived breast cancer risk, breast cancer worry, chemoprevention knowledge, self-efficacy, decision conflict, chemoprevention attitudes, intention, and informed choice, which were administered to patients at baseline, 1 month, and 6 months after randomization. **Results:** Among 282 evaluable high-risk women enrolled from November 2016 to March 2020, mean age was 57 years (SD, 9.9), including 59% white, 14% black, 21% Hispanic, and 6% other. Mean 5-year invasive breast cancer risk was 2.98% (SD, 1.42), including 67% of women with benign breast disease and 64% with a first-degree family history of breast cancer. Comparing the intervention and control arms at 1 month, there were significant differences among high-risk women in accurate breast cancer risk perceptions (56% vs. 39%, p=0.017), adequate chemoprevention knowledge (49% vs. 27%, p<0.001), informed choice (41% vs. 23%, p=0.003), and mean decision conflict (34.0 vs. 47.0, p<0.001). There were no significant differences between the two groups in other patient-reported outcomes. Among patients who completed their 6-month follow-up, only 2.3% of high-risk women in the intervention arm and 3.8% in the control arm initiated a SERM or AI for breast cancer chemoprevention. **Conclusions:** With short-term follow-up, exposure to our decision support tools was associated with improvement in decision antecedents (accurate breast cancer risk perceptions, adequate chemoprevention knowledge) and decision quality (increased informed choice, reduced decision conflict). However, actual chemoprevention uptake in both arms remained low at less than 5%. Future research should focus on targeting high-risk women with LCIS or atypical hyperplasia and better incorporating decision support into clinic workflow through EHRs and patient portals.

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# Impact of body mass index on pathological complete response after neoadjuvant chemotherapy: Results from the I-SPY 2 trial

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**Purpose:** Increased body mass index (BMI) is a risk factor for breast cancer and has been associated with poor outcomes in both premenopausal and postmenopausal breast cancer patients. Several retrospective studies have demonstrated higher BMI to be associated with inferior pathological complete response (pCR) to neoadjuvant chemotherapy, yet it remains unclear if this difference is related to chemotherapy underdosing among obese breast cancer patients. We evaluated the association between BMI and response to neoadjuvant chemotherapy (defined by pCR) in the I-SPY 2 trial, an adaptive clinical trial platform enrolling biologically high-risk breast cancer patients (triple negative, human epidermal growth factor receptor 2 (HER2) positive and MammaPrint high-risk) that utilizes standard neoadjuvant therapy regimens with treatment based on actual body weight.
**Patients and Methods**: From 3/2010 to 11/2016, 989 patients were enrolled in the I-SPY 2 trial, 978 had a recorded baseline BMI prior to treatment and were included in the analysis. Tumor subtypes were defined by hormone receptor and HER2 status. Pretreatment BMI was categorized as obese (BMI>=30 kg/m2), overweight (25=<BMI<30 kg/m2), and normal or underweight (<25 kg/m2) based on World Health Organization criteria. pCR was defined as elimination of detectable invasive cancer in the breast and lymph nodes (ypT0/Tis and ypN0) at the time of surgery. Logistic regression analysis was used to determine associations between BMI and pCR, and we reported odds ratios (OR) and 95% confidence intervals (CI). Event-free survival (EFS) and overall survival (OS) between different BMI categories were examined using Cox proportional hazards regression.
**Results:** The median age in our study population was 49 years. 35% of patients were normal/underweight, 32% overweight, and 33% obese. Black patients were more likely to be obese (P<0.0001). pCR rates differed significantly by tumor subtype (P<=0.0001) and tumor stage (P=0.0009). pCR rates were 32.8% in normal/underweight, 31.4% in overweight, and 32.5% in obese patients. In univariable analysis, there was no significant difference in pCR with BMI. In multivariate analysis adjusted for race/ethnicity, age, menopausal status, breast cancer subtype, and clinical stage, there was no significant difference in pCR to neoadjuvant chemotherapy for obese compared with normal/underweight patients (OR=1.1, 95%CI: 0.68-1.63, p=0.83), and for overweight compared with normal/underweight (OR=1, 95%CI: 0.64-1.47, p=0.88). We tested for potential interaction between BMI and breast cancer subtype, however, the interaction was not significant in the multivariate model (P=0.09) (Table 1). Multivariate Cox regression showed there was no difference in EFS (p=0.81) or OS (p=0.52) between obese, overweight and normal/underweight breast cancer patients with a median follow-up time of 4.0 years.
**Conclusions:** There was no difference in pCR rates by BMI with actual body weight based neoadjuvant chemotherapy in this biologically high-risk breast cancer population. In contrast, breast cancer subtype and stage showed predictive value for pCR in this high-risk operable breast cancer population receiving neoadjuvant chemotherapy in the I-SPY 2 clinical trial.
**Table 1:** pCR rate of different BMI categories by breast cancer subtypes.

| Breast Cancer Subtype | pCR | Normal/underweight Frequency (%) | OverweightFrequency (%) | ObeseFrequency (%) | P-value |
|---|---|---|---|---|---|
| **HR+/HER2+** | **No** | 39 (61.9) | 27 (61.4) | 32 (66.7) | 0.83 |
| | **Yes** | 24 (38.1) | 17 (38.6) | 16 (33.3) | |
| **HR+/HER2-** | **No** | 105 (80.8) | 116 (89.2) | 93 (78.8) | 0.06 |
| | **Yes** | 25 (19.2) | 14 (10.8) | 25 (21.2) | |
| **HR-/HER2+** | **No** | 7 (25.0) | 11 (35.5) | 15 (51.7) | 0.11 |
| | **Yes** | 21 (75.0) | 20 (64.5) | 14 (48.3) | |
| **HR-/HER2-** | **No** | 83 (65.4) | 58 (55.8) | 76 (60.8) | 0.33 |
| | **Yes** | 44 (34.7) | 46 (44.2) | 49 (39.2) | |

(HR: hormone receptor, HER2: human epidermal growth factor receptor 2)

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**Publication Number:** PD13-05

Delivery and activity of SN-38 by sacituzumab govitecan in breast cancer brain metastases

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**BACKGROUND**: Sacituzumab Govitecan (SG, TRODELVY™) is an FDA approved antibody drug conjugate for treatment of metastatic triple negative breast cancer (TNBC). SG has payload and linker characteristics preferable for CNS delivery including a pH hydrolysable, a payload (SN-38) that is the active 1000-fold more potent than the parent compound CPT-11 and crosses the blood brain barrier. Our preliminary data showed SG activity in intracranial xenografts leading to our hypothesis that SG would achieve concentration of SN-38 within the breast cancer brain metastases (BCBM) that would be therapeutically relevant. **METHODS:** We undertook a single center, prospective, window of opportunity trial (NCT03995706) to examine the concentrations of SG, SN-38, and SN-38G in tumors patients undergoing craniotomy for BCBM (n=20) or recurrent glioblastoma (rGBM, n=10). A single dose of SG was administered at 10mg/kg IV the day prior to craniotomy. Tumor was collected and [SN-38] was analyzed via mass spectrometry (UHPLC-HRMS). following recovery patients resumed SG at 10mg/kg IV days 1 and 8 of 21 day cycle and were assessed for response or progression every third cycle by MRI. **RESULTS:** To date 21 patients have been treated, including 11 BCBM and 10 rGBM. UHPLC-HRMS analysis was performed in the first 10 tumors (n=4 and 6 respectively). For BCBM, total concentration of SN-38 varied from 173nM to 1160nM, with a mean concentration of 626nM. All GBM patients had residual measurable disease and 4 breast patients had measurable disease. With a median follow-up of 12 weeks from the first postoperative cycle in the first 14 patients, 2 partial responses from each group were observed (ORR of 28% and 50% at 12 weeks respectively). Updated results will be presented. **CONCLUSIONS:** SG achieves therapeutically relevant concentrations of SN-38 at 150-fold mean IC50s for BCBM. Early intracranial responses are encouraging and merit further evaluation. A multi-center trial of SG for HER2 negative BCBM (SWOG S2007) will be enrolling soon.

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**Publication Number:** SS2-05

Emerging from COVID-19 pandemic: Provider perspective on use of neoadjuvant endocrine therapy (NET) in early stage hormone receptor positive breast cancer

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**Introduction**During the coronavirus 2019 (COVID-19) pandemic in USA, NET use has been recommended to allow safe deferral of surgical treatment in early stage, estrogen receptor positive breast cancer (ER+BC). In such circumstances, after NET use there is limited guidance on locoregional treatment, especially with management of the axilla. We aimed to evaluate patterns of care in early stage ER+BC during the first several months of the COVID-19 pandemic.**Method**A cross-sectional, 30-item survey was developed using a standardized survey development framework. The survey was administered May 8 - June 12, 2020 to a convenience sample of medical oncologists (MO), radiation oncologists (RO), and surgeons (SO) - breast committee members of two national cooperative groups (Alliance and SWOG) with additional participation through chain referrals. Providers were presented with general questions on NET use before and during the pandemic. They were asked their propensity for omitting axillary lymph node dissection (ALND) after NET if 1 micrometastatic node is found on sentinel lymph node biopsy, based on duration of NET.**Results**114 providers from 29 US states completed the survey - 42 (37%) MO, 14 (12%) RO, and 58 (51%) SO, the majority (N=73/96, 76%) with practices dedicated ≥ 75% to BC, at NCI designated comprehensive cancer centers 52% (N=48/94) and in large cities (N=49/94, 52%). Prior to COVID-19, most rarely (N=49/107, 46%) or sometimes (N=36, 33%) used NET for early stage ER+BC. Nearly half were willing to delay surgery up to 2 months (46%) and 3 months (21%) without use of NET (Table 1, †p<0.05). Most providers would perform a genomic assay on the biopsy specimen on all or select patients prior to NET initiation, more frequently by MO compared to RO and SO (90% vs. 75% and 60%, p<0.05). The most preferred regimen was tamoxifen (without ovarian suppression) for premenopausal patients and aromatase inhibitor for postmenopausal patients. Most planned to use NET for as little time as possible until surgery could proceed. When stratified by specialty, more MO stated they would vary the duration of therapy based on patient's risk of cancer progression. Most providers recommended omitting ALND after 1, 2, or 3 months of NET (1 month N=56/93, 60%; 2 months N=54/92, 59%; 3 months N=48/90, 53%). With longer duration of therapy, the propensity for omitting ALND decreased (definitely omit after 6 months N=25/91, 27%; probably omit after 6 months N=38/91, 42%; definitely omit after 1 year N=26/92, 28%; probably omit after 1 year N=29/92, 32%). Omitting ALND was not associated with provider's years in practice, percent of practice dedicated to BC, practice type or setting, participation in multidisciplinary tumor board, or number of COVID-19 cases in the provider's practicing state.**Conclusion**Most providers changed their management of early stage ER+BC during the COVID-19 pandemic by utilizing NET until surgery could proceed. As the duration of NET extended, more providers favored ALND in low volume axillary metastatic disease in early stage ER+BC. Additional data to inform the care on post-NET locoregional management is needed.

Table 1. Management of early stage, node negative, ER+BC during COVID-19 pandemic

| | **Total (N, %)** | **Med Onc** | **Rad Onc** | **Surgeon** |
|---|---|---|---|---|
| **How long are you willing to delay surgery (without use of endocrine therapy)?** | | | | |
| Up to 1 month | 25 (23%) | 10 (24%) | 0 | 15 (26%) |
| Up to 2 months | 51 (46%) | 17 (40%) | 7 (64%) | 27 (47%) |
| Up to 3 months | 23 (21%) | 9 (21%) | 2 (18%) | 12 (21%) |
| Up to 4 months | 3 (3%) | 2 (5%) | 1 (9%) | 0 |
| Up to 6 months | 8 (7%) | 4 (10%) | 1 (9%) | 3 (5%) |
| **Have you changed your practice during the current pandemic?** | | | | |
| Yes - institution mandated change to delay surgery | 8 (25%) | 4 (36%) | 0 | 4 (29%) |
| Yes - based on multidisciplinary team discussion (no explicit institutional mandate to delay cancer surgery) | 21 (66%) | 6 (55%) | 7 (100%) | 8 (57%) |
| No - was not allowed by institution to change | 0 | 0 | 0 | 0 |
| No - was not necessary | 3 (9%) | 1 (9%) | 0 | 2 (14%) |
| **If using endocrine therapy before surgery, which regimen are you using??** | | | | |
| Tamoxifen for all patients | 0 | 0 | 0 | 0 |
| Tamoxifen for premenopausal patients; aromatase inhibitor for postmenopausal patients | 77 (81%) | 26 (63%) | 0 | 51 (94%) |
| Ovarian suppression with aromatase inhibitor for premenopausal patients; aromatase inhibitor for postmenopausal patients | 18 (19%) | 15 (37%) | 0 | 3 (6%) |
| **How are you staging the axilla prior to starting endocrine therapy?** | | | | |
| Exam only | 28 (26%) | 8 (19%) | 2 (17%) | 18 (33%) |
| Exam + US | 77 (71%) | 30 (71%) | 10 (83%) | 37 (67%) |
| Exam + US + cross sectional image (CT scan) | 4 (4%) | 4 (10%) | 0 (0%) | 0 (0%) |
| SLNB | 0 | 0 | 0 | 0 |
| **If using endocrine therapy first (before surgery), are you?** | | | | |
| Sending genomic assay on biopsy specimen on all patients | 28 (26%) | 18 (44%) | 1 (8%) | 9 (16%) |
| Sending genomic assay on biopsy specimen on only select patients (ie. high grade, size on imaging/exam, high Ki-67) | 51 (48%) | 19 (46%) | 8 (67%) | 24 (44%) |
| Not sending genomic assay. Using PEPI score instead. | 4 (4%) | 1 (2%) | 1 (8%) | 2 (4%) |
| Not sending genomic assay. Using Magee Equations for Estimating Oncotype DX Recurrence Score instead. | 2 (2%) | 0 | 0 | 2 (4%) |
| None of above | 21 (20%) | 3 (7%) | 2 (17%) | 18 (33%) |
| **If using endocrine therapy first, what duration do you plan to use it for the average patient??** | | | | |
| Minimum 1 year for all patients | 0 | 0 | 0 | 0 |
| Minimum 6 months for all patients | 7 (6%) | 4 (10%) | 0 (0%) | 3 (5%) |

| | | | | |
|---|---|---|---|---|
| Minimum 3 months for all patients | 19 (18%) | 7 (17%) | 1 (8%) | 11 (20%) |
| As short as possible (less than 3 months), until it is safe to proceed with surgery in light of COVID-19 situation | 57 (53%) | 14 (34%) | 9 (75%) | 34 (62%) |
| Duration of therapy depends on patient"s risk of cancer progression (ie. tumor grade, percent hormone positivity) | 25 (23%) | 16 (39%) | 2 (17%) | 7 (13%) |
| **If using endocrine therapy before surgery, do you plan to re-image the breast prior to surgery??** | | | | |
| Yes, re-image all patients | 27 (25%) | 14 (34%) | 1 (8%) | 12 (22%) |
| No | 8 (7%) | 0 (0%) | 2 (17%) | 6 (11%) |
| Case by case basis | 72 (67%) | 27 (66%) | 9 (75%) | 36 (67%) |

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# Diabetes decreases overall survival in women with breast cancer in the southern community cohort study

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Background:Factors contributing to breast cancer survival disparities in underrepresented racial and ethnic groups and low-income populations are poorly understood as few clinical trials and population based studies have included these underserved populations. The Southern Community Cohort Study (SCCS), a prospective cohort of underserved, low-income adults with high representation of Black participants, provides a unique opportunity to evaluate such disparities in cancer outcomes. A previous study utilizing SCCS data found no evidence of increased *breast cancer risk* among women with diabetes in this population. The purpose of this study was to evaluate the association of diabetes with *overall survival in women with breast cancer* in the SCCS.
Methods:The SCCS enrolled approximately 86,000 participants aged 40-79 from 12 southeastern states between 2002-2009, 86% of whom were enrolled at Community Health Centers. This analysis includes women diagnosed with incident localized breast cancers identified through annual cohort linkage with 12 state cancer registries. Demographic data including participant age at breast cancer diagnosis, self-reported history of diabetes (patient answered yes to “has a doctor ever told you that you have diabetes”), body mass index (BMI), race, household income, and insurance coverage were obtained from baseline surveys, cancer type and stage data from state cancer registries, and survival data from death registries. Survival time was defined as the number of months between initial breast cancer diagnosis and death from any cause. Descriptive characteristics including mean (standard deviation) or number (%) were used to summarize demographics. We used Pearson Chi-squared analysis to examine the association between diabetes and overall survival. Multivariable Cox proportional hazards regression was used to evaluate overall survival and diabetes, adjusting for covariates including age (continuous), race, BMI (categorical by WHO classifications), household income (binary – annual income <$25,000, annual income >=$25,000), insurance coverage, cancer subtype, and cancer stage).
Results:We identified a total of 1,347 women diagnosed with breast cancer. Of these, 1,016 were diagnosed with localized disease (stage 1-3) and comprised our analytic sample. Difference in denominators reflects missing data. The women were predominantly Black (667/1,016, 65.6%), low income (719/1,016 annual income less than $25,000, 70.8%), and insured (Private insurance 220/763, 28.8%; Medicare 331/763, 43.4%; Medicaid 178/763, 23.3%). Average age at diagnosis was 60.7 years (SD 9.1, IQR 41-88). Approximately one quarter of the patients (258/994, 26.0%) self-reported diabetes and 59.6% (605/1,016) were obese (BMI >=30). The breast cancer immunohistochemistry subtypes in this cohort of women included HR+HER2- (392/564, 69.5%), HR+,HER2+ (55/564, 9.8%), HR-,HER2+ (31/564, 5.5%), and HR-HER2- (86/564, 15.3%). Women with diabetes had lower overall survival (174/258, 67.4%) than women without diabetes (587/746, 79.8%) ($p<0.0001$). In the adjusted multivariate Cox regression model, diabetes significantly decreased overall survival in women with breast cancer, hazard ratio 1.87, 95% Confidence Interval [CI] = 1.12-3.09.
Conclusion:
In a low-income, predominantly Black population with incident localized breast cancer, decreased overall survival was observed among women diabetes compared to those without diabetes. Future studies should explore additional biological, societal, and socio-economic factors affecting survival among women with breast cancer in medically underserved minority populations.

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# Phase 1/2 study of a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), BDC-1001, as a single agent and in combination with an immune checkpoint inhibitor in patients with advanced HER2-expressing solid tumors

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**Background:** To date, no immune-based therapies beyond anti-HER2 monoclonal antibodies are approved for treating patients (pts) with HER2-driven or -expressing cancers. However, pts still develop progressive disease, and new treatment options that could achieve durable antitumor efficacy are needed. Recent studies indicate that intratumoral delivery of immunostimulatory adjuvants such as toll-like receptor (TLR) 7/8 agonists can activate tumor resident antigen-presenting cells (APCs), driving uptake, processing, and presentation of tumor neoantigens to T cells that mediate antitumor immunity. To overcome limitations associated with intratumoral delivery while leveraging superior preclinical biology, BDC-1001, a novel, systemically delivered ISAC was developed. BDC-1001 consists of an investigational biosimilar of the humanized monoclonal antibody trastuzumab that is chemically conjugated to a TLR 7/8 agonist (payload) with an intervening non-cleavable linker. BDC-1001 activates human myeloid APCs while retaining antibody-mediated effector functions such as antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP). Xenograft and syngeneic tumor resistant models indicate that trastuzumab ISACs elicit potent and durable immune-mediated antitumor efficacy including complete tumor regression in a TLR- and Fc receptor-dependent manner (Ackerman et al. Cancer Res. 2019:79 [13 Suppl]; Ackerman et al. J Immunother Cancer. 2019;7:283). Importantly, BDC-1001 did not induce interstitial lung disease, cytokine release syndrome, or thrombocytopenia in non-human primate studies. A four-part phase 1/2, first-in-human study has been initiated that evaluates BDC-1001 with or without (+/-) an immune checkpoint inhibitor targeting PD-1 in pts with HER2-expressing or HER2-amplified advanced/metastatic solid tumors.
**Study Description:** This phase 1/2 dose-escalation and dose-expansion study is enrolling up to 390 pts with advanced solid tumors that are HER2-expressing (IHC2+ or 3+ protein irrespective of gene amplification) or HER2-amplified (by in situ hybridization or next-generation sequencing) and ineligible for approved anti-HER2 treatments. The primary objectives of the dose-escalation phase are to define safety and tolerability and to determine the recommended phase 2 dose of BDC-1001 as monotherapy (Part 1) and in combination with an immune checkpoint inhibitor (Part 2). Primary endpoints of Parts 1 and 2 include incidence of 1) adverse events and severe adverse events graded according to NCI CTCAE v5.0; 2) dose-limiting toxicities within a 3+3 design; and 3) potential immune-related toxicities. BDC-1001 is administered IV over 60 min q3w at increasing doses. Once safety data are available for BDC-1001, initiation of the immune checkpoint inhibitor combination is planned. The dose-expansion phase 2 portion of the trial will evaluate preliminary antitumor activity of BDC-1001 alone (Part 3) and in combination with an immune checkpoint inhibitor (Part 4) using RECIST v1.1 and iRECIST. The primary endpoint of this dose-expansion phase is overall response rate, with secondary endpoints of duration of response, disease control rate, and progression-free survival. Exploratory objectives will evaluate pharmacokinetic parameters and pharmacodynamic biomarkers associated with drug exposure. These exploratory studies will help elucidate the mechanism of action and seek to identify biomarkers to improve selection of pts most likely to benefit from treatment with BDC-1001 +/- immune checkpoint inhibitor. This global study is currently recruiting pts. For further information, visit ClinicalTrials.gov (NCT04278144).

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# Identification of pathogenic RET alterations in cell-free DNA (cfDNA) from patients with metastatic breast cancer

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**Background:** *RET* is an important proto-oncogene involved in the development of various cancers for which we have FDA approved therapies. *RET* alterations are a known mechanism of resistance against breast cancer systemic therapies and higher RET expression has been demonstrated in breast cancer brain metastases compared to their primary tumors. While the genomic characterization of *RET* alterations has occurred from bulk breast tumors, the frequency and type of *RET* alterations in metastatic breast cancer (MBC) have not been fully characterized from cfDNA. The purpose of this study was to identify the incidence of *RET* genomic alterations occurring in cfDNA from patients with MBC and elucidate which *RET* alterations may increase RET kinase activity or may function as mechanisms of resistance against the FDA approved RET inhibitor, selpercatinib.
**Methods:** We queried 16,053 reports from Guardant Health between June 2015 - October 2019 to identify the incidence of *RET* alterations detected in cfDNA from MBC. We classified each alteration type into the following categories: fusions, single nucleotide variants (SNVs), or indels. Focus was placed on characterizing *RET* SNVs. Amino acid changes occurring at conserved regions across multiple species were identified. We compared known activating mutations in *EGFR* and *ERBB2* with homologous regions in *RET*. *In silico* modeling with PyRx was used to dock selpercatinib onto the *RET* kinase (PDB 6NJA). Three-dimensional *in silico* analyses with ChimeraX was utilized to further determine which alterations may increase RET kinase activity or may induce resistance against selpercatinib.
**Results:** Nonsynonymous *RET* alterations from the Guardant Health breast cancer database were found in 162 samples from a cohort of 16,053 patients indicating an overall incidence of 1.0%. Alterations included: 3 (1.9%) *RET-CCDC6* fusions, 2 (1.2%) *RET-KIF5B* fusions, 6 (3.7%) indels, and 151 (93.2%) SNVs. Of the 151 samples with SNVs, we identified 37 (23%) and 63 (38.9%) point mutations occurring in the transmembrane/juxtamembrane and kinase domains, respectively, and 77 occurred at highly conserved regions across species. The most frequent hotspot mutations occurring in 4 or more unique breast cancers included H594P, 6 (4.0%); S696L, 4 (2.6%); C634Y/G, 5 (3.3%); R813W/Q, 4 (2.6%); and M918T, 8 (5.3%). We aligned *RET* with homologous kinases and found 8 (5.3%) *RET* mutations (R721Q, V804L, M868I, R873Q, G894S) and (A641T, S891L, D925H) that corresponded to known activating mutations in *EGFR* (E709A/K, T790M, R831H, R836C, G857V) and *ERBB2* (V659E, T862A/S, R896C), respectively. Three-dimensional analyses indicate that *RET* alterations occurring within the hinge (E805Q), HRD (H872R, R873Q), and DFG (D892Y, G894S) regions, and regulatory spine (D933N) of the *RET* kinase are postulated to induce resistance against selpercatinib.
**Conclusions:** We found that a modest incidence of *RET* genomic alterations occur in cfDNA from patients with MBC. Novel somatic alterations in *RET* were identified from Guardant Health that were not detected in the public domain. A portion of *RET* SNVs occurred at highly conserved regions across species or at known homologous kinase activating mutations suggesting these specific *RET* mutations may increase RET kinase activity and might be actionable therapeutic targets in breast cancers harboring these mutations. Three dimensional analyses of the RET protein tyrosine kinase further illustrate which specific alterations may increase RET kinase activity or induce resistance against selpercatinib.

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Relationship between body mass index and tumor subtype by menopausal status: An analysis in women with lobular carcinoma of the breast

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**Background:** Invasive lobular carcinoma (ILC) is the second most common type of breast cancer and is primarily estrogen receptor (ER)-positive. Compared to invasive ductal carcinoma, ILC is more strongly associated with risk factors that modulate sex steroid hormones, including obesity and use of hormone replacement therapy. Studies also suggest that body mass index (BMI) and metabolic syndrome may impact the molecular characteristics of ILC. We evaluated the relationship between BMI, metabolic syndrome, and tumor characteristics by menopausal status in a single institution cohort of women with newly diagnosed ILC.
**Methods:** We retrospectively evaluated ILC cases from an institutional database of patients treated between 1996 and 2020. We excluded cases with mixed ILC/IDC histology, and those with triple negative or human epidermal growth factor-2 overexpressing disease. BMI was calculated as (weight kg)/(height m)^2 and was evaluated continuously and categorically with 20-24.9 as normal weight, 25-30 as overweight, and >30 as obese. Metabolic syndrome was defined as having any 3 of the following 5 factors: obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, or diabetes mellitus. Oncotype Dx Recurrence Scores (RS) were recorded in the subset for whom scores had been obtained clinically. Data were analyzed in Stata 14.2.
**Results:** Of the 481 ILC cases studied, 147 (30.5%) were pre-menopausal at diagnosis, while 334 (69.5%) were post-menopausal, with mean ages of 48 and 64.9 years (p<0.0001). Most tumors (79.5%) were both ER-positive and progesterone receptor (PR)-positive. Post-menopausal women had significantly more ER-positive/PR-negative ILC than premenopausal women (25.3% vs 9.9%, p<0.001), were more likely to have a BMI in the overweight/obese category (53.6% vs 40.1%, p=0.016), and were more likely to have metabolic syndrome (21.9% vs 6.8%, p<0.001). Of the 143 cases with an Oncotype RS, 69.9% were intermediate, 21.7% were low, and 8.4% were high risk. Post-menopausal women had significantly higher RS than premenopausal women
when RS was treated as a continuous variable (16.9 vs 13.8, p=0.007). Among postmenopausal women, overweight/obesity status was associated with lower RS while those with normal weight had a greater proportion of high RS tumors (p=0.027). There was no association between BMI and RS in the pre-menopausal population. Similarly, there was no association between metabolic syndrome and tumor subtype in either group.
**Conclusions:** In this cohort of women with ER-positive pure ILC**,** we found that post-menopausal ILC had higher rates of overweight/obesity, metabolic syndrome, and numerically higher RS than pre-menopausal ILC. However, within the post-menopausal group, higher BMI was anti-correlated with RS whereas BMI had no impact on pre-menopausal ILC RS. Since obesity is associated with worse outcomes for breast cancer, these findings are unexpected and raise the possibility that the hormonal pathogenesis and estrogenic drive behind ILC differs in pre- vs post-menopausal women, consistent with their different PR positivity rates, possibly due to the more local production of estrogen from higher breast adiposity in post-menopausal women relative to the greater systemic ovarian production of estrogen in pre-menopausal women. These findings have potential implications for both ILC prevention and adjuvant therapy strategies.

| ***Characteristics*** | ***Premenopausal (n=147)*** | ***Postmenopausal (n=334)*** | ***P value*** |
|---|---|---|---|
| Age, mean (SD) | 48 (5.5) | 64.9 (9.7) | <0.0001 |
| Body mass index | | | 0.016 |
| BMI<25, n (%) | 88 (59.9%) | 155 (46.4%) | |
| BMI 25-30, n (%) | 39 (26.5%) | 105 (31.4%) | |
| BMI>30, n (%) | 20 (13.6%) | 74 (22.2%) | |
| Metabolic syndrome present, n (%) | 10 (6.8%) | 73 (21.9%) | <0.001 |
| ILC Stage | | | NS |
| I, n (%) | 86 (58.9%) | 224 (68.3%) | |
| II, n (%) | 40 (27.4%) | 61 (18.6%) | |
| III, n (%) | 20 (13.7%) | 43 (13.1%) | |
| ILC Grade | | | NS |
| 1, n (%) | 49 (34.3%) | 93 (28.3%) | |
| 2, n (%) | 88 (61.5%) | 222 (67.5%) | |
| 3, n (%) | 6 (4.2%) | 14 (4.2%) | |
| Hormone Receptor Status | | | <0.001 |
| ER+/PR+ | 128 (90.1%) | 236 (74.7%) | |
| ER+/PR- | 14 (9.9%) | 80 (25.3%) | |
| 21-gene Recurrence Score in women with BMI<25 | | | 0.020 |
| Low, n (%) | 10 (25%) | 2 (6%) | |
| Intermediate, n (%) | 28 (70%) | 24 (72.7%) | |
| High, n (%) | 2 (5%) | 7 (21.3%) | |
| 21-gene Recurrence Score in women with BMI>25 | | | NS |
| Low, n (%) | 6 (28.5%) | 11 (26.8%) | |
| Intermediate, n (%) | 15 (71.5%) | 27 (65.9%) | |
| High, n (%) | 0 (0%) | 3 (7.3%) | |

SD, standard deviation, NS, not significant.

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# Estrogen-based hormone replacement therapy [E-HRT] reduces all-cause, breast cancer, and Alzheimer's dementia mortality

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**OBJECTIVES.** To evaluate the long-term population-level impact of E-HRT on cause-specific and all-cause mortality in postmenopausal women in the USA, using the results of the 2017 Women's Health Initiative HRT Trial 2 update.[1] Of particular interest was the significantly reduced Breast Cancer [BrCa] mortality rates [RR=0.55, 95% C.I.=0.33-0.92].[1]

**METHODOLOGY.** In the WHI HRT Trial 2, women were randomized to receive estrogen (**E**) or placebo (**P**).[1] For our analyses, the Annualized mortality rates (AR) were extracted for women aged 50-59, 60-69, 70-79, for breast cancer, Alzheimer's dementia, and all-cause mortality. The Median follow-up was 18 years. The **A**nnualized Mortality **R**ate **D**ifference (**ARD**) between the two groups was calculated as a difference of the AR between the **P** vs. **E** (*AR in P - [minus] AR in E*), expressed per 100,000 person-years. Subsequently, the **N**umber of **A**voided **D**eaths per year (**NAD/year**) was calculated using the number of women in each age group from the 2010 US census data.

**RESULTS.** The annualized number of deaths avoided by the use of E-HRT in the US population was estimated as follows: BrCa, 9,292; Alzheimer's dementia: 18,966; and all cause-mortality: 50,008 (*Table)*.

| **Ages** | **Age 50 – 59**(N=21,506,008) | | **Age 60 – 69**(N=15,323,140) | | **Age 70 – 79**(N=9,169,601) | | **ALL ages**(N=45,998,749) |
|---|---|---|---|---|---|---|---|
| | ARD / 100,000 | NAD / Year | ARD / 100,000 | NAD / Year | ARD / 100,000 | NAD / Year | NAD / Year |
| **Breast Cancer** | 20 | 4,301 | 23 | 3,524 | 16 | 1,467 | 9,292 |
| **Alzheimer's Dementia** | 0 | 0 | 40 | 6,129 | 140 | 12,837 | 18,966 |
| **All-Cause Mortality** | 150 | 32,259 | 50 | 7,662 | 110 | 10,087 | 50,008 |

**CONCLUSIONS.** These data show a major beneficial impact of E-HRT, with over 50,000 deaths/year prevented in the USA alone. While these gains, sustained throughout the follow-up, represent undoubtedly major multi-organ metabolic benefits of estrogen, the most striking and unexpected findings involve BrCa, with over 9,000 BrCa deaths potentially avoided each year, just in the USA alone.

**RECOMMENDATION.** Adoption and implementation of E-based HRT to the current HRT medical guidelines, to extend the health benefits to millions of women, and to prevent thousands of deaths each year in the USA alone.

**REFERENCE.**1.Manson JE et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. J Am Med Assoc 2017; 318(10): 927-938.

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# Functional importance of long-tail mutations in breast cancer

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**Background:** Cancer driver genes are characterized by frequently recurrent mutations, substantial functional impact on in vitro and in vivo cancer growth, and several of the represent clinically important therapeutic targets. Whole exome and genome sequencing studies identified mutations in at least one cancer driver gene in about 70% breast cancers. These studies also revealed that each cancer also harbors hundreds to thousands of additional non-recurrent mutations which follow a long-tail distribution. Historically, these long tail “passenger” mutations are considered random due to genomic instability and not expected to contribute to the biology of the disease. We hypothesize that “long-tail” mutations could also have functional importance and contribute to the unique biology of a given cancer. The goal of the current analysis was to identify the long-tail mutations in breast cancer, and estimate their overall functional importance. **Methods**: We obtained somatic mutations from the breast cancer TCGA cohort (N=1076) and calculated the somatic mutation frequency for each gene. The dNdScv algorithm was used to estimate significantly mutated genes. A gene was considered to be in the long tail of mutations if its somatic mutation frequency was 1-3%, and the dNdScv p-value was < 0.05. We performed pathway enrichment analysis with 21 cancer pathways assembled by NanoString Technologies (Seattle, WA) for the long-tail genes using Fisher’s exact test and obtained gene dependency scores (DS) from The Cancer Dependency Map (DepMap) project which performed genome-wide pooled loss of function screening for 17,634 human genes using and CRISPR-Cas9-mediated (CRISPR) gene editing to estimate tumor cell viability after gene silencing in 563 cell lines. The more negative (i.e. lower) the dependency score the more important the gene is to sustain cell viability. We compared the DS of the long tail genes with known cancer driver genes and other human genes excluding known breast cancer driver genes. We also compared the dependency score of genes with long-tail mutations between breast cancer and other cancer types using the Mann-Whitney U test. We estimated the trend of average dependency score across genesets using the Jonckheere Terpstra test and using Kendall's tau (τ) coefficient to show the increasing (positive value) or decreasing (negative value) trend. **Results**: Seventy percent of breast cancers (n=763) carried long-tail mutations in 115 different genes. The average number of long tail mutations was N=3 (range from 1 to 118). Genes with long-tail mutations were enriched in epithelial-mesenchymal transition, extracellular matrix, angiogenesis, adaptive immunity, MAPK, innate immunity, inflammation, and RAS pathways (FDR<0.035). Genes with long-tail mutations showed the lowest average dependency score in breast cancer cell lines (n=28) with median DS= -0.080, the range of median DS was -0.079 to -0.056 in other cancer cell lines (P=0.70). In the breast cancer cell lines, known breast cancer driver genes (N=11) had the lowest DS (median=-0.352), followed by the long-tail genes (median=-0.0801), followed by all other human genes (median DS=-0.0528). An increasing trend (τ=1.78, P=0.024) of dependency score was observed across known cancer driver genes, long-tail genes, and other human genes which indicate that long-tail genes are important in cancer cell viability. **Conclusions:** Long-tail mutations are seen in most breast cancers in unique combinations. They primarily affect genes involved in key cancer pathways. Long tail genes have negative dependency scores across 563 cancer cell lines indicating functional importance in sustaining cancer viability. These results suggest that long-tail genes with mutations could contribute to the biology of breast cancers and might explain the broad range of differences in clinical behavior or morphologically similar cancers.

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Genomic profiling and clinical outcomes with first-line atezolizumab and *nab*-paclitaxel in triple-negative breast cancer: An exploratory analysis from the phase 3 IMpassion130 trial

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**Background:** The clinical implications of genomic alterations in metastatic triple-negative breast cancer (mTNBC) have not been clearly addressed. In IMpassion130, atezolizumab (A) + *nab*-paclitaxel (nP) showed improved progression-free survival (PFS) and clinically meaningful overall survival (OS) benefit vs placebo (P) + nP in PD-L1+ mTNBC (Schmid, *NEJM* 2018). The goal of this exploratory study was to evaluate the prevalence of genomic alterations and their relationship with PD-L1 status and to determine whether a prognostic or predictive role for these factors exists for A + nP in a randomized dataset. **Methods:** Primary or metastatic tumor samples from patients in the IMpassion130 biomarker-evaluable population (BEP) were centrally evaluated for short variants (SV), copy number alteration (CNA) and rearrangements by using a targeted next-generation sequencing (NGS) panel (FoundationOne). PD-L1 status was evaluated using the VENTANA SP142 assay, with PD-L1 positivity defined by PD-L1-expressing immune cells on ≥1% of tumor area. Prognostic effects of genomic alterations were evaluated in the pooled population from both treatment arms. PFS and OS (co-primary endpoints) were analyzed by Cox proportional hazards models. ClinicalTrials.gov identifier: NCT02425891. **Results:** The BEP comprised 614 patients (68% of intent-to-treat population), 605 of whom received treatment. The most common pathogenic alterations were found in the following genes: *TP53* (SV, 85%), *MYC* (CNA, 21%), *PIK3CA* (SV, 18%), *PTEN* (SV/CNA, 18%), *RB1* (SV, 7%) and *BRCA1* (SV, 9%). Primary tumors (n = 419), compared with metastatic tumors (n = 195), were more likely to bear alterations in *BRCA1* (11.9% vs 5.6%) and less likely to have *PIK3R1* alterations (4.8% vs 9.2%). *TP53* loss-of-function mutations were associated with PD-L1+ status, whereas amplifications in *VEGFA* and *CCND3* genes were significantly less associated; none of these alterations were linked with clinical outcomes favoring A + nP. Loss of *RB1* (frequency 5%) was linked with reduced PFS and OS prognosis independent of treatment (hazard ratio [HR], 2.09 [95% CI: 1.42, 3.07] and HR, 1.98 [1.26, 3.11]), respectively), and CNA in *CDKN2A* (12%) and *CDKN2B* (11%) were associated with improved PFS and OS clinical activity in the A + nP arm vs the P + nP arm (HR PFS, 0.43-0.44 and HR OS, 0.47, respectively). Three of 584 microsatellite-evaluable samples (0.5%) had MSI-H status, which was not associated with PD-L1 status; all 3 MSI-H patients were from the P + nP arm. A total of 220 of 514 evaluable samples (42.8%) had *PIK3CA/AKT1/PTEN*-altered status, which was not significantly associated with PD-L1 status or A + nP clinical outcome. **Conclusions:** In this exploratory analysis using a targeted NGS panel, we show that tumors from patients with previously untreated mTNBC had similar genomic profiles at baseline as those published for early TNBC tumors. The few alterations that were linked to PD-L1 status were not linked to clinical outcome. CNA in cell cycle genes (e.g., *RB1*) had potential prognostic value, whereas *CDKN2A* and *CDKN2B* were potentially predictive of A + nP clinical benefit favoring A + nP. These data are hypothesis generating and require validation in an independent data set.

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# Ribociclib + letrozole in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer (ABC): Expanded safety analysis of the phase IIIb CompLEEment-1 trial

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**Background:** CompLEEment-1 (NCT02941926) is an ongoing Phase IIIb trial of ribociclib (RIB) in combination with letrozole (LET) in the first-line setting for patients (pts) with HR+, HER2- ABC, reflecting a real-world clinical setting by including a more diverse pt population than those included in the pivotal MONALEESA trials. Here we report further analyses of the primary endpoint of safety from the completed Core Phase of the trial. **Methods:** CompLEEment-1 included women of any menopausal status and men with HR+, HER2- ABC treated with ≤1 line of prior chemotherapy and no prior hormonal therapy for advanced disease. Pts received RIB (600 mg QD, 3 weeks on/1 week off) in combination with LET (2.5 mg QD, continuous). Premenopausal women and men received a luteinizing hormone-releasing hormone agonist (3.6 mg goserelin or 7.5 mg leuprolide, Q28D). The primary endpoints were safety and tolerability. Updated analyses included dose reduction/interruption or treatment discontinuation due to adverse events (AEs), clinical impact of AEs of special interest (AESI), and exposure-adjusted incidence/occurrence rates (IRs) for AESI. **Results:** At data cutoff (November 8, 2019) 3,246 pts had been evaluated (median follow-up of 25.4 months), and median duration of exposure to RIB was 17.5 months; 1,301 (40.1%) pts completed Core Phase treatment, 415 of whom moved to the Extension Phase. Overall, 1,945 (59.9%) pts permanently discontinued treatment, mostly due to progressive disease (34.2%) and AEs (15.5%). Treatment-related AEs were reported in 3,091 (95.2%) pts, leading to dose modification in 2,235 (68.9%) pts. Dose modification occurred most often in pts with grade ≥3 neutropenia (dose interruption, 1,671 [51.5%] pts; dose reduction, 480 [14.8%] pts); treatment discontinuation occurred most frequently in pts with grade ≥3 increased alanine aminotransferase (ALT; 116 [3.6%] pts) or aspartate aminotransferase (AST; 68 [2.1%] pts). Grade ≥3 neutropenia occurred in 1,856 (57.2%) pts, with the median time to first occurrence of 4.1 weeks and median duration of first occurrence of 1.1 weeks. As measured by laboratory values, grade ≥2 increased ALT and AST occurred in 453 (14.0%) and 380 (11.7%) pts, respectively. Grade ≥2 QTcF prolongation was infrequent, occurring in 101 (3.1%) pts, leading 8 (0.2%) pts to discontinue from treatment. AESI rarely led to hospitalization (0 to 0.3%) and none were fatal. Exposure-adjusted IRs for AESI per 100 patient-years of exposure show that with increasing RIB exposure, the IR and the event rates for AESI decreased by a factor of ×2 to ×8 from 0-1 years compared with 1-2 years (Table 1). **Conclusions:** AEs associated with RIB + LET combination therapy were manageable, consistent with previous Phase III trials of RIB + LET - and adjusted IRs for AESI notably decreased from Year 1 to Year 2 of treatment. These data further support the use of RIB + LET for first-line treatment of HR+, HER2- ABC in both men and women of any menopausal status and in a broader and more diverse patient population.

**Table 1. Exposure-adjusted IRs for selected AESI per 100 patient-years of exposure**

| | **0-1 years** | | **1-2 years** | |
|---|---|---|---|---|
| **AESI** | **IR per 100 PTY[a]** | **Events per 100 PTY[b]** | **IR per 100 PTY[a]** | **Events per 100 PTY[b]** |
| **Neutropenia** | 276.76 | 410.22 | 92.43 | 200.83 |
| **ALT increased** | 20.37 | 41.66 | 3.79 | 6.32 |
| **AST increased** | 17.51 | 33.27 | 2.94 | 4.61 |
| **QTcF prolongation** | 8.44 | 10.22 | 1.08 | 1.26 |

[a] IR per 100 PTY: n/100 PTY, number of patients with an event divided by the corresponding sum of the exposure duration for patients, where duration of exposure in patient treatment-years (PTY) is counted up to the first qualifying event (or duration of exposure in time interval for patients without an event).

[b] Events per 100 PTY: n/100 PTY, number of events divided by the corresponding sum of the exposure duration, where duration of exposure in patient treatment-years (PTY) is duration of exposure in time interval.

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A tiered algorithm using mid-therapy ultrasound (US) response assessment and a novel gene expression signature (GES) improves the prediction of pathologic complete response (pCR) to neoadjuvant therapy (NAT) in triple-negative breast cancer (TNBC): Results from the ARTEMIS trial (NCT02276443)

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**Background**: The heterogeneity of TNBC results in mixed responses to NAST: 30-60% of patients (pts) have a pCR to standard chemotherapy with an excellent prognosis. Several methods have been used to predict pCR, most yielding a positive predictive value (PPV) of no greater that 70%. To improve prediction of pCR to NAT, we hypothesized that we can integrate mid-treatment US with molecular profiling to generate a GES, thus reducing the need for escalation of therapy (example: immunotherapy) in select patients. We used data from ARTEMIS, a prospective trial that uses molecular profiling and imaging assessment of TNBC response during therapy to personalize NAT. **Methods**: Patients begin a planned 4 cycles of AC. Those with substantial volumetric reduction (>=70%) of the primary tumor by US (SVR-US) after AC receive standard taxane-based therapy as the second phase of NAT, while those with resistant disease (including disease progression during AC) are offered therapeutic trials based upon molecular profiling of the pre-treatment biopsy. Pathologic response is assessed at surgical resection. **Results**: 167 patients had RNAseq, US and pCR data. Overall pCR was 36%. TNBCs with SVR-US after AC (n=101) had significantly higher pCR (55 vs 6%, p<0.001). SVR-US had a PPV of 0.55 and NPV of 0.94 for prediction of pCR. Given the strong NPV, we focused on improving the PPV. In the 101 TNBCs that had SVR-US after AC, we performed differential gene expression comparing those with pCR vs residual disease using 74 TNBCs as a training set and 29 as a validation/test set. Differentially expressed genes (N=500-1000) served as a feature set for a series of machine learning models, including GBM (gradient boosting machines), GLM (generalized linear models), SVM (support vector machines) and CNN (convolutional neural networks) (N train=74). CNN and GLM had similar accuracy, NPV and PPV on the validation set (N=29), therefore GLM was selected as the final model because of ease of interpretability. By combining with SVR-US, we were able to increase the PPV of the tiered model from 0.55 (SVR-US after AC) to 0.89 (SVR-US after AC+GES/GLM) (validation set). Our analysis has validated the predictive value of the GES in patients with SVR-US to 4 cycles of AC, but the entire algorithm (including TNBCs without SVR-US) requires a second validation cohort. However, if the PPV and NPV remain consistent, the impact of this strategy to determine which TNBCs require therapy escalation beyond ACàT is estimated in Table 1. **Conclusions**: We have created an integrative, tiered model combining two complementary modalities (mid-treatment US assessment of response and GES) that has substantially improved the PPV in assessing pCR to NAST using the ARTEMIS strategy.

| Table 1: PPV and NPV used to estimate the impact in escalation of therapy* | | | |
|---|---|---|---|
| Correct decision: 88% of pts | Incorrect decision: 12% of pts | | |
| Predicted pCR=pCR (True positives) Therapy correctly not escalated | Predicted non-pCR=non-pCR (True negatives) Therapy correctly escalated | Under treatment | Over treatment |
| Predicted pCR does not=pCR (False positives) Therapy incorrectly not escalated | Predicted non-pCR =pCR (False negatives) Therapy incorrectly escalated | | |
| 34% | 54% | 8% | 4% |
| *example of escalated regimen= taxane + novel agent on clinical trial or taxane + immunotherapy (if FDA approved) | | | |

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# First efficacy results of a 2-stage Simon's design randomised phase 2 of darolutamide or capecitabine in patients with triple-negative, androgen receptor positive advanced breast cancer (UCBG06-3)

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**Background**: Triple negative breast cancer (TNBC) is an heterogeneous disease and encompasses at least 4 subtypes. One of these expresses the androgen receptor (AR). Several prospective trials demonstrated antitumour efficacy with anti-androgen treatment in patients with advanced breast cancer. Darolutamide is an androgen-receptor antagonist with a potent anti-tumour efficacy in metastatic prostate cancer with a favorable safety profile. We conducted a randomized non-comparative phase II trial to study the efficacy and tolerability of darolutamide and capecitabine in AR-positive TNBC (NCT03383679).
**Material and methods**: Patients (Pts) with a metastatic, centrally reviewed, AR-positive (≥ 10% by immunohistochemistry) and TNBC who have received a maximum of one line of chemotherapy for advanced disease were eligible. They were randomised in a 2:1 ratio to receive darolutamide (D arm) 600 mg twice daily or capecitabine (C arm) at 1000 mg/m² twice daily 2 weeks on and 1-week off, until progression or unacceptable toxicity. The primary endpoint was clinical benefit rate (CBR) defined as the proportion of pts presenting a complete response (CR), partial response (PR), or stable disease (SD) at 16 weeks. Main secondary endpoints included objective response rate, overall survival, progression-free survival and safety. An interim statistical analysis was planned when 19 assessable pts will be available in the D arm. According to an optimal 2-stage Simon's design,if <5 patients
experienced a CBR the trial should be stopped for futility; if 5 or more experienced a CBR the trial should continue up to a total of 54 patients in the D arm.
**Results**: Out of 133 pts screened and centrally analyzed, from 37 centres, 54% (72/133) were AR-positive. 45 pts were randomized (29 in D arm and 16 in C arm) from April 2018 to December 2019. In arm D, median age was 60 years (range 47-88). and 13.8 % received a first line of chemotherapy for metastatic disease. A total of 19 pts were eligible and assessable for the primary endpoint in D arm. 5 CBR were confirmed at 16 weeks (26.3%; 95% CI: 9.2%-51.2 %) including 1 confirmed PR and 4 SD. In arm D, fatigue (23.8%), ASAT increased (23.8%), and blood alkaline phosphatase increased (23.8%) were the most common drug-related adverse events; the majority of them being grade 1 or 2. 6 pts presented with drug-related serious adverse events: one in D arm and 5 in C arm.
**Conclusions:** According to the planned interim analysis, the efficacy objective is met (5 CBR) in D arm. Moreover, darolutamide is well tolerated. Thus, patients are now recruited in the second stage.
**Keywords:** Androgen receptor,triple-negative breast cancer, darolutamide, advanced breast cancer

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# Updated data from SERENA-1: A Phase 1 dose escalation and expansion study of the next generation oral SERD AZD9833 as a monotherapy and in combination with palbociclib, in women with ER-positive, HER2-negative advanced breast cancer

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**Background:** AZD9833 is an oral selective estrogen receptor (ER) antagonist and degrader (SERD) in Phase 2 clinical development for the treatment of ER+ HER2- breast cancer. Here we report data from Parts C and D of the ongoing Phase 1 study (SERENA-1) examining AZD9833 in combination with palbociclib, together with updated data from Parts A and B examining AZD9833 monotherapy. **Methods:** SERENA-1 (NCT03616587) is an ongoing open-label Phase 1 study of AZD9833 in pre- and post-menopausal women with ER+, HER2- advanced breast cancer who have previously received ≥1 endocrine therapy and ≤2 prior chemotherapies. Prior treatment with fulvestrant and/or CDK4/6 inhibitors was permitted. The primary objective is to determine the safety and tolerability of once daily (QD) AZD9833, with dose-limiting toxicities (DLTs) in the first 28 days defining the maximum tolerated dose. Secondary objectives include anti-tumor response (including circulating tumor [ct] DNA response) and pharmacokinetics. Parts A (escalation) and B (expansion) assess AZD9833 as a monotherapy, and Parts C (escalation) and D (expansion) assess AZD9833 in combination with palbociclib. **Results:** At a data cut-off of March 24 2020, 17 patients had received either 150 mg or 300 mg AZD9833 in combination with palbociclib, given according to its product labeling. Eighty patients had received AZD9833 monotherapy at doses of 25, 75, 150, 300, and 450 mg QD. In patients treated with AZD9833 and palbociclib, treatment-related adverse events (AEs; experienced by ≥10% of patients) included visual disturbances*, bradycardia*, asthenia, anemia, QTcF prolongation, nausea, neutropenia, decreased white blood cell count, and vomiting (*combined terms). All instances of AZD9833-related bradycardia were Grade 1. One DLT was observed in the 150 mg cohort: CTCAE Grade 2 visual disturbances, which began on Cycle 1 Day 8 and resolved by Cycle 1 Day 9 following dose interruption. The patient restarted treatment on Cycle 1 Day 15 at 75 mg and continued this dose until data cut-off. No causally related AEs led to discontinuation of AZD9833. The tolerability of AZD9833 with palbociclib was consistent with the observed tolerability profile of AZD9833 monotherapy, and the known tolerability profile of palbociclib. Pharmacokinetic analysis showed similar AZD9833 exposure for monotherapy and palbociclib combination therapy. Similarly, palbociclib exposure was comparable with simulations using a published population pharmacokinetic model. In Part A, *ESR1* hotspot mutations were detected in ctDNA at baseline in 26/56 (46%) patients; 13/26 (50%) of these patients achieved a partial response or stable disease at 24 weeks, including 5/10 (50%) with a Y537S *ESR1* mutation. Further, in patients with *ESR1* mutations and samples available for longitudinal ctDNA analysis, 17/20 (85%) exhibited a reduction or loss of mutant *ESR1* on treatment with AZD9833. Efficacy data to be presented include objective response rate and clinical benefit rate at 24 weeks. Of note, unconfirmed partial responses have been observed in Part C after the data cut-off for this abstract. **Conclusions:** AZD9833 continues to show an encouraging efficacy and dose-dependent safety profile as a monotherapy or in combination with palbociclib. A Phase 2 study comparing the efficacy and safety of three doses of AZD9833 versus fulvestrant (NCT04214288), and a Phase 2 pre-surgical ‘window of opportunity’ study (EUDRA-CT; 2019-003706-2) are ongoing.

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# Neoadjuvant chemotherapy selectively alters spatially-defined immune landscapes in clinical luminal B HR+/HER2- breast cancers: Analysis of the breast cancer genome guided therapy study (BEAUTY)

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Introduction: The immune microenvironment of high-risk HR+ breast cancer (BC) is poorly understood. BEAUTY is a prospective neoadjuvant chemotherapy (NAC) study of stage I-III BC patients treated with neoadjuvant weekly taxane followed by anthracycline-based chemotherapy. Among clinical luminal B BC (St. Gallen criteria) from BEAUTY, we used high-plex digital spatial profiling (DSP) to characterize the intra-epithelial tumor and stromal immune landscapes to 1) assess the impact of NAC on these landscapes and 2) identify immune biomarkers predictive of response to NAC. Methods: The tissue set included FFPE sections of resected tumors from 35 patients (median 51y; range: 21-71y) with clinically-defined luminal B BC (ER > 10%/grade 2/Ki67 ≥ 15% or ER > 10%/grade 3), and 16 paired pre-NAC biopsies. Nanostring GeoMX DSP was used to quantitate 58 immune and BC biomarker proteins in intra-epithelial, cytokeratin-positive tumor segments and adjacent stromal (cytokeratin-negative/SYTO13 (nuclear stain)-positive) segments. Data were normalized using the geometric mean of two negative controls (RbIgG and MsIgG1). A general linear model with negative binomial identified differentially-expressed (DE) proteins in pre/post-NAC tumors. Based on DE protein data and biologic function, a targeted protein subset (N=19) was evaluated in pre-NAC biopsies for associations between protein abundance and residual cancer burden (RCB) class (0-II vs. III) (Wilcoxon-rank sum test: p-value < 0.025 considered significant) or RCB ‘breast only’ index (Spearman correlation). Results: Comparing tumor segments in pre-NAC specimens, intra-epithelial segments were predictably enriched in cytokeratin, ER, PR and Ki-67, but also CD127 and NY-ESO-1; whereas stromal segments were enriched in proteins associated with T cell subsets (e.g. CD3, CD4, CD8), macrophages (CD68 and CD163), antigen presentation/dendritic cells (CD11c, HLA-DR) and immune checkpoint proteins (PD-L1, PD-L2, B7-H3, TIM-3, VISTA) among others. While NAC did not alter the spatial distribution of proteins (intra-epithelial vs. stromal segments), it markedly attenuated the immune landscape, with decreased abundance of functionally-diverse immune proteins (e.g. CD45, CD3, CD4, CD127, granzyme B, CTLA4; STING, B7-H3, CD11c, and CD68, log2FC: 0.27-1.52 p < 0.05), including low abundance proteins PD-1, PD-L1, PD-L2, CD20, and OX40L (log 2FC: 0.15-1.16, p < 0.05). Both PR and Ki-67 decreased in post-NAC tumors whereas ER was not significantly altered (p < 0.05). CD8, CD14, CD163, HLA-DR, IDO-1 and TIM-3 were not significantly altered by NAC. In the pre-NAC biopsies (which had subsequent residual tumor burdens of RCB class 0 or I (n=1 each), II (n=6), and III (n=8), and median RCB ‘breast only’ index of 3.39 (range: 0.00-38.02), 19 proteins were used for RCB analysis (CD3, CD4, CD8, CD14, CD34, CD44, CD45, CD68, CD127, CD163, CTLA4, granzyme B, STING, B7-H3, fibronectin, Ki-67, HLA-DR, SMA and TIM3). Among them, stromal CD127 was significantly higher in RCB class III than RCB class 0-II (p=0.021) and RCB ‘breast only’ index was positively correlated with intra-epithelial granzyme B (rho = 0.61; p=0.012), and negatively correlated with intra-epithelial Ki-67 (rho= -0.71; p=0.0022). Conclusion: In this series of clinical luminal B BC, NAC markedly attenuated the tumoral immune landscapes with a small set of “NAC-resistant” immune proteins. Among a targeted set, stromal CD127 was significantly higher in RCB III, and RCB breast-only index was positively correlated with intra-epithelial granzyme B. These data provide insight into the impact of NAC on HR+ BC, and identify potential immune biomarkers to predict response to neoadjuvant chemotherapy.

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# Universal genetic testing in breast cancer patients: A multi-center prospective study

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**Background:** Hereditary factors play a key role in the risk of developing breast cancers. Identification of a germline predisposition can have important implications for treatment decisions, risk-reducing interventions, cancer screening, and testing for family members. **Aim:** To determine the prevalence of pathogenic or likely pathogenic germline mutations (P/LP) using a “universal” testing approach and uptake of no-cost cascade family testing in patients with breast cancer. **Methods:** We undertook a prospective multi-site study of germline genetic alterations among breast cancer patients receiving care at Mayo Clinic cancer centers in Rochester, MN; Eau Claire, WI; Jacksonville, FL and Phoenix, AZ between April 1, 2018 and March 31, 2020. Patients with a new or active breast cancer diagnosis (all stages) irrespective of cancer family history were tested with a >80-gene next generation sequencing panel.**Results:** Of 390 patients, the median age was 58 years (SD 12.3), 1% were male, 85% were white and 28% had advanced (stage 3-4) disease. P/LP were found in 12.1% (n=47) of patients, including 29 in moderate and high penetrance cancer susceptibility genes. 13 (3.3%) patients had mutations in BRCA1 or 2, while 33 (8.4%) had mutations in BRCAness (ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, NBN, PALB2, RAD50, RAD51C, RAD51D, WRN) associated genes. Of the P/LP findings the most frequent aberrations were in BRCA2 (13.5%), BRCA1 (11.5%), CHEK2 (11.5%), MUTYH (11.5%), and WRN (9.6%). Variants of uncertain significance were found in 209 (53.6%) including 26 (6.6%) with concurrent P/LP and VUS. 37 (9.4%) patients had mutations associated with published management recommendations, precision therapies and/or clinical trial eligibility. 10 (2.6%) patients had P/LP that would not have met current screening guidelines, including 4 with moderate or high penetrance mutations. Patients with younger age of diagnosis were less likely than patients with older age of diagnosis to have a P/LP mutation (OR= 0.47, 95%CI: 0.25-0.90 $p$ = 0.020). Only 10 (21%) patients with P/LP had family members undergo familial site- specific testing at no cost.**Conclusions:** In this prospective multi-center study of unselected breast cancer patients, universal multi-gene panel testing found that 1 in 8 patients harbor P/LP germline variants. Current guidelines were able to identify the majority of patients with P/LP mutations. Familial site specific testing is greatly under-utilized even when cost is not a barrier. Multigene panels impact cancer patient care by identifying precision medicine treatment interventions, and guiding long-term medical management and preventive surveillance.

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Prospective evaluation of the gut microbiome and response to neoadjuvant therapy (NAT) in early-stage triple negative breast cancer (TNBC)

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**Introduction:** Emerging data suggest that the gut microbial composition influences responses to chemotherapy and immunotherapy. However, similar data in patients with TNBC receiving NAT remains limited. Thus, we investigated the association between the gut microbial composition in patients with newly-diagnosed, early-stage TNBC and response to NAT in a cohort of patients enrolled in the ARTEMIS trial (NCT02276443). **Methods:** We performed 16S sequencing on bacterial genomic DNA extracted from pre-NAT fecal samples using the 2x250 bp paired-end read protocol. Quality-filtered sequences were clustered into Operational Taxonomic Units and classified using Mothur method with the Silva database version 128. Associations between abundance and pathologic response to NAT were assessed using the Mann Whitney U Test. A cohort of 32 patients had longitudinal samples collected. Mann-Whitney U Test and Fishers exact were used to compare clinical variables as appropriate between the pCR and non-pCR groups. **Results:** There was no significant difference in age, race or stage between the pCR and non-pCR groups (Table 1). As expected, the pCR group was enriched for high TIL (p=0.026). There was no difference in alpha-diversity of the gut microbiome between patients with NAT-sensitive (pCR) and NAT-resistant disease (non-pCR) (p=0.5). Relative to patients with NAT-sensitive disease (pCR), the gut microbiome in patients with NAT-resistant disease was enriched for Fusobacterium (p=0.009), Intestinimonas (p=0.01) and Lachnospiraceae (p=0.003) at the genus level; the median abundances between pCR and non-pCR are provided in Table 1. Longitudinal samples collected during NAT demonstrated no substantial impact of NAT on the gut microbiome.

| **Table 1: Median Microbial Abundance and Clinicopathological Variables (N=43)** | | | |
|---|---|---|---|
| | **pCR (n=18)** | **Non-pCR (n=25)** | **p- value** |
| **Microbial Abundance** | | | |
| **Fusobacterium** | $1 \times 10^{-6}$ | $1.02 \times 10^{-5}$ | **0.009** |
| **Intestinimonas** | $6.4 \times 10^{-5}$ | $4.8 \times 10^{-4}$ | **0.01** |
| **Lachnospiraceae** | $6.2 \times 10^{-3}$ | $1.0 \times 10^{-2}$ | **0.003** |
| **Age median, interquartile range (n=44)** | 45 (38-59) | 53 (46-58) | 0.61 |
| | n (%) | | |
| **Race/Ethnicity** | | | |
| **White, non-Hispanic** | 11 (61.1) | 14 (56.0) | 0.53 |
| **White, Hispanic** | 4 (22.2) | 3 (12.0) | |
| **Black** | 2 (11.1) | 7 (28.0) | |
| **Asian** | 1 (5.6) | 1 (4.0) | |
| **T category** | | | |
| **T1** | 5 (27.8) | 4 (16.0) | 0.15 |
| **T2** | 13 (72.2) | 17 (68.0) | |
| **T3** | 0 | 4 (16.0) | |
| **T4** | 0 | 0 | |
| **Nodal status** | | | |
| **Negative** | 12 (66.7) | 14 (56.0) | 0.54 |
| **Positive** | 6 (33.3) | 11 (44.0) | |
| **Stage** | | | |
| **I** | 3 (16.7) | 3 (12.0) | 0.91 |
| **II** | 11 (61.1) | 15 (60.0) | |
| **III** | 4 (22.2) | 7 (28.0) | |
| **TIL** | | | |
| **<20%** | 7 (38.9) | 19 (76.0) | **0.026** |
| **≥20%** | 11 (61.1) | 6 (24.0) | |

**Conclusions**: Taken together, these data suggest that response to NAT may be influenced by the gut microbial composition, which remains unaltered during NAT. Research efforts to modulate the gut microbiome should be further explored as a potential therapeutic strategy in TNBC.

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# Clinical outcomes of alpelisib plus fulvestrant in hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer with *PIK3CA* alterations detected in plasma ctDNA by next-generation sequencing: Biomarker analysis from the SOLAR-1 study

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**Introduction:** The PI3K pathway is often hyperactivated in cancer as a result of an altered PI3K isoform and/or loss of phosphatase and tensin homolog function. Approximately 40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer (ABC) have tumors with mutations in *PIK3CA*, which encodes the α-isoform of PI3K, p110α. These mutations are known to cause hyperactivation of the PI3K pathway, which contributes to cell proliferation, drug resistance, and poor prognoses. Alpelisib (ALP) is an α-selective PI3K inhibitor that, in combination with fulvestrant (FUL), prolonged median progression-free survival (mPFS) in pts with HR+, HER2−, *PIK3CA*-mutant ABC following progression on/after prior aromatase inhibitor in the phase 3 SOLAR-1 trial. In SOLAR-1, prospective *PIK3CA* mutation testing was performed on tumor tissue using PCR-based assays. Through retrospective analysis, efficacy of ALP was demonstrated in subgroups of pts with *PIK3CA* alteration(s) in tumor tissue and mutation(s) in ctDNA, detected by next-generation sequencing (NGS) and PCR, respectively. In this exploratory biomarker analysis, we assessed clinical outcomes of pts with *PIK3CA* alteration(s), detected in ctDNA by NGS.**Methods:** SOLAR-1 is a phase 3, randomized, double-blind, placebo-controlled study of ALP 300 mg vs placebo taken daily with FUL 500 mg every 28 days + Cycle 1 Day 15 in men and postmenopausal women with HR+, HER2- ABC. Retrospectively, the full exonic region of the *PIK3CA* gene was sequenced using the Foundation Medicine 324-gene ctDNA panel in plasma ctDNA collected at baseline. mPFS was assessed using Kaplan-Meier methodology per investigator assessment.**Results:** Of 572 pts in SOLAR-1, 381 pts (66.6%) across both *PIK3CA*-mutant and nonmutant cohorts had valid plasma ctDNA data. Of these pts, 193 (50.7%) had a *PIK3CA* alteration; 168 (87%) had PCR-detectable mutations and 147 (76%) had a single alteration. A total of 70 (36%) and 102 (53%) pts had alterations in exons 9 and 20, respectively. ALP plus FUL prolonged mPFS in pts with *PIK3CA* alterations detected in plasma ctDNA by NGS (n=101; Table). Clinical benefit was also observed in pts with PCR-detectable mutations (n=88), single mutations (n=83), and pts with mutations in exon 9 (n=34) and exon 20 (n=54). Pt numbers were low, and wide 95% CIs were observed in groups with alterations not detectable by PCR (n=13) and in pts with multiple alterations. Some limitations of this retrospective plasma analysis include that this is a subgroup (66.6%) of the SOLAR-1 pt population and that the subgroup of pts with non-altered *PIK3CA* included pts with a *PIK3CA* mutation in their tumor tissue. **Conclusions:** ALP plus FUL demonstrated clinical benefit in pts with *PIK3CA* mutations detected in plasma ctDNA by NGS, in pts with single alterations, and in pts with alterations in exons 9 and 20. Results were consistent across pt groups, except in those with alterations not detectable by PCR. In conclusion, these data demonstrate a consistent clinical benefit of ALP plus FUL in various groups of pts with *PIK3CA* alterations detected in ctDNA by NGS.

**Clinical Outcomes of Patients With *PIK3CA* Alterations Detected in Plasma ctDNA by NGS in SOLAR-1**

| | **Alpelisib + fulvestrant** | | **Placebo + fulvestrant** | | **HR (95% CI)** |
|---|---|---|---|---|---|
| | **Events/N (%)** | **mPFS, mo (95% CI)** | **Events/N(%)** | **mPFS, mo (95% CI)** | |
| *PIK3CA* altered vs non-altered | | | | | |
| Altered | 58/101(57.4) | 11.04(7.72-16.16) | 73/92(79.3) | 3.65(2.86-6.80) | 0.47(0.33-0.67) |
| Non-altered | 40/87(46.0) | 10.87(5.59-16.76) | 60/101(59.4) | 5.45(3.75-9.00) | 0.60(0.40-0.91) |
| *PIK3CA*: alteration detectable by PCR vs alteration not detectable by PCR | | | | | |
| Detectable | 52/88(59.1) | 12.48(7.36-18.37) | 66/80(82.5) | 3.58(2.37-5.65) | 0.44(0.30-0.64) |
| Not detectable | 6/13(46.2) | 8.48(2.69-NA) | 7/12(58.3) | 7.39(1.87-12.98) | 1.12(0.35-3.56) |
| *PIK3CA*: number of alterations | | | | | |
| Single | 45/83(54.2) | 12.88(7.36-18.50) | 50/64(78.1) | 3.58(1.87-6.11) | 0.43(0.28-0.65) |
| Multiple | 13/18(72.2) | 9.00(3.68-18.37) | 23/28(82.1) | 4.63(3.48-9.63) | 0.55(0.25-1.20) |
| *PIK3CA* alterations in exon 9 or exon 20 | | | | | |
| Exon 9 | 18/34(52.9) | 15.21(7.03-NA) | 29/36(80.6) | 3.66(2.86-7.36) | 0.31(0.16-0.61) |
| Exon 20 | 34/54(63.0) | 10.91(5.72-18.37) | 40/48(83.3) | 3.52(1.87-6.11) | 0.51(0.31-0.82) |

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mPFS, median progression-free survival; mo, months; NA, not available; NGS, next-generation sequencing.

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Changes in management of breast cancer patients during first wave of COVID19, throughout the area of Kent, United Kingdom. An audit of ESMO guideline implementation

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**Background:** The global COVID-19 pandemic has placed unprecedented burden on individual oncology patients, oncology departments, hospitals and national health systems. In order to protect individual patients from the risk of COVID-19 infection as well as improve capacity for COVID-19 patient management, a series of national and internationally agreed measures were proposed. During the first wave of infections the virulence and effect on cancer patients was not known. It is vitally important that the measures implemented to combat these risks are assessed and evaluated in order to learn best how to manage potential future waves of known and unknown viral infections.**Methods:** The international ESMO COVID-19 guidelines and national (NICE) guidelines were implemented across Kent, UK. All changes to treatment regimens were audited to assess what were the most frequent changes and in which patient groups could these be implemented. Data was subdivided for both early and advanced breast cancer as well as ER+, HER2+ or triple negative disease.**Results:** We collected full treatment history from 1,718 breast cancer patients currently receiving active oncology treatments. We were able to change treatment regimens due to COVID19 for 32.8% of patients. Of these 27.1% were early breast cancer patients compared with 43.7% were those with advanced metastatic disease. The most common changes for neoadjuvant changes were proceeding to surgery before completion of planned chemotherapy (10.2%), switch to 3 weekly Paclitaxel (10%) and chemotherapy break (8%). For adjuvant patients the most common changes included postponement of bisphosphonates (70.8%), chemotherapy break (13.5%), and curtailment to 6 months of adjuvant Trastuzumab (10.4%). For our palliative patients the most common changes included delay CDK4/6 inhibitor treatment (79.2%), postponement of bisphosphonates (24.8%), break in HER2 antibody (9.6%) and break in chemotherapy (8%).**Conclusions:** A large proportion of breast cancer oncology patients were deemed suitable to have a change in original planned treatment. We are fortunate to have comparatively large number of treatment options that can be customised on a patient basis to individual reduce risk of COVID-19. Further analysis is needed over time to compare the oncological outcomes of those in whom treatment was changes from the current gold standards of care.

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# Characterization of breast cancer management during the COVID 19 pandemic in a large integrated healthcare delivery system: Stage at diagnosis and timing/modality of first treatment

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**Background**: The COVID 19 pandemic has disrupted all aspects of healthcare, including the diagnosis and treatment of breast cancer. In March 2020, the Society of Surgical Oncology, the American College of Surgeons, and the American Society of Breast Surgeons issued guidelines regarding the timing of surgery for cancer patients to preserve hospital resources and minimize exposure of patients and staff to COVID 19. Recommendations included delaying breast cancer surgery if possible, and using neoadjuvant chemotherapy or neoadjuvant endocrine therapy to treat selected patients while waiting for definitive surgery. In California, the “shelter in place” (SiP) order began March 17, 2020, and both screening mammography and elective surgeries were stopped in a large, integrated health care system. We evaluated the impact of these operational changes on the presentation and treatment of breast cancer patients in our system.**Methods:**We performed a retrospective review of patients newly diagnosed between 3/17/20, the starting date of SiP, and 5/18/20, when elective operations resumed in our system. We compared this cohort to patients who were diagnosed between 3/17/19 and 5/18/19. Age, histology, anatomic staging features, grade, receptor status, and initial treatment were compared between the cohorts. For the patients who underwent surgery, we compared the time from biopsy to time to surgery (TTS) and the type of operation. Comparisons involving categorical variables were performed using the chi-square test. Normally-distributed continuous variables were compared using two sample-t-tests. P-values of <0.05 were considered statistically significant.**Results:**There were 790 patients in the 2019 cohort and 279 in the 2020 cohort. There were no significant differences in age at presentation, histologic subtypes, nodal status, or operation type between the two groups. The T-stages at presentation of the 2020 group were higher than those of the 2019 group; 29% presented with T1c tumors in 2020 vs 26% in 2019, and 37% with T2 tumors in 2020 vs 30% in 2019 (p=0.03). A higher percentage of patients presented with distant metastatic disease at the time of diagnosis in 2020 (7% in 2020 vs 2% in 2019, p<0.001), although the absolute numbers of patients were similar (19 patients in 2020 vs 17 patients in 2019). Of patients with invasive breast cancer, a higher percentage of patients presented with grade 3 tumors in 2020 (35% in 2020 vs 24% in 2019, p=0.002), and triple negative tumors (15% vs 10%, p=0.02). Fewer patients underwent surgery first in 2020 (73% in 2020 vs 85% in 2019, p<0.001) and more underwent neoadjuvant chemotherapy (13% in 2020 vs 9% in 2019, p=0.03). Only 4% of the 2020 surgery group had been placed on neoadjuvant endocrine therapy while awaiting definitive surgery. The TTS for patients with surgery as the initial treatment was significantly shorter for the 2020 group (mean 22 days in 2020 vs 31 days in 2019, p<0.001).**Conclusions:** Without screening mammography, newly-diagnosed patients in a large, integrated health care system during the COVID 19 pandemic presented with more advanced and aggressive breast cancers as compared to the equivalent time period in 2019. Fewer patients underwent surgery first, and more underwent neoadjuvant chemotherapy. The TTS for breast cancer patients in 2020 was significantly shorter than in 2019, which we hypothesize was due to the availability of operating rooms since elective operations had been stopped. This study demonstrates the ability of a large, integrated health care system to deliver timely breast cancer care to patients presenting with symptomatic disease during the constraints of the COVID 19 pandemic, and highlights the importance of screening in the early detection of breast cancer.

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# Updated results from DESTINY-breast01, a phase 2 trial of trastuzumab deruxtecan (T-DXd ) in HER2 positive metastatic breast cancer

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**Background**
Trastuzumab deruxtecan (T-DXd, DS-8201) is an antibody-drug conjugate with a HER2 antibody, tetrapeptide-based cleavable linker, and a novel topoisomerase I inhibitor payload. DESTINY-Breast01 (NCT03248492) is an open-label, international, multicenter, phase 2 study of T-DXd in patients with HER2 positive metastatic breast cancer (MBC) and supported regulatory approval in the US and Japan. Updated longer-term safety and efficacy results are presented here.
**Methods**
All patients were required to have MBC that progressed on or after T-DM1. 253 patients were enrolled and 184 received T-DXd 5.4 mg/kg, representing the primary analysis set. The primary endpoint was ORR. Additional endpoints included duration of response, PFS, and OS.
**Results**
Patients had received a median of 6 previous lines of treatment for MBC. In this updated data cutoff (8 June 2020) compared to the prior data cutoff (1 Aug 2019), median duration of follow-up has increased from 11.1 to 20.5 mo; 37 patients (20.1%) remain on treatment. Confirmed ORR was 61.4% (12 CRs) with a median duration of response of 20.8 mo; the disease control rate was 97.3% (95% CI, 93.8-99.1). The updated mPFS was 19.4 mo (95% CI, 14.1 mo-NE). Estimated OS was 85% (95% CI, 79%-90%) at 12 months and 74% (95% CI, 67%-80%) at 18 months. The preliminary mOS is 24.6 mo (estimated at 35% maturity with only 17 patients at risk at 24 months). The safety profile of T-DXd was similar as that previously reported; with an additional 9 mo follow-up, only 3 new cases of T-DXd-related interstitial lung disease (ILD) were reported. Results are summarized in the table below.
**Conclusion**
Consistent with prior results, T-DXd demonstrated high rates of durable responses in a heavily pretreated population of patients with MBC. From this single-arm, phase 2 study, the PFS and immature OS results are encouraging; these endpoints will be further evaluated in the ongoing randomized controlled studies of T-DXd. For patients who remained on treatment for this longer duration (double that of the previous report), the rate of discontinuation or ILD did not notably increase. Continued attention to pulmonary symptoms and careful monitoring is warranted.

Updated Results for DESTINY-Breast01

| | **1 Aug 2019 datacut** | **8 Jun 2020 datacut** |
|---|---|---|
| Patients remaining on treatment, n/N (%) | 79/184 (42.9%) | 37/184 (20.1%) |
| Median duration of follow-up | 11.1 months | 20.5 months |
| ORR | 60.9% | 61.4% |
| CR | 6.0% | 6.5% |
| PR | 54.9% | 54.9% |
| SD | 36.4% | 35.9% |
| Duration of response, median (95% CI) | 14.8 months (13.8-16.9) | 20.8 months (15.0-NE) |
| PFS, median (95% CI) | 16.4 months (12.7-NE) | 19.4 months (14.1-NE) |
| OS | | |
| Median (95% CI) | NE (NE-NE) | 24.6 months (23.1-NE) |
| Point estimate at 12 mo (95% CI) | 86.2% (79.8-90.7) | 85% (79-90) |
| Point estimate at 18 mo (95% CI) | -- | 74% (67-80) |
| Safety | | |
| Patients with a TEAE, n (%) | 183 (99.5%) | 183 (99.5%) |
| Grade ≥3 | 105 (57.1%) | 113 (61.4%) |
| Associated with discontinuation | 28 (15.2%) | 34 (18.5%) |
| Associated with death | 10 (5.4%) | 10 (5.4%) |
| Drug-related ILD per ILD adjudication committee[a] | 25 (13.6%) | 28 (15.2%) |
| Grade 5 drug-related ILD per ILD adjudication committee | 4 (2.2%) | 5 (2.7%) |

[a]1 grade 1 and 1 grade 3 event are pending adjudication and are not included.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS1-06

High-risk breast cancer in oldest old: Exploring the effect of different treatments on outcomes

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**Background:** Octogenarians and nonagenarians diagnosed with breast cancer have a competing risk of death from other causes and their management is frequently found to be discordant with guidelines in comparison to the younger patients, particularly with low-risk disease. There is limited information about the disease trajectory and outcomes of patients with high-risk disease. Thus, this study was conducted. **Methods:** This is a retrospective, population-based observational study. Women aged 80 years of age or older and diagnosed with non-metastatic, high-risk breast cancer in Alberta, Canada between January 2004 and December 2017 were identified from the Alberta Cancer Registry. High-risk disease was defined as having any of the following; T3/4, any N positive, triple negative, or Her-2 positive disease. A risk scoring system was generated based on the presence of two anatomical and one biological high-risk features to generate 3 risk levels. Patients' characteristics (age, Charlson comorbidity index, residence, education-, and income- quintiles), disease characteristics (stage, grade, receptor status,) treatment patterns (treatment delivered, facility) and survival were determined from linkage with administrative databases (Discharge Abstract Data, National Ambulatory Care Reporting System, and Vital statistics). Treatments were stratified into; none, hormonal treatment only (HT), surgery only (S), and surgery with any adjuvant treatment (S+A). Statistical methods included chi-square and Cox regression models. Association between patient, tumor and treatment variables and survival were assessed with uni- and multivariable analysis. Primary outcome was breast cancer specific survival (BCSS) in patients stratified by different risk levels in relation to the treatment delivered. **Results:** 1369 patients met the inclusion criteria. The median age was 84 years (interquartile range [IQR] 82-88). After a median follow-up of 35 months (m), 873 (64%) patients had died; 405 (46%) of deaths were due to breast cancer. On multivariable analysis, patients had a lower hazard of death from cancer if they were treated with S (HR = 0.51, 95%CI: 0.34, 0.77, p = 0.001) or S+A (HR = 0.41, 95%CI: 0.28, 0.6, p < 0.001) in comparison to HT alone. Patients who did not receive any form of treatment were more likely to die from breast cancer (HR 2.14 95%CI: 1.38, 3.31, p = 0.0006). Patients who had 1 or 2 risk features had higher cancer specific and overall survival if they had S or S+A (49/31m, 92/66m median differences respectively p < .0001). Those with 3 risk features showed longer survival if they received S+A (29/25m median differences p < .0001). **Conclusions and Relevance:** Our findings suggest that a significant proportion of older patients with breast cancer patients with high-risk features may have increased disease-specific mortality risk. Based on a priori risk levels, and in properly selected patients, treatment options including surgery and adjuvant treatment may be associated in longer survival.

Table 1- Population and Treatment Characteristics

| Variables | Category | Total (N=1369) |
|---|---|---|
| Age group | 80-85 | 817 (59.7 %) |
| | 86-90 | 388 (28.3 %) |
| | 91-95 | 146 (10.7 %) |
| | >95 | 18 (1.3 %) |
| Charlson Comorbidity Index | 0 | 453 (33.1 %) |
| | 1 | 361 (26.4 %) |
| | >=2 | 555 (40.5 %) |
| TNM stage | I | 239 (17.5 %) |
| | II | 663 (48.4 %) |
| | III | 422 (30.8 %) |
| T stage | T1 | 416 (30.4 %) |
| | T2 | 601 (43.9 %) |
| | T3 | 163 (11.9 %) |
| | T4 | 169 (12.3 %) |
| | Unknown | 20 (1.5 %) |
| N stage | N0 | 526 (38.4 %) |
| | N1 | 548 (40 %) |
| | N2 | 159 (11.6 %) |
| | N3 | 85 (6.2 %) |
| | Unknown | 51 (3.7 %) |
| Receptor status | ER+orPR+andHer2- | 1071 (78.2 %) |
| | Her2+ | 130 (9.5 %) |
| | ER-andPR-andHer2- | 123 (9 %) |
| | Unknown | 45 (3.3 %) |
| Risk levels | 1 | 922 (67.3 %) |
| | 2 | 371 (27.1 %) |
| | 3 | 76 (5.6 %) |
| Surgery type | No surgery | 215 (15.7 %) |
| | BCS | 364 (26.6 %) |
| | Mastectomy | 790 (57.7 %) |
| Sentinel surgery | no | 938 (68.5 %) |
| | yes | 431 (31.5 %) |
| Chemotherapy | no | 1337 (97.7 %) |
| | yes | 32 (2.3 %) |
| Radiotherapy | no | 991 (72.4 %) |
| | yes | 378 (27.6 %) |
| Hormonotherapy | no | 659 (48.1 %) |
| | yes | 710 (51.9 %) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS6-06

# The 70-gene signature (MammaPrint) accurately predicts distant breast cancer recurrence risk in patients aged ≥70 years from the population-based observational FOCUS cohort

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**Background** Predicting breast cancer recurrence in patients aged ≥70 years is challenging, as they generally have more indolent tumors and a higher chance of dying of competing causes than younger patients. The 70-gene signature test (MammaPrint) has been shown to accurately predict recurrence in women with early breast cancer and up to 3 positive lymph nodes. **Aim** To study outcome related to MammaPrint result in patients aged ≥70 years with breast cancer using a population-based cohort. **Methods** The population-based FOCUS cohort included all 2095 consecutive patients with any stage breast cancer, diagnosed between 1997 and 2004, aged ≥65 years, in the Comprehensive Cancer Center region West, the Netherlands. In the present exploratory sub-study, patients from FOCUS with the following criteria were included: ≥70 years old, T1-2N0-3M0, hormone receptor positive, HER2 negative, no neo-adjuvant treatment and available tumor specimens. MammaPrint is a genomic risk profile based on microarray gene expression analysis, classifying patients as ultralow risk (M-ULR), low (not UL) risk (M-LR) or high risk (M-HR) of developing a recurrence. Patients were considered clinically low risk (C-LR) with T1-2N0 grade 1-2 tumors and clinically high risk (C-HR) with N+ or T2/grade 3 tumors. Primary endpoint was 10-year distant recurrence free interval (DRFi) in relation to genomic risk, estimated from cumulative incidence and Fine and Gray analyses to take competing mortality into account. **Results** In this study, 422 patients were included. Median age was 78 years, 238 patients (56%) had node negative disease, 235 patients (56%) had T2 tumors and 227 patients (54%) were C-LR. Most patients were treated with endocrine therapy (ET), and 22 patients (5%) were treated with chemotherapy (CT; table 1). Overall, 50 (12%) patients were M-ULR, 226 (53%) were M-LR and 146 (35%) were M-HR. Discrepancies were found between C and M risk groups in 18/50 M-ULR patients with C-HR, and 56/146 M-HR patients with C-LR. Of the 59 patients that experienced a recurrence during 10 years of follow-up, 44 (75%) were distant recurrences. In the M-ULR group, DRFi was 2% (95%CI 0-6) after 10 years of follow-up, this was 8% (95%CI 5-12) in the M-LR group and 17% (95%CI 11-23) in the M-HR group (p<0.001). In the C-HR subgroup, none of the 18 M-ULR patients developed a recurrence, and DRFi was 10% (95%CI 3-16) in M-LR patients and 20% (95%CI 12-28) in M-HR patients (p=0.015). C risk alone was not able to predict distant recurrence risk (C-LR 8%, C-HR 14%, sHR 1.8 [95%CI 0.9-3.2); p=0.060; table 2). **Conclusion** MammaPrint accurately predicts 10-year DRFi in older patients with breast cancer. Patients classified as ultralow risk by MammaPrint had a very low chance of developing metastatic disease. Even in clinically high-risk patients who were M-ULR, recurrent disease did not occur 10 years after diagnosis. These findings are in line with published results of the STO-3 trial (JAMA Oncol, 2017) and provide foundation for de-escalation of treatment in older patients guided by genomic testing.

Table 1: Baseline characteristics. BCS = breast conserving surgery. RT = radiotherapy

| | | **M-ULR** | **M-LR** | **M-HR** |
|---|---|---|---|---|
| **Total patients** | *N (%)* | 50 (11.8) | 226 (53.6) | 146 (34.6) |
| **Age** | *Median (IQR)* | 79 (74-85) | 79 (74-84) | 77 (74-84) |
| **Histological grade [N (%)]** | *I* | 11 (22.0) | 39 (17.3) | 5 (3.4) |
| | *II* | 21 (42.0) | 92 (40.7) | 42 (28.8) |
| | *III* | 1 (2.0) | 31 (13.7) | 54 (37.0) |
| | *Missing* | 17 (34.0) | 64 (28.3) | 45 (30.8) |
| **T-stage [N (%)]** | *Tis* | 0 (0.0) | 2 (0.9) | 0 (0.0) |
| | *T1* | 17 (34.0) | 111 (49.1) | 54 (37.0) |
| | *T2* | 33 (66.0) | 113 (50.0) | 89 (61.0) |
| | *Missing* | 0 (0.0) | 0 (0.0) | 3 (2.0) |
| **N-stage [N (%)]** | *N0* | 32 (64.0) | 140 (61.9) | 66 (45.2) |
| | *N1* | 17 (34.0) | 72 (31.9) | 67 (45.9) |
| | *N2* | 0 (0.0) | 6 (2.7) | 6 (4.1) |
| | *N3* | 0 (0.0) | 2 (0.9) | 3 (2.1) |
| | *Missing* | 1 (2.0) | 6 (2.7) | 4 (2.7) |
| **Clinical risk [N (%)]** | *Low* | 32 (64.0) | 139 (61.5) | 56 (38.4) |
| | *High* | 18 (36.0) | 87 (38.5) | 90 (61.6) |
| **Local treatment [N (%)]** | *None* | 4 (8.0) | 5 (2.2) | 6 (4.1) |
| | *BCS only* | 3 (6.0) | 16 (7.1) | 13 (8.9) |
| | *BCS + RT* | 9 (18.0) | 62 (27.4) | 29 (19.9) |
| | *Mastectomy* | 34 (68.0) | 143 (63.3) | 98 (67.1) |
| **Adjuvant ET [N (%)]** | *None* | 24 (48.0) | 103 (45.6) | 40 (27.4) |
| | *Tamoxifen* | 17 (34.0) | 87 (38.5) | 80 (54.8) |
| | *Aromatase inhibitor* | 3 (6.0) | 11 (4.9) | 9 (6.2) |
| | *Unspecified ET* | 6 (12.0) | 25 (11.1) | 17 (11.6) |
| **Adjuvant CT [N (%)]** | *No* | 46 (92.0) | 217 (96.0) | 137 (93.8) |
| | *Yes* | 4 (8.0) | 9 (4.0) | 9 (6.2) |

Table 2: Primary endpoint stratified by genomic and clinical risk. sHR=subdistribution hazard ratio.

| | **M-ULR** | **M-LR** | **M-HR** | **Total** |
|---|---|---|---|---|
| **C-LR** | N=32 (14%). DRFi=3% (95%CI 0-9). sHR=1 (reference). | N=139 (61%). DRFi=7% (95%CI 3-12). sHR=2.1 (95%CI 0.3-16.5). | N=56 (25%). DRFi=13% (95%CI 4-21). sHR=4.3 (95%CI 0.5-34.7). | N=227. DRFi=8% (95%CI 4-12). |

| | | | | |
|---|---|---|---|---|
| **C-HR** | N=18 (9%).DRFi=0% (95%CI 0-0). sHR=N/A (n events=0). | N=87 (45%). DRFi=10% (95%CI 3-16). sHR=1 (reference). | N=90 (46%). DRFi=20% (95%CI 12-28). sHR=3.0 (95%CI 1.3-6.9). | N=195. DRFi=14% (95%CI 9-19). |
| **Total** | N=50 (12%). DRFi=2% (95%CI 0-6). sHR=1 (reference). | N=226 (53%). DRFi=8% (95%CI 5-12). sHR=3.8 (95%CI 0.5-28.2). | N=146 (35%). DRFi=17% (95%CI 11-23). sHR=9.8 (95%CI 1.3-72.6). | N=422. |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** OT-03-03

SGNLVA-001: A phase 1 open-label dose escalation and expansion study of SGN-LIV1A administered weekly in breast cancer

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**Background:** LIV-1 is a highly prevalent transmembrane protein in breast cancer cells. Ladiratuzumab vedotin (LV), SGN-LIV1A, is an investigational antibody-drug conjugate (ADC) that targets LIV-1 via a humanized IgG1 monoclonal antibody conjugated to monomethyl auristatin E (MMAE) by a protease-cleavable linker. LV is internalized when it binds LIV-1 on cell surfaces and MMAE is released, which binds tubulin and induces apoptosis. LV has been shown to be active and tolerable in metastatic breast cancer (mBC) at a recommended dose of 2.5 mg/kg every 21 days (Modi 2017). More frequent, fractionated dosing has improved the activity and/or safety of other ADCs. Thus, this study is actively accruing subjects with metastatic triple negative breast cancer (mTNBC; estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2) receptor-negative) and endocrine-resistant ER+ or PR+ (hormone receptor [HR+])/HER2-negative mBC to test weekly dosing of LV (Days 1, 8, and 15 of every 3-week cycle). **Methods:** This study is enrolling up to 82 subjects (42 HR+/HER2-negative and 40 mTNBC) into dose escalation and dose expansion cohorts (NCT01969643). Eligible subjects are females ≥18 years old with pathologically and radiologically confirmed metastatic HR+/HER2-negative or mTNBC with at least 1 measurable lesion per RECIST v1.1. Subjects with HR+/HER2-negative disease must have received no more than 1 prior line of cytotoxic chemotherapy in the locally advanced (LA)/mBC setting, either as single agent or combination therapy. Subjects with mTNBC must have received 1 prior line of cytotoxic chemotherapy in the LA/mBC setting. Progression within 6 months of completion of neoadjuvant or adjuvant therapy is considered an LA/mBC regimen. Subjects must have adequate organ function, ECOG status of ≤1, and no ≥ Grade 2 peripheral neuropathy. Subjects with brain lesions must have received definitive treatment of the lesions. Prior therapy with MMAE-containing agents is not allowed. Dose escalation follows the modified toxicity probability interval method (Ji 2010). Dose expansion cohorts will provide data about activity and tolerability. Tumor assessments will be conducted every 2 cycles per RECIST v1.1 and all subjects will be followed for safety. Pharmacokinetics and markers of pharmacodynamics will be assessed. Primary safety endpoint is the incidence of adverse events and dose-limiting toxicities. Key efficacy endpoints include confirmed overall response rate, duration of response, and progression-free survival.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS12-06

Phase II randomized trial of fulvestrant with or without enzalutamide in ER+/Her2- primary breast cancer (BC)

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**Background:** Almost all ER+ breast cancers express androgen receptor (AR), but its function is uncertain. AR expression is associated with more indolent tumors, however high AR expression relative to ER is associated with endocrine resistance, and in the absence of estradiol or if ER function is blocked, preclinical data would suggest that AR can take over to signal cell survival and proliferation. This non-blinded randomized phase II trial of neoadjuvant fulvestrant with or without enzalutamide was performed in women with T2 or greater ER+/Her2- primary breast cancer. **Methods:** Eligible patients were women with ECOG 0-2, ER+/Her2- primary breast cancer cT2 or greater. A total of 4 months of therapy was given (fulvestrant 500 mg IM weeks 1, 3, 5, 9, and 13). Patients were randomized to receive enzalutamide 160 mg po daily on a continual basis for 16 weeks. Stratification factors were clinical node status (N0 vs N1/2) and T-stage (T2 vs T3/4). Surgery was planned for week 17. Fresh tumor biopsies were required at study entry and at ~4 weeks on therapy. Tissue, both fresh frozen and FFPE, was also obtained at time of surgery. The PEPI score at time of surgery was the primary endpoint for efficacy. The statistical design were parallel phase II trials with the experimental arm designed as a Simon 2-stage. The expectation for the control arm was a PEPI score of 0 in 16% and 32% for the combination arm. Additional enrollment of 12 patients would ensue if 4 or more achieved a PEPI score of 0 within the first 22 patients enrolled onto the combination arm. 27 patients would be enrolled into the fulvestrant alone arm. **Results:** The Simon 2-stage criteria were met and the trial continues to accrue up to 11 more evaluable patients. Thus far, 58 patients were consented of whom 50 were treated. Median age was 61.5 years (45-83); PS 0 (0-2). Among the 46 patients with information on AEs, there are 25 patients with Grade 2 AEs, including 5 with fatigue, 3 with headache, and 2 with hot flashes. There are 5 patients with grade 3 AEs including abdominal pain, gallbladder obstruction, ALT elevation, hyperglycemia, and hypertension. We also have 2 patients with grade 4 AEs , chest pain-cardiac and cardiac disorder-other. There is no grade 5 event. Paired samples at baseline and at 4 weeks are collected so far from 49 patients. 42 patients have completed surgery, while two patients have not undergone surgery. **Conclusions:** The combination of fulvestrant plus enzalutamide had manageable side effects. The trial is now in its extended stage since PEPI score = 0 was achieved in at least 4 of the first 22 patients on the combination arm. Extensive molecular studies of paired fresh biopsies from pretreatment and at 4 weeks are underway. These analyses and correlations with clinical outcome will be described.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS15-06

The distribution of radiosensitivity index differs by PAM50 subtype in primary breast tumors

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**Background:** Prior studies identified radiosensitive and radioresistant breast tumor phenotypes and demonstrated that gene-expression signatures such as the radiosensitivity index (RSI) can be used to derive biologically rational radiation dose selection. In this study, we assessed the RSI of primary breast tumor samples and its association with PAM50 subtype.**Materials/Methods:** Primary breast tumor samples were identified from a multi-institutional tissue biorepository. Tumors were excluded if they were treated with neoadjuvant therapy or had distant metastatic disease at the time of sample collection. The RSI gene signature and PAM50 subtype were assessed through transcriptomic profiling performed on Affymetrix microarray chips. Distribution of RSI values across PAM50 subtypes was assessed with the Kruskal-Wallis test. Differences in proportions of radioresistant and radiosensitive tumors among PAM50 subtypes were assessed with the Chi-squared test, where radioresistant was defined as RSI>0.3745 based on prior studies. Clinicopathologic characteristics were obtained through clinical chart review. **Results:** A total of 637 primary breast tumors with available genomic profiling and clinical information were included for analysis. HIstologies were predominantly invasive ductal carcinoma (81.5%) and invasive lobular (11.6%). Most tumors were T1-T2 (91.7%) while 35.9% had pathologically positive lymph nodes. The distribution of RSI significantly differed by PAM50 classification (Kruskal-Wallis $p < 0.001$). Proportions of radioresistant vs radiosensitive tumors varied significantly according to PAM50 subtype and are included in the accompanying table (Chi-squared $p < 0.001$). Median follow-up was 89 months.

| | | PAM50 | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | Basal | Her2 | LumA | LumB | Normal | |
| RSI Phenotype | Radioresistantn (%) | 50 (60.2%) | 32 (42.1%) | 146 (54.4%) | 82 (45.3%) | 24 (82.8%) | 334 (52.4%) |
| | Radiosensitive n (%) | 33 (39.8%) | 44 (57.9%) | 122 (45.6%) | 99 (54.7%) | 5 (17.2%) | 303 (47.5%) |
| Total | | 83 | 76 | 268 | 181 | 29 | 637 |

**Conclusion:** Breast tumor PAM50 subtypes demonstrate significant variation in radiosensitivity. Further studies are needed to determine if genomic subtyping can refine the ability to predict clinical radiation response and further optimize individual therapy.

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**Publication Number:** PD11-06

Associations between obesity and metastasis in the Carolina breast cancer study

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**Background.** Metastatic disease accounts for the majority of breast cancer-specific mortality, and identifying women who are most at risk for metastasis remains an important challenge. Genomic risk scores are valuable tools in assessing risk of recurrence but have rarely been applied to assess risk of distant metastasis in large, diverse population-based cohorts. Such cohorts can identify important modifiers of the relationship between tumor genomics and metastasis. In particular, obesity at diagnosis has been implicated as a risk factor for breast cancer metastasis. Waist-to-hip ratio (WHR), as a measure of central adiposity, appears to increase risk of breast cancer mortality. It is important to understand how obesity impacts risk of metastasis and modifies other known prognostic factors. **Methods.** Data from the Carolina Breast Cancer Study, a prospective cohort of women with incident breast cancer that oversampled young women and black women such that each represented 50% of the study population, were used to study metastasis within five years of follow up (n=239 incident metastases in 2767 eligible participants with stage I-III disease). PAM50-derived risk-of-recurrence (ROR-PT) scores were measured using a research version of the 50-gene assay, and represent a multigene classifier incorporating tumor subtype, size, and proliferation score. Women with de novo metastasis (identified at diagnosis, n=109) were excluded, as incident and de novo metastases have different prognosis. Obesity was defined by WHR (> 0.85). Absolute risk within strata and risk differences between strata were calculated using the Kaplan-Meier estimator; models were adjusted with inverse probability weights conditional on grade, stage, age, and race, where appropriate. To examine the association between obesity and site or multiplicity of metastasis, relative frequency differences were estimated using generalized linear models. **Results.** The overall risk of metastasis in CBCS differed significantly by race (11.2% in Black women and 6.8% in non-Black women and was associated with higher ROR-PT score (19.8% in high ROR-PT vs. 6.5% in low or medium ROR-PT). 48.2% of women were classified as obese by WHR. Women with high WHR had a significantly higher absolute risk of metastasis (11.2%, 95% CI: 9.4, 13.0) relative to those with lower WHR (6.9, 95% CI: 5.6, 8.2). However, the effects of WHR on risk seemed to be isolated to those with high risk tumors. Non-obese and obese women with low-to-medium ROR-PT scores had similar risk of metastasis [$RD_{LowMed}$ (95% CI) = 1.5% (-1.5, 4.4)], while obese women with high ROR-PT scores had substantially higher risk of metastasis than non-obese women [$RD_{High}$ (95% CI) = 13.1% (4.3, 21.9); 26.2% vs. 13.1%]. Considering site of metastasis, more metastases were observed among women with high WHR at every site except brain. More occurrences of multiple metastases were also observed among obese women. **Conclusions.** Consistent with previous studies, we observed racial disparities in metastasis, with Black women having higher 5-year metastatic risk and with women with high ROR-PT scores also having higher risk. Obesity, herein measured by WHR, is an important predictor of metastatic risk and may modify the relationship between genomic risk scores and risk of metastasis.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PD15-06

# Circulating TP53 mutations in TNBC after neoadjuvant chemotherapy is associated with rapid disease recurrence: Correlative analysis from clinical trial BRE12-158

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**Background:** Neoadjuvant chemotherapy (NAC) is a standard approach for many patients with triple negative breast cancer (TNBC). Our group, and others, have previously reported that the detection of circulating tumor DNA (ctDNA) after NAC and surgery is a surrogate for the presence of minimal residual disease (MRD) leading to inferior survival outcomes. Further, our group has also reported that the emergence of somatic TP53 mutations in tissue samples post-NAC was associated with inferior survival outcomes. In this study, we sought to determine whether TP53 mutations detected in the plasma of patients with ctDNA-positivity after NAC was associated with inferior outcomes compared to non-TP53 mutated patients.
**Methods:**BRE12-158 was a phase II clinical trial which randomized early-stage TNBC patients with residual disease after NAC to post-neoadjuvant genomically-directed therapy vs treatment of physician choice. 196 patients were enrolled. Patients had blood samples collected for ctDNA at the time of post-neoadjuvant treatment assignment. ctDNA was successfully sequenced using the FoundationACT or FoundationOneLiquid Assay in 142 patients. Patients who were ctDNA positive after NAC (N=90, 63%), were selected for this comparison. Median clinical follow-up was 22.9 months. A multivariate cox proportional-hazards model was used to compare DDFS, DFS, and OS of ctDNA-positive patients with and without TP53 mutations found in the ctDNA.
**Results:** 90 patients in BRE12-158 were ctDNA-positive after NAC and surgery. 36/90 (40%) of those patients had TP53 mutations detected in their plasma. Patients with TP53-mutated ctDNA had significantly inferior outcomes and a significantly shorter time to recurrence when compared to those without TP53 mutations. Detection of TP53-mutated ctDNA was significantly associated with an inferior DDFS (median DDFS: 6.99 months vs. 48.69 months; HR=2.78, 95%CI: 1.41-5.49; p=0.0033). At 24 months, the DDFS probability was 36% in TP53-mutated patients as compared to 72% in non-mutated patients. Similarly, detection of TP53-mutated ctDNA was significantly associated with an inferior DFS (median DFS: 4.83 months vs. 48.69 months; HR=3.63, 95%CI: 1.76-7.48; p=0.00047). At 24 months, the DFS probability was 30% in TP53-mutated patients as compared to 72% in non-mutated patients. Lastly, detection of TP53-mutated ctDNA was significantly associated with an inferior OS (median OS: 17.8 months vs. Not Reached; HR=3.48, 95%CI: 1.51-8.01; p=0.0034). At 24 months, the OS probability was 42% in TP53-mutated patients as compared to 80% in non-mutated patients.
**Conclusion:** In patients with ctDNA-positivity after NAC, the presence of TP53 mutations was associated with rapid disease relapse. These data suggest that TP53 mutation status may stratify outcomes among this high-risk group of patients with ctDNA positivity in the post-neoadjuvant setting.

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# Impact of an online ductal carcinoma *in situ* (DCIS) decision support tool on awareness of treatment options and knowledge of breast cancer risks

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**Background** An interactive decision support tool (DST) was adapted to support patients diagnosed with DCIS who are making treatment decisions. The DST provides the following risk estimates over 10 years: 1) future DCIS or invasive breast cancer in the same breast, 2) the risk of dying from causes other than breast cancer, and 3) the risk of dying from invasive breast cancer. Estimates are personalized based on patient age and DCIS grade (low/intermediate versus high grade or “don’t know”) and were based on a model incorporating data from clinical trials and life tables. **Methods** The DST was implemented in collaboration with the COMET study on the website DCISoptions.org (www.dcisoptions.org). On the DST, personalized results are displayed separately using a 100-woman icon array and percentages with each outcome (future DCIS/invasive breast cancer, death due to breast cancer, death due to other causes) in a different color for each treatment selected by the patient (lumpectomy only, lumpectomy + radiation therapy, lumpectomy + endocrine therapy, lumpectomy + radiation and endocrine therapy, mastectomy with or without reconstruction, bilateral mastectomy with or without reconstruction). In addition, information regarding active monitoring was provided in descriptive terms without icon array display of personalized outcomes. DST users were defined as those who navigated to the website and entered age and DCIS grade allowing them to access the information about expected outcomes. Users were asked to complete an optional survey both prior to use of the DST and after to assess the impact of the DST on: 1) their awareness of options for DCIS treatment, 2) their willingness to consider these options, 3) their knowledge of mortality risks associated with DCIS, and 4) how helpful the DST was to them (after use only). **Results** As of June 1, 2020, there were 420 users of the DST (total) with 362 completing the pre-tool survey and 58 of whom completed the post-tool survey. Among all DST users, mean age was 54.0 (9.6 years SD) and DCIS was low/intermediate for 72.0%, high for 18.5% and unknown for the remaining 9.5%. Among users who submitted both the pre- and post-tool survey, median time spent on the tool was 10.4 minutes. Awareness of each treatment option was high and did not change with the tool: 90% among both pre-survey and post-survey users except for bilateral mastectomy which remained at 82.9% among pre-survey and post-survey responders. Among those users who completed the pre- and post-tool surveys, the DST increased the percentage of patients who believed the chance of dying from DCIS is very low from 60.3% at baseline to 74.1% ($p<0.0001$) and reduced the median estimated numerical risk of dying from DCIS in 10 years from 9.0% at baseline to 3.0% ($p<0.0001$). A large majority of DST users found the tool very helpful or helpful (79.3% of those who responded) in making a treatment decision for DCIS. **Discussion** DCIS patients have been shown to greatly overestimate the risks of dying from breast cancer and this has been associated with increased anxiety and potential overtreatment. Our personalized online DST significantly improved knowledge about DCIS risks. Future studies of the DST should assess patient characteristics associated with knowledge gains and whether improved knowledge translates to improved patient outcomes including more patient preference and values-based treatment decisions.

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# Adherence to and patient satisfaction with the combination therapy of exemestane and everolimus in postmenopausal women with HR+ HER2- advanced breast cancer: Results from the IPSOC-mamma study

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**Background**Everolimus in combination with exemestane is indicated for the treatment of hormone receptor-positive, HER 2-neg endocrine resistant advanced breast cancer in postmenopausal women. This study investigated treatment adherence, tolerability, satisfaction and efficacy.
**Methods**A prospective, non-interventional, non-controlled, multicentric observational study assessed adherence by means of a validated questionnaire ('Morisky Medication Adherence Scale') and 'Medication Event Monitoring System' (MEMS®) data. The level of adherence was calculated per patient as percentage of days on which the medicine was taken as prescribed during the total treatment period, referred to as 'unadjusted adherence rate' (UAR). Second, MEMS® data were adjusted for
treatment interruptions according to the CRF and questionnaire data, approved by the treating physician ('adjusted adherence rate' (AAR)). Successful adherence was defined as  95% –  105%. Validated questionnaires ('Patient Satisfaction with Cancer Treatment Education', 'Cancer Treatment Satisfaction Questionnaire' (CTSQ) and 'Functional Assessment of Cancer Therapy – General' (FACT-G) were used to report patients experience and satisfaction with the treatment and perceived care, questioned at initial visit and after approximately 1, 3, 6 and 12 months. The efficacy was primary analyzed through progression free survival (PFS).
**Results**Between Dec 2015 and Nov 2017, a total of 58 women (median age 65 yrs) from 7 oncology centers were included after a mean of 34m ± 36.9 (SD) of being diagnosed with stage IV disease; most (62.1%) had ≥3 organs involved and 84.5% had ≥2 prior metastatic treatment lines. The mean follow-up duration was 185.5 ± 100.0 days. The mean UAR for exemestane, everolimus and the combination were 92.9 %, 84.8 % and 81.7 % respectively. For everolimus and the combination therapy these rates differ significantly from the mean AAR, with $p < 0.05$ (see table 1). For the AAR of the combination therapy, 13.8 % of the patients showed optimal adherence (100 %).
*Table 1. UAR and AAR for Exemestane, Everolimus and the combination*

| | *Exemestane* | *Everolimus* | *Combination therapy* |
|---|---|---|---|
| UAR (%)mean ± SD | 92.97 ± 13.17 | 84.86 ± 19.40 | 81.74 ± 20.98 |
| AAR (%)mean ± SD | 93.07 ± 13.14 | 91.81 ± 15.04 | 87.55 ± 18.17 |
| Significance differenceP-value | 0.277 | < 0.001 | < 0.001 |

Six patients (10.3%) interrupted their treatment with exemestane with a mean time of treatment pause of 34.3 ± 19.1 days. The treatment with everolimus was interrupted by 36 (62.1%), with a mean interruption time of 24.3 ± 16.5 days, which corresponds with a mean of 19.6 % ± 17.6% of the total follow-up duration. Some patients interrupted their treatment multiple times. The most common side effect was mucositis (n=26 at 1 month, of whom 8 patients grade 3 and 15 patients grade 2)). Six (10.4 %) of the 58 patients stopped treatment with everolimus and exemestane due to side effects. The median PFS was 170 days. With regard to quality of life, patients scored lowest on emotional and functional well-being. However, there were no significant differences measured for the mean FACT-G score between Day0, M1 and M3 (P = 0.273). Also, patients scored overall low on the 'CTSQ'.
**Conclusion** Despite close monitoring and preventive measures to overcome side effects, adherence to everolimus and exemestane was rather low. Many patients needed to interrupt the treatment due to side effects; treatment is perceived as intensive. Nevertheless, median PFS is 170 days, even when used late in the therapeutic journey of breast cancer patients.

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Treatment persistence of residual breast tumors through an embryonic diapause-like cancer cell state with suppressed myc activity

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Systemic breast cancer treatments often fail to achieve complete and sustained responses due to drug-persistent residual tumor foci, the “seed” for eventual relapse. Recent clinical studies have revealed that the chemo-persistent tumor cells undergo extensive transcriptional reprogramming in response to neo-adjuvant treatment; however, the impact of this acquired molecular signature on the ability of residual cancer cells to survive during therapy is not clear. To further study the molecular hallmarks of chemo-persistent cancer cells, we analyzed the transcriptional signatures of post-treatment residual tumors in a large number of breast cancer patients from several neoadjuvant clinical studies. We observed that the treatment-persistent tumor cells had a distinct cellular state which molecularly resembles that of the embryonic diapause, a dormant stage of transiently suspended development in undifferentiated epiblasts triggered by stress and induced by suppression of Myc activity and overall biosynthesis. Remarkably, the propensity for residual tumors with an embryonic diapause-like (EDL) molecular signature was significantly associated with worse outcome in breast cancer patients. To dissect this distinct cancer cell state, we developed novel *in vitro* models using 3D breast cancer organoids which responded to cytotoxic treatment by generating longitudinally-persistent residual organoid fractions that phenotypically and molecularly simulated the *in vivo* emergence of post-treatment residual tumors in preclinical and clinical settings. The treatment-persistent tumor fractions in cancer organoids and in the respective *in vivo* xenografts did not exhibit significant genetic changes compared to baseline tumor cells, but had reduced apoptotic priming and an EDL transcriptional reprograming similar to that of residual tumors in patients. Similarly to embryonic diapause, residual persistent fractions in cancer organoids, xenografts and patient tumors had markedly suppressed Myc transcriptional output and biosynthetic levels. Ectopic induction of MYC expression enhanced acute chemotherapeutic cytotoxicity in breast cancer organoids. Conversely, suppression of MYC or pharmacological inhibition of Myc transcriptional co-activators, BET bromodomains, abrogated chemotherapeutic cytotoxicity and induced in breast cancer cells an EDL molecular signature characterized by below-baseline redox stress levels which were maintained during drug exposure. High-throughput interrogation of residual persistent breast cancer organoids indicated broad refractoriness to specific anticancer drug classes thought to operate through induction of cellular stress (e.g. agents targeting DNA or DNA-repair). However, maintaining the residual cells in dormancy after completion of cytotoxic chemotherapy via inhibition of Brd4/Myc axis or pharmacologically interfering with the diapause-like transcriptional reprogramming of treatment-persistent cancer cells represent potential therapeutic strategies to target chemo-persistent tumor cells. Overall, our study shows that breast tumors dynamically co-opt the stress survival mechanism of embryonic diapause to persist during treatment, and reveals an unexpected role of Myc as regulator of cancer cell entry into transient drug-refractory dormancy. The diapause-like persister organoid cancer models provide *ex vivo* tractability for studying the otherwise elusive, dormant, drug-refractory residual tumors, with potential implications in personalized medicine and drug discovery.

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# Comparative analysis of anti-proliferative effects and gene profiling of lapatinib, neratinib, and tucatinib

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**Introduction:** Human epidermal growth factor 2 (HER2/ERBB2) is frequently amplified or mutated across various cancer types. The tyrosine kinase inhibitors (TKIs) lapatinib, neratinib, and tucatinib are FDA-approved for the treatment of HER2-positive breast cancer. All three TKIs bind and inhibit the kinase domain of HER2 but differ both in the mechanism of binding and in specificity for other HER family members. Direct comparisons to differentiate the pre-clinical efficacy of the three TKIs have been limited to small-scale studies and novel biomarkers of response to further define appropriate patient populations are required. **Methods:** In this study, the anti-proliferative effects of the three TKIs were compared using a 115-cancer cell line panel, including 12 breast cancer cell lines and 22 cell lines harbouring point mutations or amplifications of *EGFR*, *HER2*, or *HER3*. Hierarchical clustering analysis was carried out to compare the $IC_{50}$ “fingerprint” of the three TKIs to 168 other anti-cancer agents. Novel markers of TKI sensitivity and resistance were identified through cross-analysis of each drug response profile with mutation, copy number variation, and gene expression data. **Results:** All three TKIs were effective against HER2-positive breast cancer models; neratinib showed the most potent activity, followed by tucatinib and lapatinib respectively (Table 1). Neratinib displayed the greatest anti-proliferative activity in *HER2*-mutant and *EGFR*-mutant cell lines. Clustering analysis revealed that the anti-proliferative profile of tucatinib was most similar to trastuzumab, while neratinib and lapatinib were most like other HER family inhibitors. Mutation and gene expression analysis identified potential markers of response for each TKI. High expression of four genes (*HER2*, *VTCN1*, *CDK12*, and *RAC1*) correlated with response to all three TKIs. DNA damage repair genes were significantly associated with resistance to the HER2-targeted TKIs. *BRCA2* mutation was correlated with neratinib and tucatinib response, and high gene expression of *ATM*, *BRCA2*, and *BRCA1* were all associated with neratinib resistance. **Conclusions:** Neratinib was the most effective HER2-targeted TKI against *HER2*-amplified, -mutant, and *EGFR*-mutant cell lines. This analysis revealed possible mechanisms that may be exploited using combinatorial strategies involving CDK inhibitors, immunotherapies, and targeting DNA repair pathways.

Table: IC50 values for neratinib, lapatinib, and tucatinib in the HER2+ breast cancer cell lines

| | IC50 values (nM) | | |
|---|---|---|---|
| Cell lines | Neratinib | Lapatinib | Tucatinib |
| AU-565 | 20 | 294 | 125 |
| BT-474 | 59 | 262 | 29 |
| HCC1954 | 138 | 1426 | 2122 |
| MDA-MB-453 | 3062 | 2844 | 5928 |
| SKBR3 | 7 | 152 | 22 |

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# Treatment-related amenorrhea with T-DM1 plus pertuzumab (KP) is lower than with docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) in the phase III neoadjuvant KRISTINE trial

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**Background:** Cytotoxic chemotherapy (CT) in combination with trastuzumab and pertuzumab (HP) is standard of care for patients (pts) diagnosed with HER2-positive early breast cancer (EBC). While highly effective, the toxicity associated with CT is challenging. In KRISTINE/TRIO-021, neoadjuvant T-DM1 was combined with pertuzumab (KP) and compared to standard TCHP. Pts. received six cycles of neoadjuvant treatment followed by adjuvant therapy (KP or HP). Pts. in the KP arm were allowed to receive standard adjuvant CT. Pathologic complete response (pCR) rate was significantly lower with KP versus TCHP and more pts. had disease progression prior to surgery with KP, resulting in a meaningfully lower event-free survival rate vs. the control (85.3% vs 94.2%). However, 3-year invasive disease-free survival was numerically similar in both arms. Neoadjuvant KP demonstrated less toxicity than standard CT, although treatment discontinuation was higher post-surgery. Association of KP and TCHP with treatment-related amenorrhea (TRA) in premenopausal EBC pts. has not been ascertained. **Methods:** All pts. with premenopausal status at study entry (those not meeting the menopause definition based on National Comprehensive Cancer Network Guidelines v3, 2012) and with menstrual period documented within 3 months of randomization, were independently evaluated for presence or absence of TRA by two reviewers. TRA, a prespecified exploratory endpoint of KRISTINE, was defined as cessation of menstruation for ≥12 months in the absence of treatment with ovarian suppression or other interventions that can induce amenorrhea. Pts. were followed from the time of study entry through the 3-year follow up period after surgery. For cases with inconsistent determination between the two reviewers, a third reviewer adjudicated. TRA rates were calculated per arm, hormone-receptor (HR) status, adjuvant CT and age group. Proportions were compared by estimating the odds ratio (OR) and the 95% confidence interval. **Results:** Of 444 pts. enrolled, 205 were excluded based on being post-menopausal per NCCN guidelines. Of 239 pts. remaining, 56 were excluded due to insufficient data. The median age of pts. included was 40 years (range: 22-53) for TCHP and 42.5 (range: 23-52) for KP. TRA was observed in 55% (50/91) of pts. treated with TCHP compared to 30% (28/92) treated with KP (OR=2.79; 95% CI 1.52-5.12). In pts. with HR-positive EBC, TRA occurred in 62% with TCHP vs 35% for KP (OR=2.998; 95% CI 1.44-6.25). In those with HR-negative EBC, TRA was observed in 42% with TCHP vs. 21% with KP (OR=2.77; 95% CI 0.88-8.72). In the KP arm, TRA was observed in 38% (8/21) of pts. treated with standard adjuvant CT vs. 28% (20/71) of those that did not (OR 1.57; 95% CI 0.57-4.36). For women age ≤ 40, the rate of TRA was 38% with TCHP vs. 17% with KP (OR=3.00; 95% CI 1.05-8.60). For those > 40 years, TRA was observed in 74% treated with TCHP vs. 39% of those with KP (OR=4.50; 95% CI 1.88-10.73). **Conclusion:** The rate of TRA with standard TCHP is nearly double that observed with KP, suggesting that targeted CT with an antibody-drug conjugate regimen is associated with less gonadal toxicity. Rates of TRA are higher in women over the age of 40 for each treatment arm however KP is associated with lower rate of TRA in each age group. Association of TRA with efficacy outcomes (pCR, iDFS) will be presented.

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# Dynamic changes of PD-L1 and T-cell activation in ECLIPSE: A phase II study investigating preoperative immune combination strategies in untreated, operable ER+ primary breast cancer

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**Background**: Whilst Atezolizumab + nab-paclitaxel is the new standard of care in patients with PD-L1+ metastatic triple negative breast cancer (BC), the role of immunotherapy in ER+ BC has yet to be defined. ECLIPSE, an open label, phase II trial, aims to evaluate the effect of short-term pre-operative immune-modulatory agent combinations on ER+ tumour immune-phenotypes (NCT03395899). Here, we examined the first results of the dynamic changes of PD-L1 expression (≥1% positive immune cell by VENTANA PD-L1 SP142 IHC) and T-cell expansion and activation after 1 cycle of atezolizumab alone or in combination with AKT, MEK or VEGF inhibitors.
**Methods**: Patients with histologically confirmed, untreated, operable ER+/HER2- primary BC received 1 cycle of atezolizumab alone or atezolizumab + ipatasertib, atezolizumab + cobimetinib, or atezolizumab + cobimetinib + bevacizumab 3 weeks prior to surgery or neoadjuvant therapy. Biopsies were obtained pre and on completion of study treatment. Dynamic changes in biomarkers were compared in 48 evaluable patients, including 41 paired samples.
**Results**: PD-L1 IC expression significantly increased after 1 cycle of treatment ($p < 0.0001$). At a 1% IC cutoff, 21/45 patients (47%) were PD-L1 IC-positive (+) at baseline while 34/44 (77%) were PD-L1 IC + post-treatment. Increased tumour cell expression was also found in post-treatment samples ($p < 0.01$). All post-treatment PD-L1 negative patients ($n = 9$) were also negative at baseline. Overall, there was a small but significant increase in CD8 + T-cells post-treatment compared to baseline ($p = 0.03$). In parallel, the number of T-cells that were positive for both CD8 and granzyme B (GZMB) - a T-cell activation marker - increased substantially ($p < 0.01$). Single GZMB+ cells and single FOXP3+ cells did not change with treatment. In 2 cases, no tumour was detected post-treatment, suggesting a major pathological response. Baseline biopsies of both patients stood out as having the largest amount of CD8+GZMB+ T-cells. Post-treatment tumour bed profiling of these patients showed major infiltration of CD8+ and CD8+GZMB+ T-cells. Dynamic gene expression analysis showed upregulation of genes related to innate immunity and a cytotoxic T-cell transcriptional signature (tGE8), ($p < 0.001$). Patients were grouped as immune-responsive or non-responsive based on a dynamic increase of CD8+GZMB+ cells. The immune-response group was characterized by increased IFN response signatures and decreased luminal gene signatures at baseline.
**Conclusions**: Our data indicate that short-term induction treatment with atezolizumab ± targeted treatments induce dynamic changes toward inflamed immune phenotypes both at the morphological and transcriptional level, in patients with operable ER+/HER2- primary BC. These findings might help identify novel immunotherapy combination strategies in this setting, alongside the most appropriate biomarkers that can aid in identifying patients most likely to benefit from these treatments.

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Assessing prognosis after neoadjuvant therapy: A comparison between anatomic ypAJCC staging, residual cancer burden class and neo-bioscore

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**Background:** Pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) in patients with breast cancer is associated with improved survival. Further assessment of the extent of residual disease, using the pathological anatomic American Joint Committee on Cancer staging method (ypStage) or the Residual Cancer Burden (RCB) method, have been shown to add prognostic information for patients with residual disease. Neo-Bioscore, an alternate system to classify response to NAC, includes clinical stage at diagnosis and biology and defines eight prognostic groups. The goal of this study was to compared three scoring systems (anatomic ypStage ($7^{th}$ ed), RCB Class and Neo-Bioscore) and assess whether RCB Class and Neo-Bioscore provide additional prognostic value in the context above anatomic ypStage, the most commonly used method for post-neoadjuvant residual disease assessment. **Methods:** Data from 5161 patients treated with NAC was pooled from 12 sites. Patients without clinical and pathological staging were excluded, as were patients with HER2+ breast cancer who did not receive neoadjuvant HER2-targeted therapy, leaving 3730 for analysis. PCR was defined as no residual invasive tumor in breast and nodes, i.e. RCB-0 or ypT0/Tis and ypN0. Patients with discordant pCR status by RCB Class vs ypStage (n=9) were excluded. Associations between each scoring system and event-free survival (EFS) were evaluated using the log rank test. EFS at 5 years was estimated using the Kaplan Meier method. Associations between Neo-Bioscore and EFS were assessed in the pCR group. For patients with residual disease, we assessed RCB and Neo-Bioscore within each ypStage. Analysis was performed overall and within subtype. Subgroups with <5 patients were excluded from the survival analyses. **Results:** ypAJCC staging, RCB class and Neo-Bioscore were all associated with EFS in the overall population and within each subtype (log rank p<0.0001). Of note, 13 patients with a Neo-Bioscore of 7 all recurred or died within 19 months of follow-up. Overall, 34% (1264/3721) of patients achieved a pCR. Their Neo-Bioscore ranges from 0-5, where 3% (37/1264) has a Neo-Bioscore of 5 despite achieving pCR. The Neo-Bioscore was not associated with EFS in case of a pCR, with EFS estimates at 5 years of 95%, 94%, 92%, 93%, 90% and 92% for Neo-Bioscores 0-5 respectively. As HR and HER2 status are components of the score, the range of Neo-Bioscore in the pCR group differs by subtype. However, similar to the overall analysis, the Neo-Bioscore was not prognostic within subtypes in case of pCR. Overall, among the patients who did not achieve pCR, both RCB class and Neo-Bioscore were associated with EFS within ypStages I, II and III. However, the ypStage within which RCB and Neo-Bioscore are prognostic is different for each subtype. RCB class was prognostic in ypStage I in both HR+ subtypes: patients with ypStage-I/RCB-I had significantly improved survival compared to patients with ypStage-I/RCB-II (5-year EFS: 100% vs 83% in HR+HER2- and 95% vs 77% in HR+HER2+). In contrast, for patients with triple negative breast cancer, RCB class was prognostic within ypStage II and III. Analysis by clinical stage and the components of the three systems that contribute most to prognosis will be presented. **Conclusions:** The degree of response to NAC adds important information to pCR versus residual disease. The Neo-Bioscore was not prognostic among patients with pCR, suggesting that clinical stage (including subtype and grade) adds little information in the setting of a pCR. In contrast, both RCB and Neo-Bioscore provide additional prognostic information to the conventional ypAJCC staging among non-pCR patients, suggesting that clinical stage, tumor biology as well as extent of residual disease all contribute to prognosis in the setting of residual disease after NAC.

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# The detection and enumeration of circulating tumor cells (CTCs) and circulating endothelial cells (CECs) in metastatic breast cancer

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**Introduction:** Circulating tumor cells (CTCs) are the roots of metastasis which is the main cause for death in metastatic breast cancer (MBC). CTCs enumeration is strongly prognostic in advanced disease and can stratify patients in two distinct disease, Stage IV $_{aggressive}$ and Stage IV $_{indolent}$. In the former disease, the detection of CTC clusters and HER2-expression increase prognostic and predictive value. The metastatic cascade is a complex, regulated process involving immune cells and endothelial cells for progression and neoangiogenesis. Circulating endothelial cells (CECs) from the inner wall of blood vessels are shed into the blood stream during formation of blood vessels which is considered a sensitive marker of endothelial damage in pathological conditions such as cancer. CECs have been also studied as a biomarker for tumor progression and monitoring anti-angiogenic therapeutic effects in MBC. We evaluated the concomitant detection of CTCs and CECs in MBC patients, along with expression of HER2 in CTCs that may offer an interesting clue to elucidate the metastasis mechanisms. **Methods:** Whole blood samples (7.5ml/each) were collected from 14 stage IV MBC patients before systemic therapy. CTCs enumeration was performed in FDA approved CELLTRACKS System (Menarini) by using CTC Kit contains specific antibodies targeting the EpCAM for capturing CTCs, anti-CK-PE (for epithelial cells), DAPI (for nucleus), anti-CD45$^-$APC (for leukocytes), and anti-HER-2/neu-FLU. The CTCs were classified as CK$^+$, EpCAM$^+$, DAPI$^+$ and CD45$^-$. Meanwhile, the same patients' blood samples (4.0ml/each) were processed for CEC analyzed by using CEC kit which immunomagnetically captures CD146$^+$ cells, and then stains the cells for CD105-PE (specific for protein endolgin), CD45-APC, nucleus-DAPI. The positive CECs were classified as CD 146$^+$, CD105$^+$, DAPI$^+$ and CD45$^-$. The associations between CTCs, HER2 expression and CECs were evaluated. **Results:** The average age of patients was 53.1. Subtypes of Luminal, HER2 positive and TNBC were 64.2% 7.2% and 28.6% respectively. Distant metastasis were found in 13 out of 14 patients, including bone (7), liver (5), Lymph nodes (5) and Pleura (2). CTCs were found positive (≥5, Stage IV $_{aggressive}$) in 5 patients (range: 5-47, mean=24), and HER expression was identified in all 5 of these cases with a range of numbers between 1 and 7 (mean=4.2). The ratios of HER$^+$ CTC/total ratios were 8.51%, 17.95%, 20%, 30.77%, and 33.33%. HER2 expression were defined officially in our lab according to the percentile of positive HER2 CTCs/Total CTCs and the expression intensity as - (<20%), + (20-39%), ++ (40-59%) and +++ (≥60%) respectively. There were 9 patients (%) were identified as CTCs negative (<5, Stage IV $_{indolent}$) with the mean=1, and HER$^+$ CTCs were found in only 2 patients with Stage IV $_{indolent}$. Meanwhile, CECs were found in all 14 patients with a range of numbers between 4 to 115. There were an average of 33 CECs in Stage IV $_{aggressive}$ disease, compared to 53 CECs in Stage IV $_{indolent}$. The average of CECs were 53.44, 12 and 37.25 in Luminal, HER2 positive and TNBC groups respectively. On the other hand, patients with HER2$^+$ CTCs had an average of 50 CECs which is significantly higher than average of 41 CECs in patients without HER2$^+$ CTCs. Moreover, there were average of 94.5, 56 and 40.22 CECs were found in groups when HER2 expression was ++/+++, above + and - respectively. The results demonstrated that although CTC enumeration have a reverse correlation with CECs numbers, HER2 expression in CTCs was significantly related with high CECs numbers. **Conclusions:** Our data provides the first evidence of potential association between CTCs and CECs in metastatic breast cancer. The association between HER2 expression and CECs offers a potential new insight to mechanism connections between CECs and disease metastasis in MBC.

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# Exploring the causal role of the human gut microbiome in breast cancer risk using mendelian randomization

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Background: Variation in the human gut microbiome may influence cancer progression and therapy response through various mechanisms including modulation of both immune and cell signalling pathways. Whilst observational epidemiological studies have provided evidence that the gut microbiome may play a role in cancer risk, such studies are prone to residual confounding, reverse causation, and other forms of bias. Therefore, the nature of these associations still remains unclear. Mendelian randomization (MR) is a causal methodology that uses genetic variants as instruments (“proxies”) for risk factors to eliminate such biases when questioning causality in observational epidemiological associations. The statistical power and precision of MR analyses can be increased by employing a “two-sample MR” (2SMR) framework in which summary data – usually from large, independent, genome-wide association studies (GWASs) reporting associations of genetic variants with exposures (here, the gut microbiome) and outcomes (here, cancer) – are synthesised to estimate causal effects of each exposure on each outcome of interest. In this study, we utilised 2SMR to interrogate causal relationships between the gut microbiome and breast cancer (BC) risk using the largest published GWASs of the gut microbiome and of clinically utilised subtypes of BC.
Methods: We performed 2SMR using summary-level data from the GWAS of the host genetic contribution to gut microbiome variation amongst European individuals (the Flemish Gut Flora Project and two German cohorts (n=3890)) combined with summary-level data from the GWAS of BC risk (Breast Cancer Association Consortium (133,384 cases stratified by Luminal A, Luminal B, Human Epidermal Growth Factor 2 (Her2) positive, Her2 negative and triple negative status and 113,789 controls, plus 18,908 BRCA1 mutation carriers (9,414 with BC)). Sensitivity analyses were also conducted to assess pleiotropy of genetic variants on BC risk, independent of gut microbiota. Analyses were conducted in R Studio using the TwoSampleMR and the MR-TRYX packages.
Results: Of the 14 microbial traits (MTs) with evidence for a host genetic contribution in the GWAS of the gut microbiome, we found evidence that abundance of a genus within a certain bacterial order decreased the risk of triple negative BC (odds ratio per standard deviation increase: 0.84; 95% CI: 0.71, 0.9; p=0.03). In addition, we demonstrated that the risk of all molecular subtypes of BC may be altered by variation in these MTs, and that these relationships differed according to subtype. Sensitivity analyses demonstrated that pleiotropy was unlikely to explain these relationships
Conclusions: In our study, we utilised two recent and novel GWASs in an MR context to appraise causality in relationships between the gut microbiome and BC risk and found evidence that certain bacteria may alter BC risk, effects of which vary according to molecular subtype. These important results generate hypotheses about mechanisms underlying the causal biology of BC subtypes and potentially facilitate the design of BC risk-reducing interventions and prevention strategies.

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# How often does retrieval of a clipped lymph node change adjuvant therapy recommendations? A prospective consecutive patient cohort

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Objectives and Rationale: For breast cancer patients receiving neoadjuvant chemotherapy (NAC) and undergoing pre-NAC axillary lymph node biopsy, NCCN guidelines recommend biopsy marker (clip) placement. This recommendation is based on reports that retrieval of the clipped node after NAC minimizes the false negative rate of sentinel lymph node biopsy (SLNB). Prior studies examining this practice in cN1 patients have reported that the clipped node is a non-SLN 20% of the time. There is limited data regarding if the clipped node needs to be retrieved among cN0 patients, and how often the post-NAC pathologic status of the clipped node has potential to change adjuvant therapy decisions. Here we aim to determine: 1) how often the clipped node is a non-SLN among both cN0 and cN1 patients, and 2) how often the retrieved, clipped node is a non-SLN and is the only positive node after NAC, potentially impacting adjuvant treatment recommendations.
Methods: A consecutive cohort of 147 patients treated with NAC and surgery at our institution between January 2019-May 2020 was prospectively examined. Prior to NAC, all patients underwent routine axillary ultrasound (AxUS). For those with an abnormal appearing node, biopsy was performed of the most suspicious lymph node and a clip was placed. All cN0 patients underwent SLNB without localization of the clipped node. Patients who converted from cN1 to cN0 underwent radioactive seed localization of the clipped node and SLNB with dual tracers (radioactive tracer and blue dye). All lymph nodes were analyzed by IHC. Any residual disease, including ITCs, was considered pathologic node positive (ypN+). Patients with DCIS/unknown breast tumor histology (N = 3), those without AxUS (N = 9), those treated with neoadjuvant endocrine therapy (N = 9) and cN1 patients without a clip (N = 2) were excluded. Descriptive analyses were performed to examine the rate of ypN+ disease among cN0 and cN1 patients, and how often the clipped node was a non-SLN containing residual disease. In the cN0 population, if the clipped node was not obtained during SLNB it was considered a non-SLN.
Results: Of 124 patients meeting study criteria, 61 were cN0 and 63 cN1. Among cN0 patients, 21 (34%) had suspicious lymph nodes on AxUS which were biopsied (negative) and clipped. All cN0 patients underwent successful SLNB, with a median of 2 SLNs removed (range 1-10). Of these, 5 (8%) were ypN+. Of the 21 patients with clipped nodes, 14 (67%) of the clipped nodes were non-SLN. If <3 SLNs were sampled, the clipped non-SLN rate was 82% (9/11). If ≥3 were sampled, the clipped non-SLN rate was 50% (5/10). Among patients with clipped nodes and ypN+ disease, there were no cases in which the clipped node was the only positive node.
Among 63 cN1 patients with clipped nodes, 55 (87%) converted to cN0 and underwent SLNB. SLNB was successful in 52/55 (95%) and a median of 3 SLNs were removed (range 1-8). Overall, 28/55 (51%) were ypN+. Of the 52 with successful SLNB, 15 (29%) of the clipped nodes were non-SLN. If <3 SLNs were sampled, the clipped non-SLN rate was 46% (6/13). If ≥3 were sampled, the clipped non-SLN rate was 23% (9/39). In one of 52 (2%) patients, the clipped non-SLN was the only positive node.
Conclusions: In this prospective study, among cN0 patients with negative pre-NAC lymph node biopsies, the clipped node was frequently a non-SLN and pathologic status of the clipped node alone did not impact management. Among cN1 patients suitable for SLNB after NAC, although the clipped node was a non-SLN 29% of the time, it was the only positive node in only one patient. The finding that the post-NAC pathologic status of the clipped lymph node alone potentially changed adjuvant treatment recommendations in only 2% (1/52) of patients warrants further investigation.

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# Alpelisib + letrozole in patients with *PIK3CA*-mutated, hormone-receptor positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) + fulvestrant: BYLieve study results

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**Introduction:** Mutations in *PIK3CA,* which encodes the α-isoform of phosphatidylinositol 3-kinase (PI3Kα), occur in ~40% of patients (pts) with HR+, HER2- ABC and can contribute to endocrine resistance. Alpelisib (ALP), a PI3Kα-selective inhibitor and degrader, plus fulvestrant (FUL) demonstrated efficacy in the phase 3 SOLAR-1 trial, which included 20 pts who had prior CDK4/6i in the *PIK3CA*-mutant cohort. Limited clinical data are available in the post-CDK4/6i setting for *PIK3CA*-mutated, HR+, HER2- ABC. BYLieve (NCT03056755), an ongoing phase 2, multicenter, open-label, 3-cohort noncomparative study, is the first trial evaluating ALP + endocrine therapy (FUL or letrozole [LET]) in pts with *PIK3CA*-mutated, HR+, HER2- ABC who progressed on/after prior therapy, including CDK4/6i. In the prior CDK4/6i + aromatase inhibitor (AI) cohort (Cohort A), pts received ALP + FUL. With median follow-up of 11.7 months (mo), the primary endpoint in Cohort A was met—50.4% of pts were alive and without disease progression (PD) at 6 mo per local investigator assessment (n=61; 95% CI, 41.2%-59.6%). Median progression-free survival (mPFS) was 7.3 mo (n=72; 95% CI, 5.6-8.3 mo); AEs were consistent with prior observations. Now, we report on the cohort of pts who received a CDK4/6i + FUL as immediate prior therapy before enrollment (Cohort B). **Methods:** Daily oral treatment in Cohort B consisted of ALP 300 mg + LET 2.5 mg. Each cohort planned to enroll at least 112 pts with centrally confirmed *PIK3CA* mutation, based on immediate prior treatment of either a CDK4/6i + AI (Cohort A), a CDK4/6i + FUL (Cohort B), or systemic chemotherapy or endocrine therapy (which may also include prior CDK4/6i + FUL; Cohort C, follow-up ongoing). The primary endpoint, the proportion of pts with centrally confirmed *PIK3CA* mutation alive without PD at 6 mo per local investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, is assessed for each cohort separately and is met if the lower bound of the 95% CI is >30%. Men and premenopausal women were allowed goserelin 3.6 mg subcutaneously or leuprolide 7.5 mg intramuscularly every 28 days. **Results:** 126 pts whose immediate prior treatment was CDK4/6i + FUL were enrolled into Cohort B: 115 had centrally confirmed *PIK3CA* mutations. Median follow-up was 15.0 mo (range, 1-31 mo); 58 (46.0%) had ≥2 lines of prior therapy in the metastatic setting, and 103 (81.7%) pts progressed on prior AI therapy. The primary endpoint was met with 46.1% (95% CI, 36.8%-55.6%) of pts alive without PD at 6 mo. mPFS was 5.7 mo (95% CI, 4.5-7.2 mo). The most frequent all-grade AEs (≥25%) were diarrhea (67.5%), hyperglycemia (63.5%), nausea (54.8%), decreased appetite (44.4%), stomatitis (34.1%), fatigue (31.0%), rash (31.0%), and vomiting (24.6%). Most frequent grade ≥3 AEs included hyperglycemia (25.4%), rash (9.5%), and rash maculopapular (7.9%). Incidence of AEs leading to treatment discontinuation was 14.3% (n=18); most frequent AEs leading to discontinuation were rash (4 pts, 3.2%, including rash maculopapular), fatigue, and diarrhea (3 pts, 2.4% each). **Conclusion:** Alpelisib in combination with LET following progression on FUL + CDK4/6i and prior AIs was effective in this noncomparative trial. Consistent with the known safety profile of alpelisib, manageable toxicities were observed. These data suggest that alpelisib in combination with LET may be an effective treatment option for pts with *PIK3CA*-mutated, HR+, HER2- ABC in the post-CDK4/6i setting.

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# Clinical behavior and outcomes of *BRCA*-mutated breast cancer in young patients according to type of *BRCA* mutation and hormone receptor status: Results from an international cohort study

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**Background:** Young breast cancer patients (pts) carrying a germline *BRCA* mutation (*mBRCA*) have similar outcomes as non-carriers. However, there is currently lack of evidence regarding the impact of *mBRCA* type and hormone receptor status on clinical behavior and outcomes of *mBRCA* breast cancer. We aim to address these questions in the largest dataset to date of young *mBRCA* breast cancer pts.
**Methods:** This was an international, multicenter, hospital-based, retrospective cohort study. Women harboring deleterious germline *mBRCA1* or *mBRCA2* that received a diagnosis of stage I-III invasive early breast cancer at age ≤40 years between January 2000 and December 2012 were included. Baseline pts, tumor, and treatment characteristics, pattern and risk over time of disease-free survival (DFS) events, and survival outcomes (DFS, distant recurrence-free interval [DRFI] and overall survival [OS]) were compared between *mBRCA1* and *mBRCA2* pts overall and by hormone receptor status. Multivariate Cox proportional hazard models were used to compare hazard rates (HRs).
**Results:** 1,236 young *mBRCA* breast cancer pts were included. Among 808 and 428 pts with *mBRCA1* or *mBRCA2,* respectively, 191 (23.6%) and 356 (83.2%) had hormone receptor-positive tumors while 617 (76.4%) and 72 (16.8%) hormone receptor-negative disease (p<0.001). Compared to *mBRCA2* breast cancer pts, those with *mBRCA1* were younger, more likely to have reported Jewish ancestry, had more grade 3 tumors, less nodal involvement, lobular histology and HER2 positivity, and received more frequently chemotherapy (all p<0.001). More *mBRCA1* pts with hormone receptor-positive tumors did not receive adjuvant endocrine therapy (14.7% vs. 4.2%, p<0.001). No difference between *mBRCA1* and *mBRCA2* pts was observed in risk-reducing mastectomy (43.9% vs. 46.0%; p=0.371) or salpingo-oophorectomy (48.3% vs. 48.8%; p=1.0). Median follow-up was 7.9 years (range 5.6-10.6 years). Second primary breast cancers (17.0% vs. 12.2%, p=0.025) and non-breast primary malignancies (4.3% vs. 1.9%, p=0.033) were more frequent among *mBRCA1* pts compared to *mBRCA2* pts, while distant recurrences were less frequent (10.4% vs. 15.4%, p=0.013). 8-year DFS was 62.8% and 65.9% for *mBRCA1* and *mBRCA2* pts, respectively (adjusted HR 0.76; 95% CI 0.60-0.96). The worse DFS in *mBRCA1* was observed regardless of hormone receptor status ($p_{interaction}$=0.848): hormone receptor-positive (adjusted HR 0.77; 95% CI 0.58-1.03) and hormone receptor-negative (adjusted HR 0.73; 95% CI 0.48-1.13). No differences in DRFI and OS were observed between *mBRCA1* and *mBRCA2* pts. Compared to pts with hormone receptor-negative disease, those with hormone receptor-positive breast cancer had higher chances of developing distant (± loco-regional) recurrences (16.1% vs. 9.0%; p<0.001) and less frequent second primary malignancies (BC: 12.1% vs. 17.9%, p=0.005; non-BC: 2.8% vs. 4.0%, p=0.216). No differences in DFS and OS were observed between pts with hormone receptor-positive or negative breast cancer. However, there was a trend towards worse DRFI in women with hormone receptor-positive breast cancer as compared to those with hormone receptor-negative disease (8-year DRFI: 83.4% vs. 90.1%; adjusted HR 1.39; 95% CI 0.94-2.05).
**Conclusions:** In this large unique dataset, young *mBRCA1* breast cancer pts had worse DFS than those with *mBRCA2* mostly due to higher rates of second primary malignancies. Hormone receptor positivity had no positive prognostic value in young *mBRCA* breast cancer pts with a trend towards worse DRFI in those with hormone receptor-negative disease. These results provide important information for counseling young *mBRCA* breast cancer pts regarding treatment, prevention and follow-up care strategies.

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# Prospective testing for *PIK3CA/AKT1/PTEN* alterations in tumor tissue from 1440 patients with advanced hormone receptor-positive HER2-negative breast cancer (HR+/HER2**-** BC) or triple-negative breast cancer (TNBC) screened for the IPATunity130 randomized phase 3 trial

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**Background** The PI3K/AKT signaling pathway plays a significant role in both HR+ BC and TNBC. IPATunity130 is a double-blind, placebo-controlled, randomized phase 3 trial of ipatasertib in combination with paclitaxel in patients with *PI3K/AKT1/PTEN*-altered HR+ or TNBC. A next-generation sequencing (NGS)-based assay from Foundation Medicine Inc. (FMI) was used to select patients prospectively for enrollment in this trial.**Patients and methods** An investigational clinical trial assay (CTA) of a composite 3-gene biomarker signature [Kim, Lancet Oncol 2017] based on the FoundationOne® CDx assay was used to identify patients with PI3K/AKT pathway-activated tumors as eligible for enrollment in IPATunity130 (NCT03337724). Qualifying alterations for the 3-gene signature (referred to as 'biomarker-positive') comprised activating mutations in *PIK3CA* and/or *AKT1*, and/or loss of function (LOF) alterations in *PTEN* represented by homozygous or heterozygous deletions, dominant-negative mutations, or inactivating mutations under loss of heterozygosity. Study sites were required to submit formalin-fixed paraffin-embedded archival or fresh biopsy tissue derived from primary or metastatic tumors for patient screening. IPATunity130 includes three independent cohorts: Cohort A (biomarker-positive TNBC); Cohort B (biomarker-positive HR+/HER2– BC); and Cohort C (biomarker-negative TNBC). **Results** In total, 1736 patients were screened, from whom 1690 samples were tested by FMI. Of these, 1475 (87%) produced a valid NGS result. The remaining 215 (13%) failed quality control for reasons including insufficient tissue, DNA yield, lab error, and computational failure. Alteration status for *PIK3CA* and/or *AKT1* and/or *PTEN* was positive in 703 (49%) of 1440 CTA-evaluable samples. In the HR+/HER2– cohort, the breakdown of CTA-positive samples was 301/356 (85%) *PIK3CA/AKT1* mutations and 86/356 (24%) *PTEN* LOF alterations. In TNBC, 183/347 (53%) had *PIK3CA/AKT1* mutations and 193/347 (56%) had *PTEN* LOF alterations. CTA results according to baseline characteristics are shown overall and by subtype below.

| Subgroup | | *PIK3CA/AKT1/PTEN* alteration, n/N (%) | | |
|---|---|---|---|---|
| | | Overall | HR+/HER2– | TNBC |
| All patient samples | | 703/1440 (49) | 356/647 (55) | 347/793 (44) |
| Age, years | ≤50 | 219/475 (46) | 99/195 (51) | 120/280 (43) |
| | >50 | 484/965 (50) | 257/452 (57) | 227/513 (44) |
| Sample source | Primary | 456/941 (48) | 232/414 (56) | 224/527 (43) |
| | Metastatic | 222/448 (50) | 112/213 (53) | 110/235 (47) |
| Geographic region | North America | 60/102 (59) | 33/49 (67) | 27/53 (51) |
| | Asia-Pacific | 172/330 (52) | 81/145 (56) | 91/185 (49) |
| | Europe | 301/633 (48) | 171/310 (55) | 130/323 (40) |
| | Rest of world | 170/375 (45) | 71/143 (50) | 99/232 (43) |

The most common mutations detected outside the 3-gene biomarker signature in the screened population were in the *TP53*, *BRCA1*, *RB1*, *BRCA2*, and *NF1* genes in the TNBC cohort and the *TP53*, *GATA3*, *CDH1*, *MAP3K1*, and *ESR1* genes in the HR+/HER2– cohort. In the HR+/HER2– cohort, 30 (14%) of 213 metastatic tumors had *ESR1* mutations compared with 10/414 (2%) primary tumors. Tumor *BRCA1* mutations were more common in patients aged ≤50 years whereas *MAP3K1* mutations were more common in those aged >50 years.**Conclusions** IPATunity130 is the first reported pivotal trial to utilize the 3-gene biomarker CTA in HR+/HER2– BC and TNBC to screen for patients with PI3K/AKT pathway-activated tumors. The 3-gene biomarker CTA detected alterations in 49% of screened patients, with a higher prevalence of *PIK3CA/AKT1/PTEN* alterations in HR+/HER2– BC than TNBC. Additional analyses are planned to assess correlations between clinical outcomes and tumor characteristics.

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# Incidence and survival of inflammatory breast cancer between 1973 - 2015 in the surveillance, epidemiology and end results (SEER) database

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PurposeInflammatory breast cancer (IBC) is a rare and aggressive variant of breast cancer characterized by erythema, edema, and “peau d’orange” of the breast progressing within six months. We assessed the incidence and survival of IBC in the US currently, compared to historical results.
MethodsUsing SEER*Stat, a case list of IBC patients diagnosed between 1973-2015 (n = 29,718) was extracted from the SEER 18 registries by defining IBC using a combination of morphology, stage, and extent of disease criteria. Age-adjusted incidence rates, relative survival rates, and mean survival time were calculated. Significance was determined as non-overlapping 95% confidence intervals.
ResultsThe overall incidence of IBC from 1973 - 2015 is 2.76 (2.73, 2.79) cases per 100,000 people, with white patients having an incidence rate of 2.63 (2.60, 2.67), black patients 4.52 (4.39, 4.65), and patients of other race 1.84 (1.76, 1.93). The relative rate of 5-year survival for IBC patients as a whole is 40.5% (39.0%, 42.0%), with white patients having a rate of 42.5% (40.7%, 44.3%) and black patients’ survival rate 29.9% (26.6%, 33.3%) (**see Table 1**). White patients diagnosed in 1988-1992 have a mean survival time of 81.9 (53.5, 110.3) months, while those diagnosed in 2008-2012 have mean survival time of 101.9 (90.0, 113.7) months. In contrast black patients diagnosed in 1988-1992 have a mean survival time of 48.5 (37.5, 59.4) months, while those diagnosed in 2008-2012 have mean survival time of 84.3 (77.2, 91.4) months (**see Table 2**).
ConclusionsOur results suggest that IBC survival has moderately increased in recent years. However, despite the overall improvement in survival for all racial groups, there remains a persistent survival disparity between white and black patients that has not narrowed over two decades. Further research is urgently needed to understand and address this disparity.

**Table 1:** Relative Survival Rates for inflammatory breast cancer by race, %(95% CI). “Cohort”: cohort analysis, “Period”: period analysis. Significance relative to black patients, determined by non-overlapping 95% CI calculated via the Greenwood method and demonstrated by * for cohort and $^{+}$ for period analysis.

| | | **5-year** | **10-year** | **15-year** | **20-year** |
|---|---|---|---|---|---|
| Black | Cohort | 29.8 (26.7, 32.9) | 14.8 (10.9, 19.4) | 10.4 (5.0, 18.1) | 3.7 (0.7, 11.2) |
| | Period | 29.9 (26.6, 33.3) | 18.4 (15.2, 21.8) | 16.7 (12.9, 20.9) | 16.2 (9.1, 25.1) |
| White | Cohort | 44.0* (42.4, 45.7) | 30.6* (28.2, 33.0) | 22.1* (18.8, 25.6) | 17.5* (13.4, 22.0) |
| | Period | 42.5$^{+}$ (40.7, 44.3) | 30.7$^{+}$ (28.9, 32.5) | 25.1$^{+}$ (22.7, 27.5) | 22.1 (19.2, 25.2) |
| Other | Cohort | 46.8* (41.5, 51.8) | 26.3 (18.5, 34.7) | 19.1 (10.3, 29.9) | 14.1 (3.8, 31.0) |
| | Period | 43.6$^{+}$ (38.0, 49 .0) | 32.6$^{+}$ (26.7, 38.7) | 30.5 (22.8, 38.6) | 26.9 (18.3, 36.3) |
| All | Cohort | 41.9* (40.5, 43.3) | 28.0* (25.9, 30.0) | 21.3* (18.3, 24.4) | 15.6* (12.1, 19.5) |
| | Period | 40.5$^{+}$ (39.0, 42.0) | 28.9$^{+}$ (27.4, 30.4) | 24.0$^{+}$ (22.0, 26.1) | 21.5 (18.9, 24.2) |

**Table 2:** Mean Survival Months by Race Before and After Imputation Using Cox Model Adjusted for Age and Race (95% CI). Significance relative to white patients, determined by non-overlapping 95% CI and demonstrated by *.

| | **Mean Survival Time (Months)** | | | |
|---|---|---|---|---|
| | African American | | White | |
| Year | Unadjusted | Adjusted | Unadjusted | Adjusted |
| 1988-1992 | 46.4* (37.4, 55.4) | 48.5 (37.5, 59.4) | 71.3 (65.9, 76.7) | 81.9 (53.5, 110.3) |
| 1993-1996 | 49.1* (41.8, 56.4) | 61.0 (48.2, 73.8) | 68.1 (64.6, 71.6) | 86.1 (59.0, 113.2) |
| 1997-2002 | 47.4* (43.7, 51.2) | 63.8* (55.3, 72.3) | 64.8 (62.9, 66.7) | 99.8 (81.0, 118.7) |
| 2003-2007 | 41.0* (39.5, 42.5) | 72.1* (66.6, 77.7) | 49.9 (49.1, 50.6) | 98.2 (86.8, 109.6) |
| 2008-2012 | 25.7* (24.8, 26.4) | 84.3 (77.2, 91.4) | 28.7 (28.2, 29.1) | 101.9 (90.0, 113.7) |

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Humanized anti-CD47 monoclonal antibody magrolimab (Hu5F9-G4) plus trastuzumab potentiates antibody-dependent cellular phagocytosis (ADCP), and cooperate to inhibit human HER2+ breast cancer (BC) xenografts growth *in vivo*

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**Background:** Cancer cells overexpress CD47 to evade phagocytic programmed cell removal (PrCR) by macrophages of the innate immune system. Blocking CD47 using magrolimab (Hu5F9-G4), an anti-CD47 humanized monoclonal antibody, works via preventing CD47 signaling via macrophage Sirpα to allow PrCR, as well as using an Fc-receptor mechanism to encourage macrophage-mediated phagocytosis. We have previously shown that magrolimab in combination with tumor-targeting antibodies (e.g. rituximab) further enhances magrolimab's anti-cancer effects in preclinical models and in the clinic [Advani R, et al. N Engl J Med 2018; 379:1711-1721]. We therefore hypothesized that magrolimab combined with anti-HER2 monoclonal antibody would synergize to promote ADCP *in vitro*, and HER2+ breast xenograft growth inhibition *in vivo*. **Methods:** To test this hypothesis, 1 x $10^5$ CFSE-labeled HER2+ BT474 and SKBR3 cells were plated in 96-well ultra-low attachment plates in serum-free media. Isotype control antibody, trastuzumab, magrolimab, and trastuzumab + magrolimab combination (10µg/ml) were added, and allowed to incubate at 37°C for 30 mins. 5 x $10^4$ human macrophages were then added each well, and were co-cultured for 2 hours. Human macrophages were stained with anti-CD11b, and phagocytosis was determined as the percentage of cells that were CD11b+ and CSFE+ using a BD LSR Fortessa Analyzer. For *in vivo* tumor xenograft growth kinetics, GFP+/Luciferase+ BT474 cells (1X$10^5$) were implanted with 25% Matrigel into the mammary fat pads of 4-8 week-old NOD scid gamma (NSG) female mice. Twenty-five days after engraftment, trastuzumab (100ug) was administered via intraperitoneal (IP) injection weekly, magrolimab 250ug IP was administered every other day, and PBS control was administered IP at 100uL once weekly, and tumor growth was monitored for 17 weeks by bioluminescence (IVIS) after D-luciferin injection, and quantified using Image 4.0. **Results:** SKBR3 and BT474 parental and Trastuzumab-resistant lines demonstrated significantly increased susceptibility to ADCP when opsonized with combination treatment of trastuzumab + magrolimab (15.34, 95%CI= 12.2 to 16.6) compared to trastuzumab (9.66, 95%CI=1.861 to 7.7579, p = 0.034), or magrolimab alone (10.23, 95%CI=1.254 to 7.037, p = 0.0083). Treatment with magrolimab maintained tumor burden within the starting range but further progressed upon treatment cessation (2.09x$10^9$, CI95% = 2801531434 to 15343840962, p = 0.0006). Trastuzumab treatment resulted in lower starting range tumor burden, but also demonstrated progression once treatment was stopped (1.72x$10^6$, CI95% = -695208489 to -86402608, p = 0.0052). However, in the combinatorial treatment arm, tumors were significantly below the starting range and did not show signs of tumor progression within the 10-week non-treatment period (8.51x$10^5$, CI95%= -311406356 to -66914472, p = < 0.0001). **Conclusion:** We conclude magrolimab plus trastuzumab cooperate to inhibit HER2+ xenograft growth *in vivo*, and that treatment effect persists even after treatment is stopped. Our e*x vivo* data suggests one mechanism to explain the observed tumor growth inhibition is increased susceptibility to ADCP when HER2+ tumors are opsonized by the combination of trastuzumab + magrolimab. Future clinical translation of this combination is warranted.

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Comparison of liquid biopsy and tissue based detection of*PIK3CA*mutations in HR positive metastatic breast cancer patients

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The treatment of hormone receptor positive metastatic breast cancer patients has changed dramatically over the last few years and combination strategies attempting to overcome resistance of the disease are gaining importance. After introducing CDK 4/6 inhibitors in the treatment one of the subsequent strategies is definitely targeting PI3 kinase pathway. Several drugs have been tested, but only recently, SOLAR-1 phase III trial demonstrated the benefit of adding alpelisib to fulvestrant, with acceptable tolerability. With this trial the importance of *PIK3CA,* testing was postulated. In the present study a comparison of liquid biopsy and tissue-based detection of *PIK3CA* mutations in HR positive metastatic breast cancer patients was performed. **Materials and Methods**: Plasma and the most recent tumor tissue were screened for *PIK3CA* hotspot mutations from 58 patients with metastatic hormone-receptor positive breast cancer. For plasma samples, SiMSen-Seq NGS sequencing was used covering 11 frequent *PIK3CA* mutations, which were applied for stratification in SOLAR-1. Only plasma samples with variant allele frequency (VAF) >1% were considered as positive. For tumor tissue samples, targeted Ion Torrent NGS was used. Matched tissue plasma samples were available from 40 patients.**Results**: *PIK3CA* mutations were detected in 25/50 (50.0%) tissue samples and in 18/48 (37.5%) plasma samples. VAF ranged from 4.4 to 72.9% with an average of 28.7% in tissue samples, and from 1.1% to 49.9% with an average of 8.2% in plasma samples. In tumor samples, the most frequent variant was H1047R (11/25, 44.0%), followed by E545K (8/25, 32.0%), E542K (4/25, 16.0) and H1047L (2/25, 8.0%). In plasma samples, the most frequent *PIK3CA* variant was H1047R (12/18, 66.7%), followed by E542K (6/18, 33.3%), and E545K (2/18, 11.1%). Double mutations in plasma samples occurred in two patients (both with H1047R + E542K). In 15/48 (31.3%) plasma samples, 19 low-level mutations (AF between 0.1% and 1.0 %) were detected, with an average of 0.49% (range 0.18-0.98).Matched tissue and plasma samples were available from 40/58 (68.9%) patients with a median time between matched tissue and plasma collection of 285 days ($25^{th}$-$75^{th}$ percentile: 24-1833 days). The overall concordance rate between plasma and tissue samples was 62.5% (25/40 patients). In detail, 8/40 patients (20.0%) had the same *PIK3CA* mutation in plasma and tumor tissue, while in 17/40 patients (42.5%) were tested negative in both sample types Discordant results occurred in 15/40 samples (37.5%). Specifically, nine patients had a *PIK3CA* mutation in the tissue sample only, while four patients had a *PIK3CA* mutation in the plasma sample only. In addition, in two patients a different *PIK3CA* mutation was detected in the plasma sample compared to the tissue sample.**Conclusion**: SiMSen-Seq based detection of *PIK3CA* mutations from plasma demonstrated promising results for selection of candidate patients for Alpelisib treatment. However, these results will be validated in a larger cohort of patients. Our data align with FDA recommendation to initially carry out the mutation testing in ctDNA. Only if the test is negative for *PIK3CA* mutations in plasma, patients should undergo testing for *PIK3CA* mutations in tumor tissue.

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# Proteomic analysis of breast cancer formalin-fixed paraffin-embedded clinical specimens identifies biologically-important subtypes with distinct clinical outcomes

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**Background:** Genomic classification of breast cancer has advanced breast cancer diagnosis and outcomes. However, extensive heterogeneity still exists beyond their DNA or RNA profiles. Newer classifications based on protein profiling are being developed to investigate the molecular oncology of breast cancers at the level where most drugs act. Using a recently-developed technology, we performed global proteomic profiling of 300 breast cancer specimens linked to outcome data. **Methods:** Sections of 75 samples from each PAM50 intrinsic subtype (Luminal A, Luminal B, Her2-enriched, Basal-like; n = 300) were macrodissected and analyzed using the Single-Pot Solid-Phase enhanced Sample Preparation Clinical Tissue Proteomics, a highly sensitive 11-sample multiplex massspectrometry protocol applicable to formalin-fixed, paraffin embedded (FFPE) specimens. This methodology enables comprehensive quantification of protein expression for classifier and biomarker discovery. Patients were diagnosed during 2008-2013 (n = 178, dataset I) and 1986-1992 (n = 122, dataset II). **Results:** In-depth proteomic analysis measured 9088 proteins in total, including 4214 proteins quantified in every sample. Consensus clustering of 174 evaluable cases in dataset I identified four distinct groups based on expression values for 1054 highly variant proteins. Cluster 3 (n = 47, mostly basal-like with HER2-Enriched) displayed the most favorable recurrence free survival (RFS) when compared to other clusters (HR = 0.22, 95%CI [0.08-0.63], p = 0.005). This cluster was enriched for immune related pathways including antigen processing and presentation and type I & II interferon signaling, and displayed high tumor infiltrating lymphocyte counts, characterizing this cluster as “immune hot”. In contrast, cluster 2 (n = 50, mostly basal-like) exhibited the poorest RFS (HR = 2.88, 95%CI [1.45-5.70], p = 0.002) and was enriched for proteins related to stromal and extracellular matrix with few immune related peptides. Cluster 1 (n = 34, luminal B and HER2-Enriched) was associated with lipid metabolism, whereas cluster 4 (n = 43, mostly HER2-Enriched with luminal A and luminal B) had a profile enriched for extracellular matrix, blood coagulation and complement activation. **Conclusions:** Global proteomic analysis on FFPE specimens can characterize the heterogeneity of breast cancer in a reliable and clinically-applicable high throughput manner. Our methodology identifies protein candidates that potentially serve as therapeutic targets and could be adapted to archived clinical specimens from other tumors.

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# Survival outcomes after chemotherapy in invasive lobular carcinoma compared to estrogen receptor positive invasive ductal carcinoma

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**Introduction**
Invasive lobular breast cancer (ILC) accounts for 10-15% of all invasive breast carcinomas and has distinct clinical and biological characteristics compared with the more common invasive ductal carcinoma (IDC). They are generally ER-positive (ER+) with the exception of a small number of pleomorphic cases and there is some evidence that the 10-year survival rate of women with ILC is lower than that for ER+ IDC. Furthermore, studies have shown that ILC may be less sensitive to chemotherapy than IDC, with lower rates of complete pathological response after neoadjuvant chemotherapy, but it is not clear what effects this has on long term survival. The aim of this study was to investigate whether ER+ ILC patients who received chemotherapy (neoadjuvant or adjuvant) had similar outcomes to ER+ IDC patients who received chemotherapy.

**Methods**
Patients were diagnosed at Guy's & St Thomas' NHS Foundation Trust between 1971 and 2016 and were eligible for inclusion into the study if they were female, had been diagnosed with either IDC or ILC, if their tumours were ER+, and if they received chemotherapy. They were followed up from date of primary diagnosis until 30$^{th}$ June 2019 and were assumed to be alive in the absence of a reported death date. Patients with estrogen receptor negative (ER-) tumours were excluded, due to well-known chemosensitivity in these breast cancer subtypes. Data used was requested from the Guy's & St Thomas' Breast Cancer Database.

**Results**
Of 5526 patients diagnosed with ILC or IDC between 1971 and 2016, 3945 were ER+ with 3436 IDC and 509 ILC. ER+ IDC and ILC had similar survival for the first 10 years after diagnosis after which outcomes began to diverge with worse outcomes in ILC. The 10-year and 15-year survival of 59.3% and 47.5% respectively were seen in IDC, and 58.6% and 44.6% in ILC. 1327 ER+ patients who received chemotherapy were selected for analysis, of which 161 (12.1%) were ILC and 1166 (87.9%) were IDC. 159 (12.0%) of patients received neo-adjuvant chemotherapy, while 1168 (88.0%) received adjuvant chemotherapy. In chemotherapy patients, 10-year survival was 53.1% in ILC and 54.0% in IDC, and by 15 years this was 35.1% and 44.7% respectively. In ER+ chemotherapy patients, there was no evidence of a crude association between histological subtype and survival (HR: 1.19, 95% CI: 0.97, 1.47) using Cox regression. However, the multivariate Cox regression model estimated a significantly worse outcome in ILC compared to IDC (HR: 1.28, 95% CI: 1.02, 1.60), adjusted for chemotherapy (neo-adjuvant or adjuvant), stage (I-IV), grade, HER2 status, time period of diagnosis, and surgery type (mastectomy or excision). When stratified by chemotherapy, this association was only observed in patients that received adjuvant treatment.

**Conclusion**
This study suggests that ER+ ILC patients who received adjuvant chemotherapy may have a worse outcome than ER+ IDC when adjusted for stage and grade. This is a potentially important finding but needs to be studied in a larger population treated with modern chemotherapy regimens. Other studies have shown that the outcome for ILC is better in the first 5 years after diagnosis compared to ER+ IDC but worsens after 10 years, as it does in this study. Thus, having long follow up is essential in order to be able to detect any differences in survival between ILC and ER+ IDC. Nonetheless, this study has displayed a significant difference in survival between ER+ ILC and ER+ IDC receiving adjuvant chemotherapy, and thus recommendations for adjuvant chemotherapy may need to be considered separately for the two subtypes. Furthermore, it would be beneficial to develop a tool that could help in identifying cases of ILC that would most benefit from chemotherapy.

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Radiomic phenotypes from dynamic contrast-enhanced MRI (DCE-MRI) parametric maps for early prediction of response to neoadjuvant systemic therapy (NAST) in triple negative breast cancer (TNBC) patients

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**Background and Purpose:**Early and accurate assessment ofbreast cancer response to NAST is important for patient management. In this study, we investigated the value of radiomic phenotypes derived from semi-quantitative and quantitative DCE-MRI parametric maps for early prediction of NASTresponse in TNBC patients. **MATERIALS AND METHODS**:This IRB approved study included 74 patients with stage I-III TNBC who were enrolled in the prospective ARTEMIS trial (NCT02276443). Pathologic complete response (pCR) and non-pCR were assessed by surgical histopathology after NAST (pCR=34; non-pCR=40).MRI scans were obtained at 3 time points during the NAST treatment with every 2-week anthracycline-based chemotherapy (AC): at baseline (BSL=74), post-2 cycles of AC (C2= 27) and post-4 cycles of AC (C4= 27). Patients went on to receive taxane-based chemotherapy prior to surgery. Tumor regions of interest (ROIs) were segmented by a breast radiologist at the early-phase subtractions of DCE-MRI scans using in-house developed software, followed by co-registration of the ROIs with quantitative ($K_{trans}$, $V_e$and $K_{ep}$), and semi-quantitative DCE parametric maps (Maximum Slope Increase (MSI), Positive Enhancement Integral (PEI) and Peak Signal Enhancement Ratio (SER)).A total of 93 first order radiomic features were extracted from the tumor ROIs of each time point semi-quantitative DCE parametric map, while a total of 390 extracted radiomic features (first order-histogram features and second order grey-level-co-occurrence matrix) were extracted from each quantitative DCE parametric map using an in-house developed Matlab software.Radiomic features at each time point and changes between the 3 time points were compared between pCR and non-pCR using Wilcoxon Rank Sum test and Fisher's exact test. Area under the receiver operating characteristics curve (AUC) was used to determine which features predicted pCR.Logistic regression was performed for feature selection, and used to build the radiomic phenotype model. The model performance was assessed by leave-one-out cross validation and 3-fold cross validation.
**RESULTS:**Thirty-three radiomic features from PEI map were significantly different between pCR and non-pCR. The PEI most significant features were changesbetween BSL and C4 in skewness, mean and median (AUC=0.87, 0.85 and 0.87, p=<0.001, 0.001 and 0.002 respectively). Additionally, 31 MSI features were significantly different between pCR and non-pCR. The top 2 features were the interscan-change in skewness between BSL and C2 (AUC=0.80, P=0.007) and C4 standard deviation (AUC=0.80, P=0.006). Four BSL $V_e$radiomic features were statistically significant between pCR and non-pCR with the best being range of difference variance (AUC=0.64, P=0.03). One BSL $K_{ep}$feature (Angular-Variance of Information measure of correlation-2) was able to differentiate pCR from non-pCR (AUC=0.64, P=0.04). Five C4-$K_{trans}$ features were able to differentiate pCR and non-pCR, with the most significant being mean value (AUC=0.86, P=0.001). BSL-$K_{ep}$radiomic model built from 24 features (AUC=0.80, p=0.003) and combined ($K_{trans}$, $V_e$and $K_{ep}$)C2-radiomic model consisting of 20 features (AUC=0.97, p=0.01) showed the best performance for prediction of pCR.
**CONCLUSIONS:**Radiomic phenotypes form DCE-MRI parametric maps were useful for differentiation between pCR and non-pCR and showed promise as noninvasive imaging biomarkers for early prediction of NAST response in TNBC. Potentially, DCE-MRI radiomic features may be used for development of diagnostic predictive model for early noninvasive assessment of NAST treatment response in TNBC patients.

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# Lower rates of neuropathy with oral paclitaxel and encequidar (oPac+E) compared to IV paclitaxel (IVPac) in treatment of metastatic breast cancer (mBC): Study KX-ORAX-001

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**Background:** Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity associated with IVPac. Primarily sensory, CIPN is an often irreversible condition primarily affecting the hands and feet associated with pain, numbness, tingling, and sensitivity to cold and has a significant impact on quality of life and treatment tolerance. Risk of CIPN increases with age, dose intensity, cumulative dose, and preexisting conditions including diabetes.
**Methods:** Study KX-ORAX-001 was a phase III, randomized, international study in women with mBC for whom treatment with IVPac was recommended. Eligible patients were randomized 2:1 to receive oPac+E or IVPac. Patients continued treatment until discontinuation due to progressive disease or toxicity. oPac 205 mg/m$^2$ was given once daily for 3 days weekly. E 12.9 mg was given 1 hour before each dose of oPac. IVPac 175 mg/m$^2$ was infused over 3 hours every 3 weeks. The primary endpoint was efficacy defined as tumor response confirmed by BICR at two consecutive evaluations. Key secondary endpoints included PFS, OS. Safety was monitored throughout the study.
**Results:** A total of 402 mBC patients were enrolled, 265 randomized to oPac+E and 137 to IVPac (ITT population). 399 patients were treated and comprise the safety population. The confirmed response rate was significantly greater in the oPac+E group vs IVPac (35% vs 23%) for the ITT population. Median overall survival was (27.7 vs 16.7 months, ITT) at the time of the analysis. Long-term follow up for final determination of PFS and OS is ongoing.Incidence of neuropathy-related TEAEs were lower in patients receiving oPac+E vs IVPac: Overall (21% vs 64%; all grades), grade ≥3 (2% vs 15%). Cumulative risk for neuropathy with IVPac was >50% by week 8 and was 83% at week 88. In contrast, the cumulative risk of neuropathy with oPac+E rose slowly and plateaued at 34% at week 88. Treatment discontinuations due to neuropathy occurred only in the IVPac arm (8%). Dose reductions due to neuropathy were reported in 8% of IVPac treated patients and in 2% of oPac+E treated patients. In agreement with the lower rates of peripheral neuropathy in patients treated with oPac+E, there was lower use of medications used for the treatment of neuropathic symptoms. Use of gabapentin or pregabalin was 12% for patients receiving oPac+E vs 40% for IVPac treated patients.
**Conclusions:** oPac+E was associated with greater efficacy in the treatment of patients with mBC and a lower incidence of neuropathy, slower onset and lesser severity of neuropathic events compared to IVPac 175mg/m$^2$ administered every three weeks. Fewer patients receiving oPac+E required dose reduction due to neuropathy and no patients receiving oPac+E discontinued treatment due to neuropathy. Reduction in neuropathy may improve quality of life and allow longer administration of effective therapy while maintaining dose intensity.

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Role of the calcium-sensing receptor (CaSR) in invasive lobular breast carcinoma metastasis to the ovary

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Invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer, after the more common invasive ductal carcinoma (IDC). ILC accounts for 10 to 15% of all invasive breast carcinomas, affecting approx. 26,000-40,000 women in 2020 in the US alone. Despite 95% of ILC being Luminal A conferring patients a favorable prognosis, patients with ILC have poorer long-term outcomes when compared to patients with Luminal A IDC. ILC spread to common sites of ER+ breast cancer metastasis such as the bones, but are also three times more likely to spread to the ovaries, peritoneum, and gastrointestinal tract compared to IDC, and these unique aspects of metastases remain poorly understood. To better understand metastasis to the ovary we performed DNA and RNA sequencing of 11 pairs of primary breast tumor and ovarian metastasis as well as 13 orphan breast cancer ovarian metastases. Our cohort was enriched for lobular histology, with 13 samples originating from ILC, 6 from IDC and 6 from mixed ILC/IDC. We found mutations in *CDH1* (43%), *PIK3CA* (40%), and *FOXA1* (29%) highlighting the enrichment in ILC cases present in our cohort. Gene expression analysis lead to identification of 874 differentially expressed between primary tumors and ovarian metastases. We identified the calcium-sensing receptor CaSR as one of the top upregulated in ovarian metastases compared to primary tumor in 10 out of the 11 paired samples. Other genes highly expressed in ovarian metastases included TAC3, GLRA2, ALLC, MUC19, CHRNA2, PIP, CST4, and TEX15. Pathways analyses showed an enrichment of signaling through glutamate receptor and glycine receptor families. To assess the contribution of CaSR to breast cancer cell proliferation and metastatic properties, and due to the absence of breast cancer cell lines expressing CaSR, we generated CaSR overexpression models using lentiviral infection in MDA-MB-134, MDA-MB-330, BCK4 and SUM44PE ILC cell lines. While overexpression of CaSR alone did not confer a cell growth advantage or migratory ability to the cell lines, stimulation with calcium or a calcium mimetic resulted in enhanced migration in transwell assays in 3 of the 4 cell lines. Scratch assays further confirmed the stimulation of cell migration in cells with CaSR overexpression in the presence of calcium. Cell migration in CaSR overexpression models could be stimulated with the calcimimetic R568, and inhibited by the calcilytics NPS2143, and F-actin staining confirmed the need to activate the receptor to enhance migratory properties. Our studies further revealed that the induced migratory properties of CaSR overexpressing cells required estradiol and ER signaling, and that migration could be blocked with ER inhibitors such as ICI 182,780 and tamoxifen. Western blotting data revealed that the enhanced cell migratory properties of CaSR overexpressing cells was via activation of the MEK/ERK pathway and migration could be inhibited using specific small molecule pathway inhibitors.Altogether, our study provides insight on the potential mechanism by which upregulation of the CaSR supports breast cancer ovarian metastasis. We hope that these studies will not only deepen our understanding of ILC ovarian metastasis but will eventually lead to the development of more effective therapies and improve the outcome of patients with this understudied type of breast cancer.

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# Racial disparities in pathological complete response among breast cancer patients receiving neoadjuvant chemotherapy

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**Background**: With the increasing use of neoadjuvant chemotherapy in breast cancer patients, it is important to better understand how host factors interact with tumor characteristics to determine response to neoadjuvant chemotherapy. Pathological complete response (pCR) is a strong surrogate for long term survival in certain subtypes of breast cancer. Racial disparities in breast cancer survival have been well documented, but few studies have been conducted to examine the extent of racial disparities in pCR after neoadjuvant chemotherapy. **Method**: We established a cohort of patients with breast cancer treated at an academic medical center in the ethnically diverse City of Chicago — the Chicago Multiethnic Epidemiologic Breast Cancer cohort (ChiMEC). Among patients who received neoadjuvant chemotherapy, we examined whether racial disparity existed in the rate of pCR, defined as ypT0/isypN0. Multivariable logistic regression models were used to estimate the odds ratios (ORs) of black relative to white patients, adjusting for clinical tumor stage and molecular subtype. We also explored whether there were racial difference in treatment characteristics, including days from diagnosis to the first neoadjuvant chemotherapy and dosage of 7 most commonly used drugs (Carboplatin, Cyclophosphamide, Docetaxel, Doxorubicin, Paclitaxel, Trastuzumab and Pertuzumab) using Wilcoxon rank-sum tests. **Results**: The study consisted of 595 stage I-III breast cancer patients who received neoadjuvant chemotherapy (51% Whites and 40% Blacks). Among them, 32.5% of the White patients achieved pCR while only 23.9% of the Black patients achieved pCR (**Table**). After adjusting for tumor subtype and clinical stage, Black patients still had a significantly lower odds of achieving pCR compared to Whites (OR=0.67, 95% CI: 0.44-1.00). The racial difference in pCR rates existed in all four molecular subtypes, though most pronounced in the HR-/HER2+ subgroup (OR=0.35, 95% CI: 0.13-0.97). Further adjusting for time from diagnosis to first chemotherapy reduced the racial difference (OR=0.76, 95% CI: 0.50-1.15), suggesting that some of this racial disparity could be explained by delay in treatment initiation. This hypothesis is also supported by the observation that the largest racial difference in treatment initiation was in the HR-/HER2+ subgroup, with White patients taking an average of 30.9 days to get their first chemotherapy after diagnosis while Black patients taking an average of 45.4 days ($P$ = 0.019). In addition, the study found that Black patients received significantly less cycles of Cyclophosphamide and Doxorubicin (i.e., the AC regimen) than White patients ($P$ = 0.024). **Conclusion**: Our study showed that Black patients had a lower pCR rate after neoadjuvant chemotherapy, and this racial disparity was largest among HR-/HER2+ patients. Although delayed initiation of treatment may partially contribute to this racial disparity, treatment differences in this single institution study are relatively small so most of racial disparity in response to neoadjuvant therapy could be due to biological difference beyond subtypes. Host and tumor characteristic that modulate response to therapy in diverse populations deserve further exploration to optimize design of innovative clinical trials and reduce disparities in clinical outcomes.

Racial disparity in pCR stratified by subtype and adjusted for tumor and treatment characteristics

| | pCR rate | | Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* | Adjusted Odds Ratio (95% CI)$^{+}$ |
|---|---|---|---|---|---|
| | White | Black | Black vs. White | Black vs. White | Black vs. White |
| Overall | 32.5% | 23.9% | 0.66 (0.45-0.96) | 0.67 (0.44-1.00) | 0.76 (0.50-1.15) |
| Subtype | | | | | |
| HR+/HER2- | 17.5% | 12.3% | 0.66 (0.27-1.63) | 0.69 (0.28-1.72) | 0.74 (0.30-1.85) |
| HR+/HER2+ | 28.6% | 22.9% | 0.74 (0.31-1.77) | 0.77 (0.32-1.86) | 0.86 (0.35-2.09) |
| HR-/HER2+ | 70.0% | 43.3% | 0.33 (0.12-0.88) | 0.35 (0.13-0.97) | 0.44 (0.16-1.23) |
| TNBC | 35.4% | 26.3% | 0.65 (0.35-1.21) | 0.78 (0.42-1.47) | 0.88 (0.47-1.68) |
| * adjusted for subtype, clinical T stage and clinical N stage | | | | | |
| $^{+}$ adjusted for subtype, clinical T stage, clinical N stage and days from diagnosis to first chemotherapy | | | | | |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PD9-06

# Peripheral blood gene signatures predict response to neoadjuvant chemotherapy in breast cancer patients

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Purpose: Neoadjuvant chemotherapy (NAC), the standard of care for a subset of breast cancer patients, is known to have immunologic effects. With emerging data showing improved response rates with anti-PD-1/PD-L1 immunotherapy in combination with chemotherapy, the effects of NAC on systemic and local anti-tumor immunity require further study. Biomarkers of anti-tumor immunity are needed to identify which patients are most likely to respond to immunotherapy. Our previous work has shown that changes in the peripheral blood can be observed over the course of NAC for breast cancer. Peripheral blood biomarkers are attractive because of the relative ease of sampling compared to site of disease. Residual cancer burden (RCB) is a useful surrogate marker of long-term prognosis, as patients who experience a pathologic complete response (pCR) have better outcomes than those with residual disease (RD). Methods: We previously identified an 8 gene signature of cytotoxicity, derived from single cell RNA sequencing of PD-1$^{Hi}$ CD8+ T cells, which are enriched for tumor-reactive T cells. Using a custom NanoString panel, we tested expression of this gene signature in whole blood collected prior to definitive surgery in 88 breast cancer patients (TNBC, n=21; HER2+, n=17; ER+, n= 54; PR+, n=53) across two cohorts (VUMC, n=58; DFCI, n=30), 64 of whom had received NAC (pCR, n=11; RD, n=53). We further investigated peripheral blood gene expression using RNA sequencing (n=58; 34 post-NAC, 24 untreated). Results: In two cohorts of breast cancer patients, expression of the 8 gene signature (*FGFBP2* + *GNLY* + *GZMB* + *GZMH* + *NKG7* + *LAG3* + *PDCD1* - *HLA-G*) was highest in patients with RD who experienced a recurrence within three years compared to those with pCR ($p<0.01$) or those with the highest RCB (RCB III) compared to those with RCB 0/I/II who did not have a recurrence with three years ($p<0.05$). RNA sequencing showed higher expression of interferon alpha, interferon gamma, and complement gene sets in patients experiencing a pCR compared to those with RD by gene set enrichment analysis (FDR-corrected q-values < 0.05). Conclusions: Expression of immune-related genes in the peripheral blood may predict response to NAC in breast cancer patients and be a useful biomarker for those who would benefit from additional therapies. These results will be further tested in a large cohort of longitudinal samples from breast cancer patients receiving NAC alone or in combination with pembrolizumab from the I-SPY-2 trial, to determine whether peripheral blood gene signatures can predict response to immunotherapy in breast cancer.

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**Publication Number:** PS16-06

# Identification of pathogenic FGFR1, FGFR2, and FGFR3 alterations in cell-free DNA (cfDNA) from patients with metastatic breast cancer

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**Background:** *FGFR* alterations are a known mechanism of resistance against breast cancer systemic therapies with higher FGFR RNA expression in breast cancer brain metastases compared to their primary tumors. While the genomic characterization of *FGFR* alterations has occurred from bulk breast tumors, the frequency and type of *FGFR* alterations in metastatic breast cancer (MBC) have not been fully characterized from cfDNA. The purpose of this study was to identify the incidence of *FGFR1, FGFR2,* and *FGFR3* genomic alterations in cfDNA from patients with MBC and elucidate which *FGFR* alterations may increase FGFR kinase activity or may function as mechanisms of resistance against the FDA approved FGFR inhibitor, erdafitinib.
**Methods:** We queried 16,053 reports from Guardant Health between June 2015 - October 2019 to identify the incidence of *FGFR1, FGFR2,* and *FGFR3* alterations detected in cfDNA from MBC. We classified each alteration type into the following categories: copy number variation (CNV), fusion, indel, or single nucleotide variant (SNV). Focus was placed on characterizing *FGFR1, FGFR2,* and *FGFR3* SNVs. We compared known activating mutations in *EGFR, ERBB2,* and *BRAF* with homologous regions in *FGFR1, FGFR2,* and *FGFR3*. *In silico* modeling with PyRx was used to dock erdafitinib onto FGFR1 (PDB 4V05), FGFR2 (PDB 5B7V), and FGFR3 (PDB 6LVM) kinases. Three-dimensional *in silico* analyses with ChimeraX was utilized to further determine which alterations may increase FGFR1, FGFR2, and FGFR3 kinase activity or may induce resistance against erdafitinib.
**Results:** The incidence of nonsynonymous alterations occurring in *FGFR1,* 2213 (13.8%); *FGFR2,* 1017 (6.3%); and *FGFR3,* 144 (0.9%) were identified in the Guardant Health MBC database. *FGFR1, FGFR2,* and *FGFR3* alterations are detailed in **Table 1**. We identified 40 (9.15%) and 167 (38.2%), 55 (7.2%) and 310 (40.4%), and 31 (27.4%) and 32 (28.3%) mutations occurring in the transmembrane/juxtamembrane and kinase domains of *FGFR1, FGFR2,* and *FGFR3*, respectively. Hotspot mutations were observed at R54C/S/G/R and N546K/D/S in *FGFR1*, D304N and N549K/D/S in *FGFR2*, and at S408/F/C/L/Y in *FGFR3*. We aligned *FGFR1, FGFR2,* and *FGFR3* with homologous kinases and found 12 unique samples with mutations in our *FGFR1* dataset corresponded to known activating mutations in *EGFR* and *ERBB2*; 18 samples with mutations in our *FGFR2* dataset corresponded to known activating mutations in *EGFR*, *ERBB2*, and *BRAF*; and 1 mutation in our *FGFR3* dataset corresponded to a known activating mutation in *ERBB2*. *FGFR1* mutations C488S, V492M, M535I, L569V and FGFR2 mutations L550V, E565A, Y566N, S568C, G570R, G685E are postulated to induce resistance against erdafitinib.
**Conclusions:** We found that 21% of MBC in this dataset harbor *FGFR* genomic alterations detected from cfDNA. Novel somatic alterations in *FGFR1, FGFR2,* and *FGFR3* were identified from Guardant Health that were not detected in the public domain. A portion of *FGFR* SNVs occurred at known homologous kinase activating mutations in *EGFR, ERBB2,* and *BRAF* suggesting these specific *FGFR* mutations may increase FGFR kinase activity and might be actionable therapeutic targets in breast cancers harboring these mutations. Three dimensional analyses of the FGFR protein tyrosine kinase further illustrate which specific alterations may increase FGFR kinase activity or induce resistance against erdafitinib.

| Gene | CNV (%) | Fusion (%) | Indel (%) | SNV (%) |
|---|---|---|---|---|
| FGFR1 | 1770 (80%) | - | 6 (0.3%) | 437 (19.7%) |
| FGFR2 | 224 (22%) | 15 (1.5%) | 11 (1.1%) | 767 (75.4%) |
| FGFR3 | - | 24 (16.7%) | 7 (4.9%) | 113 (78.4%) |

**Table 1.** Incidence and type of *FGFR* alterations in Guardant Health MBC database

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# Efficacy and safety of larotrectinib in patients with TRK fusion breast cancer

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**Introduction:** Larotrectinib is a first-in-class, CNS-active, highly selective tropomyosin receptor kinase (TRK) inhibitor approved by the US Food and Drug Administration and European Medicines Agency for the treatment of adult and pediatric patients with tumor agnostic indication for TRK fusion-positive cancer. Larotrectinib produced an objective response rate (ORR) of 79% in 159 patients with TRK fusion-positive cancer across various tumor types (Hong DS et al. *Lancet Oncol*. 2020). Here we report the efficacy and safety of larotrectinib in the six patients from the NAVIGATE phase II study (NCT02576431) with TRK fusion-positive breast cancer. **Methods:** Data were obtained for patients with breast cancer harboring a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion and treated with larotrectinib in the NAVIGATE study. All patients received 100 mg twice daily on a continuous 28-day schedule. Responses were investigator-assessed per RECIST v1.1 (data cut-off: July 15, 2019). **Results:** A total of 6 patients with TRK fusion breast cancer were included: 3 with secretory carcinomas, 2 with triple-negative breast cancer (TNBC), and 1 with ER+/HER2− disease. The median age was 49 years (range 32-65). One of the patients with secretory breast cancer was male. All of the secretory cases and 1 TNBC patient harbored an *ETV6-NTRK3* fusion, 1 TNBC patient had an *LMNA-NTRK1* fusion, and the ER+/HER2− patient had a *TPM3-NTRK1* fusion. Four patients had received ≥3 prior systemic therapies. The majority of patients had metastatic disease (n=5); 1 patient had locally advanced disease. The ORR was 83% (95% confidence interval [CI] 36-100) with 5 partial responses, while the ER+/HER2− patient had progressive disease. One of the TNBC patients had brain metastasis with complete resolution of CNS disease while on therapy. The median time to response was 1.7 months (range 0.9-1.9) and the duration of treatment ranged from 0.9 to 12+ months, with 4 patients (3 secretory and 1 TNBC) continuing on therapy at time of data cut. Median duration of response was not reached (95% CI 8.2-NE). Median progression-free survival was 9.1 months (95% CI 1.0-NE). Median overall survival was not reached at a median follow-up of 7.4 months. Four of the 6 patients had worst-grade adverse events (AEs) Grade 1-2; the most common Grade 1-2 AEs were dizziness and nausea. One patient had Grade 3 hepatocellular injury and Grade 4 hepatitis that were related to larotrectinib. There were no discontinuations due to AEs. **Conclusion:** Larotrectinib demonstrated an ORR in breast cancer patients similar to the ORR reported for larotrectinib across all tumor types, which supports the routine testing for *NTRK* gene fusions in patients with breast cancer regardless of histology.

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# Fluoroestradiol F18 positron emission tomography diagnostic performance to characterize estrogen receptor status in breast cancer

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**Background**
Estrogen receptor (ER) status by immunohistochemistry (IHC) of breast cancer tissue is currently used to direct endocrine therapy. Fluoroestradiol F18 (18F-FES) is a noninvasive method to determine the presence and ligand-binding function of the ER in metastatic breast cancer lesions throughout the body. Concordance of imaging and tissue assays should be established for 18F-FES PET to be an alternative or complement to tissue biopsy for metastatic lesions.
**Objective**
We conducted a meta-analysis of published results comparing 18F-FES PET and tissue assays of ER status in patients with breast cancer.
**Method**
PubMed and EMBASE were searched for English-language manuscripts with at least 10 patients and low overall risk of bias. We used hierarchical summary receiver-operating characteristic (HSROC) curve models for four analyses.
-For the first three analyses, IHC was used as the standard for tissue reference assay: i)18F-FES PET performance for nonbreast lesions in patients with metastatic breast cancer; ii)18F-FES PET performance for breast tumors; iii)18F-FES PET performance for all lesions (combined analysis);
-The last analysis assesses 18F-FES PET performance with all evaluable studies, which used a variety of standards for the tissue reference.
**Results**
PubMed and EMBASE searches identified 103 breast cancer studies involving 18F-FES PET, and 12 studies met the criteria for inclusion in our meta-analysis. Results are presented in Table 1.

| | **Number of studies** | **Pooled number of ER-positive lesions** | **Sensitivity (95% confidence region)** | **Pooled number of ER-negative lesions** | **Specificity (95% confidence region)** |
|---|---|---|---|---|---|
| Nonbreast lesions, IHC | 4 | 69 | 0.78 (0.65-0.88) | 44 | 0.98 (0.65-1) |
| Breast lesions, IHC | 3 | 60 | 0.86 (0.73-0.94) | 18 | 0.76 (0.52-0.90) |
| Combined, IHC | 7 | 143 | 0.83 (0.72-.90) | 64 | 0.83 (0.64-0.93) |
| Combined, all reference standards | 11 | 211 | 0.81 (0.73-0.87) | 116 | 0.86 (0.68-0.94) |

*Table 1: $^{18}$F-FES PET test accuracy results*
Tests of homogeneity did not find differences in sensitivity or specificity among the studies in the primary analysis or other analyses with IHC as the tissue reference standard.
Examining all tumor sites and all breast cancer stages, our results are consistent with other published meta-analyses (Table 2).

| Study | **Van Kruchten 2013 [1]** | **Evangelista 2016 [2]** | **Chae 2019 [3]** | **Combined, IHC** |
|---|---|---|---|---|
| Sensitivity (95% Confidence Region) | 0.84 (0.73-0.91) | 0.82 (0.74-0.88) | 0.83 (0.72-0.91) | 0.83 (0.72, 0.90) |
| Specificity (95% Confidence Region) | 0.98 (0.90-1.00) | 0.95 (0.86-0.99) | 0.93 (0.74-0.99) | 0.83 (0.64-0.93) |
| *[1]Van Kruchten et al., "PET Imaging of Oestrogen Receptors in Patients with Breast Cancer."* | | | | |
| *[2] Evangelista et al., "18F-Fluoroestradiol Positron Emission Tomography in Breast Cancer Patients."* | | | | |
| *[3] Chae et al., < Diagnostic Accuracy and Safety of 16α-[18F]Fluoro-17β-Oestradiol PET-CT for the Assessment of Oestrogen Receptor Status in Recurrent or Metastatic Lesions in Patients with Breast Cancer >.* | | | | |

*Table 2: Comparison with other published meta-analyses*
**Conclusion**
A strong correlation has been demonstrated between ER status determined by IHC of tissue from a single lesion and 18F-FES PET in this meta-analysis, which validates the accuracy of 18F-FES PET assessment of metastatic ER status. These results suggest that 18F-FES PET is useful for characterization of ER status of metastatic breast cancer lesions. Moreover, 18F-FES has been approved by the FDA in May 2020 as an adjunct to biopsy in recurrent and metastatic breast cancer.

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# Phase I/II trial of H3B-6545, a novel selective estrogen receptor covalent antagonist (SERCA), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer

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**Background**: Addition of CDK 4/6 inhibitors to endocrine therapy has provided significant improvements in outcomes for patients (pts) with metastatic breast cancer (mBC). However, acquired resistance to front-line therapy remains a challenge, and response to late lines of therapy is poor. H3B-6545 is a selective, orally available, small molecule covalent antagonist of the estrogen receptor (ERα) H3B-6545 binds covalently to a cysteine residue at position 530 of both wild-type and the constitutively active mutant ERα proteins, including Y537S. H3B-6545 demonstrated significant antitumor activity in multiple PDX breast cancer models, including those with mutated *ESR1* (the gene encoding ERα).**Methods**: This is a multicenter phase I/II trial. The primary objective of the phase I is to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) in pretreated pts with ER+, HER2- mBC. Secondary objectives include safety and antitumor activity. The primary objective of the phase II is to estimate the objective response rate (ORR) and secondary objectives include clinical benefit rate (CBR), progression-free survival (PFS) and safety. The trial was designed to exclude a lower limit of ORR of 5% at one-sided level of significance of 0.05 and a power of 90%.
**Results**: Between August 2017 and February 2020, 130 pts were enrolled; 47 in the Phase I part and 83 in the Phase II part of the trial. A total of 105 pts, including 73 patients on 450 mg, were response-evaluable. The phase I evaluated once daily doses from 100 to 600 mg. No dose-limiting toxicities (DLT) were observed at doses up to 450 mg and 2 DLTs were observed in 2 (grade 3 fatigue and grade 3 drug eruption) of 7 pts on the 600 mg cohort. Consequently, the dose of 450 mg was selected as the RP2D. Median age was 62 years (range: 31 to 87 years), 82% had liver and/or lung metastases, and the median number of prior therapies for metastatic disease was 3 (range: 1 to 10), with 41% of the pts receiving ≥ 4 prior therapies in the metastatic setting. Prior CDK4/6 inhibitors, fulvestrant, and chemotherapy were received by 87%, 71%, and 54% of the pts, respectively. 75 pts (58%) had detectable *ESR1* mutations. As of May 31, 2020, grade 2 or higher adverse events reported in ≥10% were anemia (20%), fatigue (16%), nausea (14%), diarrhea (11%) and AST increase (11%). Three cases of grade 4 AE were reported (serum bilirubin, urinary tract obstruction, and hyponatremia), all considered related to disease progression. Grade 1 sinus bradycardia (asymptomatic) was reported in 35% and grade 2 (symptomatic, no intervention needed) was reported in 4%. Grade 2 and 3. QTcF prolongation were reported in 2 and 3 patients, respectively. There were no treatment-related deaths. In the response-evaluable group, 13 confirmed partial responses (PR, 12%. 90% confidence limits: 7.5%-19%), including 11 PRs (15%, 90% confidence limits: 8.7%-23.7) on 450 mg dose, were observed, thus achieving the primary objective of the trial. Stable disease (SD) and clinical benefit rates (≥23 weeks) were 45% and 33% respectively at 450 mg and 46% and 34%, respectively on all doses. Responses were observed in heavily pretreated pts, pts with visceral metastases and in pts who received prior fulvestrant, prior CDK4/6 inhibitor, and/or prior chemotherapy, in the metastatic setting. Three PRs (25%) and 4 SDs were observed in 12 pts in whom clonal *ESR1* Y537S was the main ERα driver. Median PFS, in all pts and in pts with clonal *ESR1* Y537S was 3.7 months and 7.3 months, respectively. **Conclusions**: H3B-6545 has a manageable safety profile and demonstrated single-agent anti-tumor activity in heavily pretreated ER+, HER2- mBC patients including those with a constitutively active clonal *ESR1* Y537S mutation.

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# Unstable mutational profile and heterogeneity of residual breast tumor following neoadjuvant therapy from comprehensive genomic and transcriptomic sequencing

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**Background:** In patients with early breast cancer, neoadjuvant therapy is widely performed as standard of care. While the molecular targeting strategy makes progress in HER2 positive breast cancer, the optimal regimens for ER+/HER2- breast cancer (BC) and triple negative breast cancer (TNBC) remain undecided. Furthermore, there are few strategies for patients who do not achieve complete pathological response (pCR) who have worse prognosis. To address these unmet clinical needs, there is urgent need to examine the genomic alterations and immune microenvironment of residual tumors after neoadjuvant therapy. Here, we conducted a comprehensive analysis integrating genomic, transcriptomic, and clinical data to investigate the difference between primary breast cancer and residual disease. **Materials and Methods:** Using the large prospectively ascertained ethnically diverse Chicago Multi-Ethnic (ChiMEC) cohort of 562 participants with integrated genomic data, we identified 176 patients with breast cancer who underwent sequencing with Tempus xT next-generation sequencing panel including DNA- and whole-transcriptome RNA-sequencing. These included 131 primary breast tumors and 45 residual tumors after neoadjuvant therapy. We compared mutation rates between primary tumor and residual tumor in ER+/HER2- BC and TNBC. We also investigated homologous recombination deficiency (HRD) scores, tumor mutational burden (TMB), degree of immune infiltration, and microsatellite instability (MSI), and their association with survival. **Results:** Out of the 176 patients, there were 72 ER+/HER2- BC, 42 TNBC, and 44 HER2 positive cases. Among patients with HR+/HER2- BC, residual tumors had higher mutation rates in *PIK3CA* (61% vs 33%), *CDH1* (33% vs 17%), *CCND1* (39% vs 7%), *FGF3* (28% vs 0%), *FGF4* (33% vs 2%), *FGF19* (33% vs 2%), and *GATA3* (44% vs 7%) than primary tumors, but lower rates in *TP53* (28% vs 48%), *MAP3K1* (6% vs 40%), *KMT2D* (0% vs 33%), *MCL1* (0% vs 30%), *SPEN* (6% vs 20%), *ZFHX3* (0% vs 20%), *ARID1A* (11% vs 16%), *KMT2C* (0% vs 19%), *LZTR1* (0% vs 19%), *BCORL1* (6% vs 17%), *NOTCH3* (6% vs 17%), *FAT1* (0% vs 17%) and *LPR1B* (0% vs 17%). Relative to primary TNBC tumors, residual TNBC tumors exhibited higher mutation rates in *PTEN* (10% vs 3%), *CCNE1* (10% vs 3%), *CIC* (10% vs 0%), and *KMT2D* (10% vs 3%). Conversely, residual TNBC tumors had relatively lower rates of *MCL1* (0% vs 21%), *RB1* (0% vs 12%), *CDH1* (0% vs 12%), *KMT2C* (11% vs 18%), and *PIK3CA* (0% vs 15%), *CDKN1B* (0% vs 12%) and *ETV6* (0% vs 12%). There was a significant trend of higher TMB (>5.0 mutations/megabase, m/MB) associated with improved disease-free survival among the 176 patients ($P$=0.031). TMB was not significantly different between primary tumors and residual tumors, or across subtypes. Microsatellite instability (MSI) status was high in 3 patients (1.6%) and equivocal in 5 patients (2.7%). TMB in MSI-high or MSI-equivocal tumors was significantly higher than TMB in tumors with microsatellite stability (37.7m/MB vs 5.3m/MB, $P$<0.001). HRD scores were highest in TNBC, and lowest in ER+/HER2- breast cancers ($P$=0.022). There was no significant association between the HRD scores and survival. To date, tumors from 106 patients have undergone immune profiling, with estimation of immune cell infiltration, macrophages, B cells, CD4, CD8, and NK cells. Initial analysis showed no association between immune profiling and survival. **Conclusion:** These comprehensive analyses demonstrated that mutation status in HR+/HER2- breast cancers and TNBC differs between primary and residual tumors after neoadjuvant therapy. We identified genomic alterations and pathways in residual tumors that could be further explored as potential targets in the adjuvant setting to improve long term outcomes for patients who do not achieve pCR.

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# Incidence and management of central nervous system metastases in patients with inflammatory breast cancer

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**Background**: Patients (pts) with inflammatory breast cancer (IBC) have a high risk of central nervous system (CNS) metastasis (mets) with their associated impact on longevity and quality of life. Given evolving CNS-directed treatments, including focal radiation (RT), we compared the proportion of pts diagnosed with asymptomatic CNS mets before and after 2012 as data from Phase III trials in the preceding years (yr) increasingly supported the use of stereotactic radiosurgery (SRS). Specific attention was paid to pts treated with tri-modality therapy (TMT), defined as preoperative systemic therapy, surgery, and RT to determine whether screening for asymptomatic CNS mets would be beneficial. **Methods**: We retrospectively reviewed the records of pts diagnosed with IBC 1997-2019 and enrolled in an IRB-approved registry at a dedicated IBC center. CNS met-free survival time was defined as the time from IBC diagnosis to date of CNS mets. Alive CNS met-free pts were censored at their latest survival date and death was treated as a competing risk. Cumulative CNS mets incidence was computed. Analyses were stratified based on stage at diagnosis (III vs. de novo IV) and receipt of TMT. For pts completing TMT, the completion date was the starting point for cumulative incidence calculations. Overall survival (OS) was estimated as the time from CNS mets diagnosis to death, with censoring for pts who were still alive. **Results**: A total of 531 pts were identified; 372 (70%) with stage III; 159 (30%) with de novo Stage IV disease. The median follow-up for pts presenting with stage III and stage IV disease at diagnosis was 5.6 yr and 1.8 yr, respectively. 124 pts had CNS mets; 5 of them at diagnosis. CNS was the first site of mets or progression in 50 pts (9.4%). The cumulative incidence of CNS mets stratified by stage at diagnosis and receipt of TMT is seen in Table 1. Among the 50 de novo Stage IV pts who completed TMT, 4 developed CNS mets prior to surgery. The median overall survival (mOS) after CNS mets was 0.6 yr (IQR: 0.2 - 1.4). Results stratified by tumor subtype were: HER2+ disease (n=51) 1.4 yr (IQR: 0.6 - 3.7); hormone receptor+/HER2- (n=27) 0.6 yr (IQR: 0.2 - 1.2); triple negative (n=40) 0.2 yr (IQR: 0.1 - 0.5). Most pts with CNS mets (87/124, 70%) had neurologic symptoms prompting imaging. There was no difference in the proportion of asymptomatic pts diagnosed with CNS mets prior to or after 2012. Management of CNS mets was as follows: 47 pts (38%) received whole brain RT (WBRT) alone, 22 (18%) SRS alone, 15 WBRT + SRS (12%), 6 resection + WBRT (5%), and 5 resection + SRS (4%). The remaining pts received several of these modalities with or without intrathecal chemotherapy (13, 11%) or CNS treatment was not documented (16, 13%). A total of 258/531 pts have died (49%). Of these pts, 103 (40%) had CNS mets. 67/103 (65%) died due to CNS mets. **Conclusions:** Among pts with IBC completing TMT, the incidence of CNS mets is as high as 20% both in de novo Stage IV pts at 1 yr and in Stage III pts within 5 yrs, supporting routine surveillance brain MRI among pt with Stage IV disease. The majority of pts continue to receive WBRT with its resultant toxicities. Efforts should be made to identify CNS mets early to facilitate more focal therapy. Future research on systemic therapy with CNS penetrance for IBC patients should be pursued. These data support an ongoing prospective study of screening brain MRI in pts with Stage III IBC to quantify the incidence of CNS mets, utilization of WBRT and impact on neurologic quality of life (NCT04030507).

Cumulative Incidence of CNS Mets

| | *No.* | *1 year* (95% CI) | *2 year* (95% CI) | *3 year* (95% CI) |
|---|---|---|---|---|
| Stage III (All) | 372 | 5% (3-7) | 9% (6-12) | 18% (14-23) |
| Stage IV (All) | 154 | 17% (12-24) | 30% (22-37) | 42% (32-51) |
| Stage III (TMT) | 304 | 5% (3-8) | 11% (8-16) | 19% (14-24) |
| Stage IV (TMT) | 46 | 21% (10-34) | 28% (16-43) | 35% (20-50) |

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Trilaciclib improves overall survival when given with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: Final analysis of a randomized phase 2 trial

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**Background**
Trilaciclib is an intravenous (IV) cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Preliminary data showed that adding trilaciclib prior to gemcitabine plus carboplatin (GCb) significantly increased overall survival (OS) compared with GCb alone among patients with metastatic triple-negative breast cancer (mTNBC) (Tan et al., Lancet Oncol. 2019;20:1587-1601). Here, final antitumor efficacy results (objective response rate [ORR], progression-free survival [PFS], and OS) are reported for the whole study population, and in cohorts according to CDK4/6 dependence and level of programmed death ligand-1 (PD-L1) expression.
**Methods**
This was a randomized, open-label, phase 2 study of patients with mTNBC who had received ≤2 previous lines of chemotherapy in the recurrent/metastatic setting (NCT02978716). Patients were randomized (1:1:1) to receive GCb on days 1 and 8 (group 1, n=34), trilaciclib prior to GCb on days 1 and 8 (group 2, n=33), or trilaciclib alone on days 1 and 8 and prior to GCb on days 2 and 9 (group 3, n=35), in 21-day cycles. PFS and OS (prespecified secondary endpoints) were assessed in the intention-to-treat (ITT) population, and ORR in response-evaluable patients.
Patient tumors were characterized as CDK4/6 independent (basal-like) or indeterminate (HER2-enriched, normal-like, luminal A/B) according to the established PAM50 signature, or CDK4/6 dependent (luminal androgen receptor) or indeterminate (basal-like 1/2, mesenchymal) according to the established Lehmann signature. PD-L1 expression was scored as negative or positive if <1% or ≥1% of the total tumor area contained PD-L1-labelled immune cells, respectively, using the Ventana SP142 assay. Association of CDK4/6 dependence and PD-L1 expression with antitumor efficacy was assessed using proportional hazards regression.
**Results**
Median follow-up was 8.4 months (range: 0.1-25.7) for group 1, 14.0 months (1.3-33.6) for group 2, and 15.3 months (3.5-33.7) for group 3. The ORR among response-evaluable patients was 7/24 (29.2%) in group 1, 15/30 (50.0%) in group 2, and 12/31 (38.7%) in group 3. Median PFS (95% confidence interval [CI]) in the ITT population was 5.7 (3.3, 9.9) months in group 1, 9.4 (6.1, 11.9) months in group 2, and 7.3 (6.2, 13.9) months in group 3, with hazard ratios (HRs) of 0.62 ($P$ = 0.2099) and 0.63 ($P$ = 0.1816), for groups 2 and 3 versus group 1, respectively. Overall, 73.5%, 39.4%, and 57.1% of patients in groups 1, 2, and 3 had died. Median OS (95% CI) was 12.6 (6.3, 15.6) months in group 1, not reached (NR) (10.2, NR) in group 2 (HR = 0.31, $P$ = 0.0016), and 17.8 (12.9, 32.7) months in group 3 (HR = 0.40, $P$ = 0.0004). For groups 2 and 3 combined, median OS was 19.8 (14.0, NR) months (HR = 0.37, $P$ <0.0001 vs group 1). ORR, PFS, and OS were comparable in tumors categorized as CDK4/6 dependent, independent, or indeterminate. Antitumor efficacy by PD-L1 status is provided in the **Table**.

| | **Group 1** | | **Group 2** | | **Group 3** | |
|---|---|---|---|---|---|---|
| | **PD-L1 +ve** | **PD-L1 -ve** | **PD-L1 +ve** | **PD-L1 -ve** | **PD-L1 +ve** | **PD-L1 -ve** |
| Patients, n | 17 | 10 | 16 | 10 | 16 | 16 |
| ORR, n (%) | 4 (23.5) | 3 (30.0) | 8 (50.0) | 4 (40.0) | 7 (43.8) | 4 (25.0) |
| Median PFS, months (95% CI) | 3.5 (2.2, NR) | 9.5 (5.2, NR) | 7.9 (4.3, NR) | 11.9 (8.8, NR) | 9.0 (6.2, NR) | 6.9 (6.4, NR) |
| *P* value (Wald Test) | - | - | 0.347 | 0.604 | 0.069 | 0.766 |
| HR (95% CI) | - | - | 0.70 (0.3, 1.5) | 0.76 (0.3, 2.2) | 0.46 (0.2, 1.1) | 1.16 (0.4, 3.1) |
| Median OS, months (95% CI) | 10.5 (6.3, 18.8) | 13.9 (12.6, NR) | 20.1 (10.2, NR) | NR (9.4, NR) | 32.7 (15.3, NR) | 17.8 (12.9, NR) |
| *P* value (Wald Test) | - | - | 0.028 | 0.083 | 0.02 | 0.239 |
| HR (95% CI) | - | - | 0.35 (0.1, 0.9) | 0.34 (0.1, 1.2) | 0.33 (0.1, 0.8) | 0.57 (0.2, 1.5) |

HR and *P* values are for comparisons between group 2 versus group 1, and group 3 versus group 1.+ve, positive; -ve, negative; CI, confidence interval; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

**Conclusions**
Mature data from this study confirm that administering trilaciclib prior to GCb enhances antitumor efficacy compared with GCb alone, with statistically significant improvements in OS. Subgroup analyses suggest that adding trilaciclib prior to GCb benefits patients regardless of CDK4/6 dependence status and PD-L1 expression. Additional immune subtyping analyses are ongoing and will be presented.

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# Plasma exosomal miRNAs: A minimally invasive diagnostic biomarker for inflammatory breast carcinoma

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**Background.** Inflammatory Breast Cancer (IBC) is a rare, but aggressive subtype of breast carcinoma with dermal lymphatic invasion in young females. IBC is poorly diagnosed as it develops vast rapidly relative to other non-IBC and without distinct lumps formation, moreover, it is usually misdiagnosed with mastitis. Nanosized exosomes (20-200nm) circulating in liquid biopsies are a promising minimally invasive diagnostic alternative to standard biopsies. In cancer microenvironment, they modulate cancer progression via shuttling their encapsulated microRNAs (miRNAs) into recipient cells to either trigger signaling or induce malignant transformation of targeted cells. While small non-coding regulatory miRNAs are an already known cancer biomarkers, exosomal miRNAs serve as a novel class of diagnostic biomarkers. The present study aims to evaluate the expression levels of exosomal miRNAs relevant to IBC pathogenesis. **Design/Materials/Methods.** This is a prospective case-control study that includes 77 females; 57 were diagnosed with breast cancer (34 non-IBC and 23 IBC), while 20 were healthy volunteers. All have signed an informed consent to be enrolled in this investigation. Patients included were neither pregnant nor issued with bloodborne or autoimmune disease, while healthy subjects had no oncologic history. Plasma circulating exosomes were isolated using precipitation and ultracentrifugation methods. The successful isolation was verified by dynamic light scattering (DLS), transmission electron microscopy (TEM), Western blot (WB), and Dot blot (DB). The expression level of exosomes-derived miR-181b-5p, miR-222-5p and let-7a was quantified by qPCR. Afterwards, that expression level was verified in the human non-IBC MDA-MB-231 and IBC SUM149 cell lines. **Statistics.** Difference between groups was tested using Student's t-test through IBM SPSS statistics software package, version 24. A $p < 0.05$ was considered significant. **Results.** DLS and TEM analysis revealed that nanovesicles with 146.65 nm were successfully isolated. Moreover, CD63, HSP70, Alix90 and GM130 antibodies used in DB and WB have further confirmed the successful isolation. Relative to non-IBC, our qPCR showed that plasma exosomes-derived miR-181b-5p and miR-222-5p were significantly ($p <0.0001$ and $p <0.01$, respectively) upregulated in IBC, whereas exosomal let-7a was significantly ($p <0.0001$) downregulated in IBC. Further, the expression levels of miR181-5p and miR-222 were upregulated in SUM-149-derived exosomes relative to those of MDA-MB-231-derived exosomes ( Both $p < 0.001$), while the expression levels of let-7a did not significantly change. Diagnostic accuracy of the candidate plasma exosomal miRNAs was assessed via receiver operating characteristic (ROC) curves analysis. Interestingly, Area Under Curve (AUC) was 0.826 for miR-181-5p ($p <0.0001$), 0.7212 for miR-222-5p ($p <0.0001$), and 0.9188 for let7a ($p <0.01$). Additionally, bioinformatical analysis for predicted targets of the identified exosomal miRNAs will be assessed. **Conclusion.** Exosomes derived miR-181-5p, miR-222-5p and let7-7a may act as non-invasive diagnostic biomarkers to discriminate IBC from non-IBC patients.

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# Predicting breast cancer risk for women veterans

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**Background**Accurate breast cancer risk assessment allows personalized approach in breast cancer screening and/or prevention. Breast cancer risk prediction models have been developed. Independent prospective validation however was needed before broad clinical applications. The Department of Veterans Affairs (VA) Million Veteran Program (MVP) is one of the largest biobanks in the world. Important attributes include: large sample size (>830,000, April 20), national coverage, multi-ethnic representation, access to bio-specimens from which multi-omics measurements have been conducted, thousands of biomedical phenotypes derived from our baseline and life style surveys and electronic health records (EHR). About 9% of MVP registrants are women. Breast cancer risk prediction models were evaluated in a prospective cohort of women in MVP.
**Methodology**More than 350000 MVP participants completed genotyping to date. Breast cancer diagnoses were captured from the EHR. Ethnicity was determined by a supervised learning algorithm, Harmonized Ancestry and Race/Ethnicity (HARE), that used genetically inferred ancestry to refine self-identified race/ethnicity. Clinical breast cancer risk prediction instruments were based on personal health, lifestyle, demographics, family history, and environmental exposure. Polygenic Risk Score used in this study is comprised of 313 single nucleotide polymorphisms (PRS313). Clinical risk models tested were: BPC3, Lit and Breast Cancer Risk Assessment Tool (BCRAT, a version of the Gail's model). The BPC3 and Lit models were tested by deploying the iCARE (Individualized Cancer Absolute Risk Estimator) with or without incorporation of PRS313. The BCRAT was deployed in the R package "BCRA" (Breast Cancer Risk Assessment v. 2.1 by F. Zhang). The performance of the risk prediction models was assessed by Area under the Receiver Operating Characteristic Curve (AUC-ROC). The observed absolute risk over expected absolute risk was compared for each decile.
**Results**35133 genetic females were identified without a prior breast cancer diagnosis. By HARE definition, 10717 were African Americans (AA), 317 non-Hispanic Asians (ASIAN), 19941 non-Hispanic whites (EU), 1803 Hispanic (HIS) and 1355 unassigned. The median age of this cohort at MVP entry was 55. 369 subjects developed incident breast cancers with a median follow up of 4 years. These new cases were identified from Cancer Registry (292 cases) and EHR search for compatible ICD plus CPT codes (77 cases). The breast cancer incidence rate was 2.6/1000/year. iCARE-lit model was tested in 2731 AA women (38 incident breast cancers), 9027 EU women (111 incident breast cancers), and 10254 non-AA women (122 incident breast cancers) that had comprehensive risk factor evaluation (<4 missing). The AUC with the iCARE-lit model alone is 0.569 for AA, 0.563 for EU, and 0.565 for non-AA. Incorporation of PRS313 into the iCARE-lit model improved the AUC to 0.573 for AA, 0.645 for EU and 0.638 for non-AA. Additionally, iCARE-lit plus PRS313 estimated that 15% (AA), 7.3% (EU) and 7.7% (non-AA) of the women would have a lifetime risk of >20%. The iCARE-BPC3 had similar performance as iCARE-lit. The AUC of BCRAT alone was 0.648 for EU (20550 with 179 incident breast cancers) and 0.661 for AA (10462 with 96 incident breast cancers). Incorporation of PRS313 to BCRAT improved the AUC to 0.682 (EU) and 0.658 (AA). BCRAT plus PRS313 estimated that 5.6% (AA) and 4.4% (EU) of the women would have a lifetime risk of >20%.
**Discussion**We prospectively evaluated and validated the performance of breast cancer risk prediction models as reported from case control studies. Longer follow up of more women in MVP will provide better assessment esp. for AA women. Prospective validation of these risk prediction models provides strong rationale for further development of these models in the clinical setting.

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# Association between pathological response and tumor genomic profiling in triple negative breast cancer patients treated with neoadjuvant chemotherapy

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**Background**: Triple negative breast cancer (TNBC) has a marked molecular diversity that promotes clinical heterogeneity. Less than 40% of TNBC patients will achieve a pathological complete response (pCR) to standard neoadjuvant chemotherapy. Patients who do not achieve pCR have a high risk of disease recurrence and subsequent death from breast cancer. Molecular characterization may identify TNBC patients unlikely to achieve pCR and subsequently develop recurrent disease. **Methods**: We are conducting a multicenter prospective study of clinical stages II and III TNBC patients treated with neoadjuvant docetaxel and carboplatin. We performed tumor whole exome sequencing on 56 patients pre-treatment samples to identify somatic mutation associated with pCR. Thirteen matching samples from cycle 1 day 3 (C1D3) were also analyzed to assess changes in somatic mutation profiles. **Results**: In this biomarker study, thirty-seven (66.1%) patients are Caucasians, 17 (30.4%) African American. Nineteen (33.9%) achieved pCR following six cycles of neoadjuvant docetaxel and carboplatin. 9063 variants were detected in 5386 unique genes. The overall mutation burden for patients who achieved pCR was not significantly different from non-pCR patients (median of 80 variants, IQR 51-135 in pCR, vs median 72, IQR 44-102 in non-pCR, Wilcoxon rank sum test p=0.78). As expected, *TP53* is the most frequently mutated gene observed in 48 of all 56 patients (85.7%). There was a non-significant trend with lower *TP53* mutations occurring in 78.9% of patients with pCR, versus 89.2% of non-pCR patients (OR 0.46, 95% CI 0.07 - 2.83; p value 0.42). *BRCA2* somatic mutations were observed in 5.4% and 5.3% of pCR and non-pCR samples, respectively. No *BRCA1* somatic mutations were identified. *EGFR*, *RAD51AP2*, *SDK2*, *L1CAM*, *KPRP*, *CACNA1S*, *CFAP58*, *COL22A1*, and *COL4A5* were differentially mutated and almost exclusively found in pCR samples. *PCDHA1* and *TRMT9B* were observed in 18.9% and 16.2%, respectively, of non-pCR samples only. There was a trend of higher variant counts in the thirteen matched samples at C1D3 (median of 82, IQR 49-157) versus corresponding pre-treatment samples (median of 72, IQR 42-92), Wilcoxon rank sum test p=0.29, suggesting clone emergence under treatment pressure. Using the Molecular Signatures Database v7.1, several gene families involved in immune related pathways showed differences between pCR and non-pCR samples. Additionally, borderline differences in hedgehog signaling pathway were identified between pCR and non-pCR samples. There were no differences in apoptosis, DNA repair, EMT, inflammatory response, NOTCH signaling pathways. **Conclusion**: Across TNBC tumors analyzed, *TP53* mutation frequency does not differ in pCR versus non-pCR patients. Somatic mutations in *EGFR*, *RAD51AP2*, immune pathways genes, and hedgehog signaling pathway genes may predict pCR to docetaxel and carboplatin chemotherapy.

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Molecular imaging of hypoxia and granzyme B alterations during combination treatment with immunotherapy in triple negative breast cancer

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**Background:** Although a portion of triple negative breast cancer (TNBC) is sensitive to chemotherapeutic treatment with agents such as paclitaxel (PTX), patients have a high risk of recurrence and short overall and progression-free survival. Clinical trials for TNBC using immune checkpoint inhibitors such as anti-programmed cell death 1 (PD1) have met some success; however, only a small percentage of patients have a positive response to immunotherapy and there is risk for severe side effects. Therefore, there is a need for improvements in monitoring and predicting patient-specific response. The goal of this study is to use non-invasive visualization of the tumor microenvironment to collect longitudinal information that can be used to study tumor response to immunotherapy. By applying positron emission tomography (PET) imaging techniques to investigate changes in the tumor microenvironment (hypoxia and immune cell activation), we seek to predict early response to immunotherapy and better identify which treatments will be effective for individual tumors in TNBC. **Methods:** A TNBC mouse mammary carcinoma cell line, 4T1, was transduced with CMV-luciferase and $2x10^5$ cells were injected into the third mammary fat pad of 5-6 week old female Balb/c mice (N=28). Mice in cohort 1 received: PTX (10 mg/kg), anti-PD1 (200 µg), both, or vehicle control (saline) (n=4/group). Mice in cohort 2 received: anti-PD1 (n=5), combination PTX/anti-PD1 (n=4) , or vehicle control (saline; n=3). Treatments were administered intraperitoneally on days 0, 2, and 5 for cohort 1 (n=16) who underwent granzyme B-PET imaging ([$^{68}$Ga]-NOTA-GZP-PET) and on days 0, 2, 5, and 8 for cohort 2 (n=12) who underwent hypoxia imaging with [$^{18}$F]-fluoromisonidazole (FMISO)-PET imaging. Bioluminescence (BLI) imaging and caliper measurements were performed to track tumor size changes at multiple timepoints and tumors were collected for histological validation on day 20. Mean standard uptake value ($SUV_{mean}$) was calculated as percent of day 0, and statistical analyses were performed with unpaired t-tests and Wilcoxon-rank sum tests. **Results:** Voxel analysis of GZP-PET images revealed an 42.9% increase in T cell activation of TNBC tumors treated with single-agent PTX compared to anti-PD1 alone on day 3 ($p=0.08$). FMISO-PET revealed that tumors treated with anti-PD1 alone had lower hypoxic fraction compared to control group tumors ($p=0.10$) and tumors treated with combination PTX/anti-PD1 ($p=0.17$) on day 3. BLI data showed that treatment with PTX and anti-PD1 significantly decreased viability signal between days 3 and 6 for cohort 1 ($p=0.04$). Non-responders to treatment had a significantly higher tumor volume compared to responders starting on day 6 ($p<0.05$). $SUV_{mean}$, indicating T cell activation, was significantly higher for responders compared to non-responders on days 3 and 6 ($p<0.05$). There was a signifciant decrease in hypoxia, as measured thorugh FMISO-PET $SUV_{mean}$ on day 6 for responders compared to non-responders ($p=0.04$). **Conclusion:** It is known that the tumor microenvironment can impact neovascularization, tumor cell invasion, tumor oxygenation and growth. Results from this study show that noninvasive PET imaging can provide data on changes in T cell activation and hypoxia in response to chemotherapeutic treatment and immunotherapy in TNBC. Utilizing clinically-translatable advanced imaging strategies to understand the biologically distinct features of the TNBC tumor microenvironment can aid in personalizing anti-cancer therapies. **Acknowledgements:** We thank the American Cancer Society for RSG-18-006-01-CCE, NIH NCI R01 CA240589, and NIH P30CA013148.

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Neoadjuvant endocrine therapy helps identify HER2 up-regulation in patients with hormone receptor-positive HER2-negative breast cancer

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**Background:** Endocrine therapy provides significant improvement in the long-term outcomes of patients with hormone receptor-positive (HR+) breast cancer (BC). However, metastatic recurrences of endocrine resistant disease develop in about 20-25% of patients and remain a major cause of BC mortality. Up-regulation of the HER2 growth factor receptor represents a common escape strategy used by cancer cells to survive and continue to proliferate in an ER-independent manner. Neoadjuvant endocrine therapy (NET) offers a unique opportunity to identify responsiveness of HR+ BCs and detect tumors that display up-regulation of HER2, an early endocrine resistance mechanism. **Methods:** A single arm, interventional, exploratory clinical trial evaluating four weeks of NET in early stage HR+/HER2-negative BC patients was conducted at our institution (NCT03219476). The primary objective was to assess changes in HER protein expression (HER1-4) from diagnostic core biopsies to surgically resected tumors treated with NET. Secondary objectives included assessment of other molecular markers, tumor proliferation and volumetric responses. Optimized protocols for immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) were used to assess HER2 status in the pre- and post-treatment tumor specimens. Chi-square and t-tests were performed. Linear regression multivariate analysis was performed to evaluate association of covariates with the primary outcome with 80% power at a significance level of 0.05. Here we present the changes in HER2 protein expression with NET in this study. Up-regulation was defined as an increase of ≥ 1 in IHC scores (ordinal 0,1,2,3) or gene amplification by FISH. **Results:** Thirty-seven patients with cT1-T3, cN0 HR+/HER2-negative BC were enrolled. Median age at diagnosis was 64 yrs (42-81) and median BMI was 28.3 (19.3-55.1). Most patients were post-menopausal (83.8%). Median tumor size clinically was 1.3 cm (0.5-7.7). Most tumors were low (42.1%) or intermediate (47.4%) grade and invasive ductal histology was seen in 70%. Median tumor size at surgery was 1.2 cm (0.09-4). One patient had a complete pathologic response (pCR) at surgery. Seven patients had pN1 disease at surgery (six with 1 lymph node involved, one with pN1mi). There was no significant change in ER-positivity between pre and post-treatment specimens. However, a trend towards decrease in PR-positivity was seen in post-treatment tumors consistent with functional ER pathway disruption (p=0.08). On HER2 protein assessment by IHC, most patients had IHC 0 (37.8%) or IHC 1+ (54%) at diagnosis. Significant up-regulation in HER2 protein was seen in 46% (17/37) of patients (p=0.0004), whereas down-regulation was detected in only 5% (2/37) and no change in the remaining 49% (18/37). Three patients converted to HER2-positive status (IHC 3+ or FISH amplified) at surgery and received adjuvant trastuzumab-based treatment. No significant associations were identified between any clinicopathologic covariates and change in HER2 protein expression. **Conclusions:** HER2 was up regulated in 46% of tumors after short-term NET in patients diagnosed with early stage HR+/HER2-negative BC. Short-term NET is a promising strategy to identify HR+ tumors that up-regulate HER2 as an early escape pathway and endocrine resistance mechanism. Patients with such HER2 up-regulated tumors after NET may benefit from HER2-directed therapies upon disease recurrence or as adjuvant combination therapy. These findings need to be further explored in larger randomized clinical trials.

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**Publication Number:** PD9-07

# Genomic landscape of metastatic breast cancer (MBC): Comprehensive cell-free DNA analysis from over 10,000 patients and comparison with primary breast cancer

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**Background:** Current tissue-based genomic sequencing datasets typically reflect early stage, mostly treatment-naïve cohorts, and fail to capture the genomic landscape of advanced disease, including mutations conferring acquired resistance to therapy. Plasma cell-free DNA (cfDNA) can provide information on somatic alterations non-invasively and can capture spatial tumor heterogeneity. Here, we studied cfDNA from 15,564 blood samples from 12, 827 patients (11.5% of patients had serial samples) with MBC, and analyzed the differences in mutational landscape between cohorts of heavily pre-treated and primary untreated breast cancers. **Materials and methods:** Deidentified aggregate genomic data from stage III/IV breast cancer clinical samples submitted for cfDNA next-generation sequencing (NGS) analysis with Guardant360 (Guardant Health, Inc; Redwood City, CA, USA) assay between 11/25/16 and 5/26/20. This clinical assay detects somatic single nucleotide variants (SNVs), indels, copy number gains, and fusions in either all or a subset of exons in up to 74 genes. We compare the observed alterations to events detected from whole-exome sequencing data representing ~1,000 untreated primary breast cancers from The Cancer Genome Atlas (TCGA) project. **Results:** In the overall cohort (N = 12, 827), the average patient age was 61 (range 18-100); 99% were female. Of the 11,290 pts with at least one samples with a non-synonymous alteration, the most frequently mutated genes were *TP53* (53%), *PIK3CA* (38%), *ESR1* (28%), *ATM* (13%), *GATA3* (10%), and *ARID1A* (10%) at varying allelic frequencies with dynamic changes over time (in pts with serial specimens) highlighting clonal heterogeneity and temporal evolution. Copy-number gains were most frequent in *FGFR1* (13%), *CCND1* (11%), *EGFR* (9%) and *PIK3CA* (9%), but fusions were infrequent (below 1%), with fusions involving *FGFR3* (n=22), *FGFR2* (n=12), *ALK* (n=7), *NTRK1* (n=6), *RET* (n=4), and *ROS1* (n=1). Overall, patients had significantly higher frequency of actionable alterations based on ctDNA analysis, as compared to that observed in TCGA. Similarly, non-synonymous mutations were identified in genes associated with acquired resistance, including *ESR1* (28%), *ERBB2* (9%), *PTEN* (8.1%), *RB1* (7.7%), *NF1* (6.2%), and *AKT1* (4%), mutated at frequencies significantly exceeding those observed in TCGA. Finally, we developed a novel classifier to identify the breast cancer receptor subtypes based on differential genomic profile, which was further validated in an independent genomic dataset. **Conclusions:** In the largest dataset to date, we provide the comparative genomic landscape of the various SNVs, indels, copy-number gains, and fusions identified by next generation sequencing of cfDNA in patients with MBC, compared to primary breast cancer. Interestingly, both targetable genomic alterations and resistance mutations occur at frequencies much higher than observed in primary breast cancer, highlighting the genomic complexity of MBC and potential need for combinatorial therapy. Finally, we describe a novel classifier for detection of HR+ and HER2+ tumors, which could be particularly valuable clinically given the receptor switch with tumor evolution and practical difficulty with serial tissue biopsies in MBC. Comparison of genomic signature profiles between MBC and primary breast cancer will be presented at the meeting.

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Myc regulates alternative splicing through a network of RNA binding proteins in breast cancer

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The oncogenic transcription factor MYC is one of the most frequently altered genes in cancer and is highly dysregulated in aggressive tumor types, including triple negative breast cancer (TNBC). Although direct targeting of MYC or its regulators in human tumors has proved difficult, the undisputed clinical relevance of this transcription factor warrants continued study for therapeutic targeting of MYC-driven processes in tumors. Recently, we and others have shown the tumorigenic capacity of MYC is critically dependent on the RNA splicing machinery and on several splicing factor RNA-binding proteins (RBPs). Dysregulation of alternative mRNA splicing, a key step in gene expression regulation, is a hallmark of cancer, and can lead to the expression of isoforms driving tumor initiation, progression or drug resistance. Understanding which component(s) of the RNA machinery are regulated by MYC, and the functions of MYC-induced spliced isoforms, may reveal new targets that circumvent prior failures of directly targeting MYC.
Here, we examine MYC-induced changes in gene expression and alternative splicing through RNA-sequencing of breast cell lines and tumors. Using a mammary epithelial cell line with an inducible MYC system, we identified over 4,000 MYC-induced alternative splicing events as well as 378 MYC-induced RBPs. Co-expression network analysis of these RBPs in TCGA breast tumor RNA-seq data uncovered 8 RBP modules, four of which are highly correlated with MYC activity and highly expressed in TNBC. One of these modules is preserved across almost all other TCGA tumor types and remains highly correlated with MYC activity, suggesting a pan-cancer role of this co-expression module. We are now defining the functional role of these RBP modules in MYC-driven tumorigenesis in breast cancer models, as well as identifying their downstream oncogenic splicing targets. Our research project will define the role and regulation of alternative splicing in breast cancer, and more specifically in aggressive tumor types such as TNBC. Our findings will provide mechanistic insight into the role of MYC-driven splicing in tumor maintenance and will uncover novel therapeutic targets for MYC-active tumors.

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# Rna genetic testing improves detection of patients with hereditary breast cancer

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Background: DNA genetic testing is commonly used to inform treatment decisions for breast cancer patients. In recent years, RNA genetic testing has shown promise for increasing the detection of disease-causing variants and decreasing inconclusive results. Here we describe the impact of concurrent DNA and RNA genetic testing on identifying breast cancer patients with germline cancer predisposition who may have been missed by DNA-only testing. Methods: We performed a retrospective review of breast cancer patients who received concurrent DNA and RNA hereditary cancer panel testing between March 2019 and February 2020 at Ambry Genetics. Patients underwent DNA and RNA genetic testing of up to 18 hereditary cancer genes at the discretion of the ordering healthcare provider (*APC, ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, NF1, PALB2, PMS2* exons 1-10, *PTEN, RAD51C, RAD51D,* and *TP53)*. Breast cancer patients with positive results, defined as the presence of a pathogenic or likely pathogenic variant in any of these 18 genes, were selected for inclusion in this study (n=946). Results: Concurrent DNA and RNA genetic testing led to the identification of 23 breast cancer patients with positive results who would have otherwise received inconclusive or negative results with DNA-only testing. These cases represented 2.4% of all positive results reported in the 18 genes studied (n=23/946). The majority of RNA-related positive results occurred in either *ATM* (n=14) or *BRCA1/2* (n=7). The remaining two cases involved alterations in *NF1* and *PMS2*. Guidelines for risk-reducing breast surgery (*BRCA1/2*) and breast imaging surveillance (*ATM, BRCA1/2, NF1*) were relevant for 30.4% and 95.7% of patients with RNA-dependent positive results, respectively. In addition, treatment options such as PARP inhibitors or clinical trial eligibility were potentially implicated for 91.3% of RNA-dependent positives (*BRCA1/2*, *ATM*). In 16 of the 23 cases, variants would have been detected by DNA-only testing but would have remained inconclusive without supporting RNA data. In the remaining 7 cases, abnormal RNA results led to the identification of pathogenic/likely pathogenic intronic variants beyond the analytical range of DNA testing. Thus, these seven patients would have received negative results from DNA-only testing. Four of these cases involved pathogenic/likely pathogenic intronic variants in *ATM* and three involved pathogenic intronic variants in *BRCA1*. Conclusions: One in 41 breast cancer patients who test positive on concurrent DNA and RNA genetic testing would have received negative or inconclusive results from DNA-only testing. These findings demonstrate the impact of a comprehensive diagnostic testing approach that includes concurrent DNA and RNA analysis and highlights the important implications for the personalized management of these breast cancer patients including potential missed opportunities for early detection and prevention of additional cancer and familial testing in the absence of RGT.

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# Lenvatinib plus pembrolizumab for previously treated, advanced triple-negative breast cancer: Early results from the multicohort phase 2 LEAP-005 study

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**Background:** Triple-negative breast cancer (TNBC) is associated with poor survival outcomes and treatment options are limited. These tumors lack therapeutic targets and become rapidly resistant to chemotherapy. The anti–PD-1 antibody pembrolizumab showed durable antitumor activity and manageable safety in patients with TNBC in the KEYNOTE-012, KEYNOTE-086, and KEYNOTE-119 studies. The combination of lenvatinib, an antiangiogenic multiple receptor tyrosine kinase inhibitor, with pembrolizumab has shown promising clinical outcomes in early-phase clinical trials across several cancer types. LEAP-005 (ClinicalTrials.gov, NCT03797326) is an ongoing study evaluating the efficacy and safety of lenvatinib combined with pembrolizumab in patients with previously treated advanced solid tumors. Here, we report the first results from the TNBC cohort of LEAP-005. **Methods:** This ongoing, multicohort, open-label, phase 2 study enrolled patients aged ≥18 y with previously treated, histologically or cytologically confirmed advanced TNBC. PD-L1 expression was assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100). Patients received lenvatinib 20 mg once daily orally plus pembrolizumab 200 mg every 3 weeks intravenously for a maximum of 35 pembrolizumab doses, then lenvatinib alone until progressive disease or unacceptable toxicity. Primary endpoints were objective response rate (ORR) by blinded independent central review per RECIST version 1.1 and safety. Key secondary endpoints were disease control rate (DCR; defined as best overall response of complete response [CR], partial response [PR], or stable disease [SD] per RECIST v1.1), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Safety was monitored through 30 days after the last dose of study drug (90 days for serious AEs), with AEs graded using NCI CTCAE v4.0. **Results:** 31 patients have been enrolled in the TNBC cohort of LEAP-005. Median age was 56 y (range, 37 to 85), 58% had received ≥2 prior lines of therapy, and 26% had CPS ≥10 tumors. As of the April 10, 2020 data cutoff, median follow-up was 7 mo (range, 4 to 13). ORR was 29% (95% CI: 14–48), with 1 CR and 8 PRs. 9 pts had SD, and the DCR (CR + PR + SD) was 58% (95% CI: 39–76). 4 responses (1 CR and 3 PRs) were in patients with CPS ≥10 tumors (n=8) for an ORR of 50% (95% CI: 16–84), and 5 responses (all PRs) were in patients with CPS <10 tumors (n=22) for an ORR of 23% (95% CI: 8–45). Median DOR was not reached (range, 0+ to 8+ mo); 7 (78%) responses were ongoing at data cutoff. Median PFS was 4 mo (95% CI: 2–NR), with a 6-mo rate of 49%. Treatment-related AEs (TRAEs) occurred in 97% of pts; 10% discontinued due to TRAEs. 55% of pts had grade 3-5 TRAEs (1 death due to subarachnoid hemorrhage). **Conclusions:** Lenvatinib in combination with pembrolizumab showed promising antitumor activity with manageable toxicity in patients with previously treated advanced TNBC. Based on these early data, the cohort will be expanded to include 100 patients.

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# Incidences of endometrial events and frequencies of endometrial invasive diagnostic procedures in breast cancer survivors on tamoxifen: A nationwide study

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**Background**Breast cancer survivors who taking tamoxifen as adjuvant therapy have been reported to have more endometrial lesions. According to guidelines, a gynecological assessment is recommended for postmenopausal women, but there is no mention of premenopausal women. The purpose of this study is to compare the risk of endometrial cancer by age at diagnosis, and to investigate frequencies of gynecological exam in breast cancer patients taking tamoxifen in South Korea.
**Methods**A nationwide retrospective cohort study was conducted using South Korea Health Insurance Review and Assessment Service claims data. Between 2010 and 2015, a total of 60,545 (mean follow-up, 66.0 months) newly diagnosed female breast cancer survivors were included. Endometrial evaluation and Dilatation & Curettage (D&C) proportion were analyzed by age at diagnosis. The incidence of endometrial cancer and benign lesions were calculated as incident cases per person-year and analyzed with the Kaplan-Meier method. **Results**The 26,374 patients who taking tamoxifen were divided into four groups by age at diagnosis. The incidence rate of endometrial cancer per 1,000 person-years was 1.13 and 1.45 for age range 50-59 and over 60 and 0.62 and 0.82 for in age under 40 and range 40-49. However, D&C proportion did not all differ from 10 to 11% in each subgroup.
**Conclusions**This nationwide cohort study showed that the risk of endometrial cancer in premenopausal breast cancer women taking tamoxifen was lower than that of postmenopausal women. However, the invasive diagnostic procedure such as aspiration, biopsy, polypectomy and D&C was proceeding at a level that makes no difference with those in postmenopausal women.

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# Trastuzumab deruxtecan (T-DXd; DS-8201) with nivolumab in patients with HER2-expressing, advanced breast cancer: A 2-part, phase 1b, multicenter, open-label study

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**Background**
T-DXd is a novel antibody-drug conjugate composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and membrane-permeable topoisomerase I inhibitor payload. In a phase 2 study in patients (pts) with HER2+ (IHC 3+ or IHC 2+/ISH+), unresectable or metastatic breast cancer (MBC) previously treated with trastuzumab emtansine (T-DM1), the confirmed ORR (cORR) with T-DXd was 60.9% and median PFS (mPFS) was 16.4 mo (Modi *NEJM* 2020). In pts with HER2-low (IHC 2+/ISH−, IHC 1+) advanced BC, cORR was 37.0% and mPFS 11.1 mo in a phase 1 study (Modi *J Clin Oncol* 2020). Recently, T-DXd was approved for the treatment of adult pts with HER2+, unresectable or MBC who have received ≥ 2 prior anti-HER2-based regimens (US) or had prior chemotherapy and are refractory to or intolerant of standard treatments (Japan). In preclinical models, T-DXd combined with an anti-PD-1 antibody had greater efficacy than either agent alone (Iwata *Mol Cancer Ther* 2018). We conducted a phase 1b, open-label, multicenter, 2-part study of T-DXd in combination with nivolumab (Nivo) in pts with HER2-expressing (by centrally testing) MBC or advanced urothelial cancer (DS8201-A-U105; NCT03523572); interim results for the BC cohorts are presented.

**Methods**
Pts were aged ≥18 y and immune checkpoint inhibitor naive. Pts were enrolled in the United States and Europe. In part 1 (dose escalation), pts received T-DXd 3.2 or 5.4 mg/kg intravenously (IV) every 3 weeks (q3w) and Nivo 360 mg IV q3w to determine the recommended dose for expansion (RDE). In part 2, the RDE was given to 2 MBC cohorts: HER2+ (IHC 3+ or IHC 2+/ISH+) disease that progressed on prior T-DM1 or HER2 low (IHC 1+ or IHC 2+/ISH−) disease that progressed on prior standard treatments. The primary efficacy endpoint is cORR by independent central review (ICR) per RECIST version 1.1 in part 2. Additional endpoints include duration of response (DOR), disease control rate (DCR), PFS, OS, safety, and pharmacokinetics.

**Results**
52 pts with MBC were enrolled. In part 1, 4 pts received T-DXd 3.2 mg/kg (HER2+, n=3; HER2 low, n=1), 3 pts received 5.4 mg/kg (all HER2+). In part 2, 45 pts received the RDE of T-DXd 5.4 mg/kg and Nivo 360 mg (HER2+, n=29; HER2 low, n=16 [13 HR+]); median follow-up time was 7.0 and 6.9 mo, respectively.
All pts (n=48) who received RDE were female; median duration of follow-up was 6.9 mo. HER2+ pts had a median age of 55 y and median of 5 prior lines of metastatic/locally advanced therapy. At data cutoff (June 8, 2020), 56.3% of pts remained on treatment (median treatment duration: T-DXd, 6.5 mo; Nivo, 5.2 mo). HER2 low pts had a median age of 47 y, median of 4 prior lines, and 50.0% remained on treatment (median: T-DXd, 6.3 mo; Nivo, 4.9 mo).
In pts treated at RDE, the cORR by ICR in the HER2+ cohort was 59.4% (19/32, 18 PR) and for the HER2 low cohort was 37.5% (6/16, all PR). The DCR was 90.6% and 75.0% in the HER2+ and HER2-low cohorts, respectively. Median DOR was not reached in either cohort; median PFS was 8.6 mo (95% CI, 5.4-NE) for the HER2+ cohort and 6.3 mo (95% CI, 2.3-NE) for the HER2 low cohort.
Adverse events (AEs) grade ≥3 occurred in 43.8% (18.8% related to T-DXd, 18.8% to Nivo) of pts treated at RDE (n=48); anemia (16.7%) and transaminase increase (6.3%) were most common. Nausea (54.2%), fatigue (45.8%), and alopecia (41.7%) were the most common any-grade AEs. 5 pts (10.4%, all HER2+) had treatment-related interstitial lung disease (ILD) as adjudicated by an independent committee (grade 5, n=1; grade 2, n=4). No other deaths associated with a drug-related AE occurred.

**Conclusions**
In pts with HER2-expressing MBC, T-DXd plus Nivo demonstrated antitumor activity consistent with prior studies of T-DXd and had an acceptable safety profile in this interim analysis; whether adding IO therapy to T-DXd benefits pts requires longer follow-up and additional studies.

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# A Phase 2 study of poziotinib in patients with HER2-positive metastatic breast cancer heavily pre-treated with HER2-targeted therapy

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*Background:* Poziotinib is a novel pan-HER inhibitor that irreversibly blocks the EGFR family of tyrosine-kinase receptors and inhibits the proliferation of tumor cells. This study evaluates the safety and clinical activity of poziotinib in patients with HER2-positive metastatic breast cancer (MBC) who received at least 2 therapies (trastuzumab and TDM-1) in dose-schedule ranging study. *Methods:* Patients were treated with oral poziotinib in 2 dose cohorts: 24mg daily 2 weeks/1 week off and 16mg daily continuously in a 21-day cycle. Dose reduction was allowed if toxicity observed. Patients continued treatment until disease progression, death, intolerable AE, or for a maximum of 24 months. The primary endpoint was the objective response rate (ORR), evaluated using RECIST 1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and safety.
*Results:* Sixty-seven patients (33 in 24mg; 34 in 16mg) were enrolled (57 evaluable) in 2 cohorts; all patients either completed or discontinued (36 PD, 5 deaths due to PD, 16 AEs) the study with 1 completed 25 months of treatment. The median (range) age was 57 (29-94) years. Patients were heavily pretreated and the median (range) lines of previous therapy were 7 (2-13) and 4 (2-16) in 2 cohorts respectively [unique drugs 3 (2-5) and 3 (1-9)]; 75% received pertuzumab in addition to trastuzumab and TDM-1 and 37% received at least one tyrosine kinase inhibitor (TKI). The mean relative dose intensity was 57% and 51% with 67% and 47% had dose reductions in 2 cohorts respectively. Common Grade ≥3 treatment-related AEs were similar to other 2$^{nd}$ generation TKIs and include diarrhea (30%), rash (28%) and stomatitis (7%). The ORRs were 27% and 26% with the corresponding median DORs of 5.6 and 13 months respectively. 3 patients in 16mg dose had a CR and another 2 patients had an unconfirmed CR. The DCRs were 50% and 70% in 2 cohorts along with median PFS of 4.1 and 5.8 months respectively. The ORRs were 25% each in 2 cohorts in 24 and 20 heavily pre-treated patients with ≥4 lines of therapy that included trastuzumab, TDM1 and pertuzumab. The ORRs were 23% and 0% in 2 cohorts with 13 and 10 patients received at least one tyrosine kinase inhibitor (TKI) as the sample sizes were small to make any meaningful evaluation.
*Conclusion:* Poziotinib has demonstrated clinical activity in this dose-ranging study with tumor reduction shown in the majority of patients along with durable responses in this heavily pre-treated MBC patients. Safety profile was mechanism related and was similar to other 2nd generation TKIs.

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Glycemic index, glycemic load and breast cancer risk: Results from the prospective NutriNet-Santé cohort

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**Background:** Evidence is accumulating that high dietary glycemic index (GI) and glycemic load (GL) are risk factors for several metabolic disorders, e.g. diabetes or cardiovascular diseases, but evidence on GI/GL and cancer is less consistent. However, mechanistic data suggest that food with high-GI may contribute to carcinogenesis through the insulin resistance pathway.**Objective:** The objective was to study the associations between dietary GI/GL and breast cancer risk.**Design:** Population based prospective cohort study.**Setting and Participants:** 81,526 women aged ≥18y (mean age: 40.8±14.0y), free of cancer at baseline and with no prevalence or incidence of diabetes, from the French NutriNet-Santé cohort (2009-2019) were included in the analyses. 24-hour dietary records linked with a nutritional composition table for >3,500 food/beverage items containing GI values and carbohydrate content enabled us to compute average dietary GI and GL.**Main outcome measures:** Associations between GI; GL; proportion of energy and proportion of carbohydrates from low-GI (GI≤55) and from medium/high-GI (GI>55) foods and risk of breast cancer were assessed by Cox proportional hazard models adjusted for known risk factors (sociodemographic, anthropometric, lifestyle, medical history, and nutritional factors).**Results:** A higher dietary GL was associated with higer postmenopausal breast cancer risk (n=572, hazard ratio for quintile 5 versus quintile 1: 1.64 confidence interval 1.06-2.55 $P_{trend}$=0.03). Percentage of energy intake from medium/high-GI foods was associated with higher breast cancer risk ($HR_{Q5vs.Q1}$=1.34 (1.05-1.71), $P_{trend}$=0.04), more specifically postmenopausal breast cancer ($HR_{Q5vs.Q1}$=1.36 (1.00-1.84), $P_{trend}$=0.02). Carbohydrates intake from medium/high-GI foods was also associated with higher breast cancer risk ($HR_{Q5vs.Q1}$=1.34 (1.05-1.71), $P_{trend}$=0.04) in both premenopausal ($HR_{Q5vs.Q1}$=1.49 (1.03-2.17), $P_{trend}$=0.04) and postmenopausal ($HR_{Q5vs.Q1}$=1.44 (1.08-1.93), $P_{trend}$=0.03) women, whereas carbohydrates from low-GI foods was associated with lower breast cancer risk ($HR_{Q5vs.Q1}$=0.74 (0.59-0.92), $P_{trend}$=0.04), only among postmenopausal women ($HR_{Q5vs.Q1}$=0.69 (0.52-0.92), $P_{trend}$=0.03).
**Conclusion:** The consumption of foods with high-GI was associated increased breast cancer risk. If these results are confirmed dietary GI and GL should be considered as modifiable risk factor for primary breast cancer prevention.

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# Use of low-dose tamoxifen to increase screening sensitivity in mammography of premenopausal women

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**Background**. High mammographic density decreases sensitivity of both 2D and 3D mammography. Tamoxifen reduces mammographic density thereby potentially increasing screening sensitivity. We tested if low-dose tamoxifen could be used to increase sensitivity of mammography in premenopausal women.

**Methods**. Mammography screening sensitivity was calculated using the Swedish KARMA prospective screening cohort including 28,282 premenopausal women. Two models were fitted to estimate screening sensitivity and tumor size based on density level at baseline. BI-RADS dependent sensitivity was estimated in each of the four categories (A, B, C, D). The 2.5 mg tamoxifen arm of the KARISMA tamoxifen trial was used to define the change of mammographic density after exposure to low-dose tamoxifen. The models predicted screening sensitivity and tumor size in the KARMA cohort assuming that all women were exposed to 2.5 mg of tamoxifen. Reduction in interval and advanced cancers were estimated in women with mammographic density decrease of 10%, 20%, 30% and 50%. Mammographic density was measured as percent density and a computerized BI-RADS score was estimated using the STRATUS tool.

**Results**. During 8 years of follow-up, 287 (56%) screening detected and 230 (44%) interval cancers were diagnosed in the KARMA cohort. The screening sensitivities, before exposure to tamoxifen, were 77%, 69%, 53%, 46% for BI-RADS categories A, B, C and D, respectively. The mean density decrease after exposure to 2.5 mg of tamoxifen was 17.4% and the BI-RADS category dependent change in sensitivity was 0% (p=0.95), 2% (p=0.01), 4% (p<0.001), and 5% (p<0.001), respectively. A density decrease of ≥20% would reduce the number of interval cancers with 24% (p<0.01) and the probability of identifying >20 mm tumors with 4% (p<0.01).

**Conclusion**. Low-dose tamoxifen has the potential to increase the sensitivity of a screening mammogram and thereby reduce the proportion of interval and advanced cancers.

**Table.** Number of interval cancers per 100,000 age standardized screened women, change in number of interval cancers after tamoxifen exposure, by percentage mammographic density decrease. Density response is presented using density responder cut-offs and is stratified by computer-generated BI-RADS categories A+B, C, D. The normal (unexposed) group is included as the reference.

| Number of interval cancers (N) | Normal | Density responder cut-off (%) | | | |
|---|---|---|---|---|---|
| | group | ≥10 | ≥20 | ≥30 | ≥50 |
| BI-RADS A+B | 155 | 107 | 102 | 100 | 88 |
| BI-RADS C | 382 | 356 | 339 | 299 | 253 |
| BI-RADS D | 276 | 197 | 180 | 160 | 129 |
| BI-RADS A to D combined | 813 | 660 | 621 | 559 | 470 |
| | | *Difference compared to normal group, N (%)* | | | |
| BI-RADS A+B | ref. | -48 (-31) | -53 (-34) | -55 (-35) | -67 (-43) |
| BI-RADS C | ref. | -26 (-7) | -43 (-11) | -83 (-22) | -129 (-34) |
| BI-RADS D | ref. | -79 (-29) | -96 (-35) | -116 (-42) | -147 (-53) |
| BI-RADS A to D combined | ref. | -153 (-19) | -192 (-24) | -254 (-31) | -343 (-42) |

Number of interval cancers were significantly reduced in each density decrease group, p<0.01.

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# Association between biomarkers and response to pembrolizumab in patients with metastatic triple-negative breast cancer (mTNBC): Exploratory analysis from KEYNOTE-086

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**Background:** In the phase 2 KEYNOTE-086 study (NCT02447003), pembrolizumab monotherapy had durable antitumor activity in a subset of patients with previously treated mTNBC (cohort A; n = 170) and in patients with previously untreated PD-L1-positive mTNBC (cohort B; n = 84). In this exploratory analysis of KEYNOTE-086, we evaluated the association between several biomarkers and response to pembrolizumab. **Methods:** Cohort A enrolled patients regardless of PD-L1 expression who had documented disease progression following ≥1 systemic therapy for metastatic disease. Cohort B enrolled patients with PD-L1-positive (combined positive score [CPS] ≥1) tumors who had not received prior systemic therapy for metastatic disease. Immunohistochemistry was used to measure PD-L1 CPS and CD8 density; H&E staining for percentage of stromal tumor infiltrating lymphocytes (sTILs); RNA-sequencing for 18-gene T-cell-inflamed gene expression profile (GEP), angiogenesis, and glycolysis signatures; and whole exome sequencing (paired tumor and germline) for TMB (TMB-H defined as ≥175 mut/exome), HRD-LOH (DNA damage), Signature 3, and APOBEC. Biomarkers were analyzed as continuous variables in cohorts A and B combined and individually. Area under the receiver operating characteristic curve was estimated between each biomarker and overall response rate (ORR). Wald test *P*-values were calculated using logistic regression adjusted for cohort and Eastern Cooperative Oncology Group performance status. Germline and somatic *BRCA1/2* mutations were pooled; one-sided *P*-value was calculated using Fisher's exact test. Spearman's correlation was used for correlations. **Results:** Biomarker data were available in the following number of patients: 253 (99.6%; PD-L1), 204 (80.3%; CD8), 187 (73.6%; GEP), 171 (67.3%; TMB/HRD), 228 (89.8%; sTILs), 163 (64.2%; Signature 3/APOBEC), and 132 (52.0%; angiogenesis/glycolysis). When data from cohorts A and B were combined, PD-L1 CPS (median 2; IQR 0-10), CD8 (median 159; IQR 62-319), GEP (median -0.34; IQR -0.57 to -0.11), TMB (median 82 mut/exome; IQR 50-139), and sTILs (median 5; IQR 2-20) were significantly associated with ORR (**Table**). There were moderate correlations between PD-L1 and GEP (r = 0.532), PD-L1 and sTILs (r = 0.451), and GEP and sTILs (r = 0.490). No correlation was observed between TMB and PD-L1 (r = 0.038), GEP (r = -0.035), and sTILs (r = -0.031). When cohorts were combined, TMB was significantly associated with ORR, PFS, and OS after adjustment for PD-L1, GEP, CD8, or sTILs. HRD-LOH score, Signature 3, and APOBEC were not significantly associated with ORR (**Table**); *P* for *BRCA1*/2 was 0.2385. The angiogenesis signature was associated with lack of response while the glycolysis signature was associated with response to pembrolizumab (**Table**). **Conclusions:** In this exploratory biomarker analysis from KEYNOTE-086, higher levels of PD-L1, GEP, TMB, CD8 IHC, sTILs, and the glycolysis signature were associated with increased response to pembrolizumab monotherapy. These findings may help identify patients with mTNBC who are most likely to respond to pembrolizumab.

Table. Association of Biomarkers as Continuous Variables With Pembrolizumab Objective Response

| **Biomarker** | **Combined Cohorts AUC** | **Combined Cohorts *P**** | **Combined Cohorts Multitest corrected *P*** | **Cohort A AUC** | **Cohort B AUC** |
|---|---|---|---|---|---|
| PD-L1 | 0.674 | 0.040 | - | 0.544 | 0.654 |
| GEP | 0.748 | 0.003 | - | 0.837 | 0.561 |
| TMB | 0.627 | 0.007 | - | 0.548 | 0.710 |
| CD8 IHC | 0.76 | 0.00002 | 0.00012 | 0.85 | 0.68 |
| sTILs | 0.671 | 0.012 | - | 0.632 | 0.641 |
| HRD | 0.394 | 0.874 | - | 0.522 | 0.316 |
| Signature 3 | 0.683 | 0.072 | - | 0.697 | 0.736 |
| APOBEC | 0.528 | 0.537 | - | 0.674 | 0.623 |
| Angiogenesis | 0.677 | 0.009 | 0.045 | 0.661 | 0.731 |
| Glycolysis | 0.612 | 0.009 | 0.036 | 0.859 | 0.459 |
| AUC, area under the curve.<br>*One-sided *P*-values are shown for all biomarkers except for Signature 3 and APOBEC, for which 2-sided *P*-values are shown. | | | | | |

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Identification of novel molecules that enhance neratinib efficacy in triple-negative breast cancer by high-throughput RNA interference

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**Background**: Neratinib is a potent, irreversible pan-HER inhibitor that inhibits the ErbB family members EGFR, HER2, and HER4 and downstream signal transduction of these receptors. Triple-negative breast cancer (TNBC) is a heterogeneous disease that lacks druggable levels of receptors for estrogen, progesterone and HER2 and therefore challenging to treat. There is evidence that some cases of TNBC have activated signaling pathways mediated by ErbB family members that may contribute to aggressive behavior. The purpose of this preclinical study was to identify and validate kinases whose targeting may enhance the antitumor activity of neratinib in TNBC cell lines. **Methods**: *In vitro* proliferation assays were used to evaluate the efficacy of neratinib in TNBC cell lines. Baseline and post-neratinib-treatment expression of EGFR and phosphorylated EGFR (phospho-EGFR) were assessed via Western blot analysis in 18 TNBC cell lines. Reverse-phase protein array (RPPA) was used to profile and validate the signaling networks induced by neratinib. To identify potential targets or pathways that may synergize with neratinib treatment, we performed high-throughput RNA interference (HT RNAi) screening using a 709-kinome library. CellTiter-Blue, sulforhodamine B, and soft-agar assays were performed to evaluate the antiproliferative effect of neratinib alone and with target inhibitor. Mammary fat pad xenograft models were used to evaluate the efficacy of neratinib alone or with inhibitor *in vivo*. **Results**: *In vitro* proliferation assays showed that the half-maximal inhibitory concentration ($IC_{50}$) of neratinib in tested TNBC cell lines ranged from 0.16 µM to 1.25 µM. RPPA and Western blot analyses revealed that the efficacy of neratinib correlated with phospho-EGFR expression levels across the TNBC cell lines tested ($R^2 = 0.3245$). Among the tested TNBC cell lines, SUM149 cells (*PIK3CA* wild-type) were selected for high throughput RNAi screening because this cell line has high EGFR expression and is moderately sensitive to neratinib ($IC_{50} = 0.35$ µM). We identified the 40 most relevant kinase targets by the sensitivity index analysis, and further pathway analysis identified PI3K/AKT/mTOR (drug: everolimus) and MAPK (drug: trametinib) as major canonical pathways whose targeting enhanced the cytotoxic effect of neratinib. Everolimus (mTOR inhibitor) produced a strong antiproliferative effect when combined with neratinib in most tested TNBC cell lines (12 of 15 cell lines; combination index [CI] values, 0.1-0.5) and was more effective in *PIK3CA*-mutated compared to wildtype cell lines. Trametinib (MEK inhibitor) showed a moderate antiproliferative effect (effective in 10 of 15 cell lines; CI values, 0.2-0.9). Synergistic antitumor effects of neratinib combined with everolimus or with trametinib were also observed in anchorage-independent growth conditions ($P < 0.05$). *In vivo* experiments demonstrated that neratinib plus everolimus and neratinib plus trametinib combinations inhibited tumor growth in the SUM149 xenograft model for than single drug (neratinib, 42.3% growth inhibition; everolimus, 29.7%; trametinib, 47.1%; neratinib plus everolimus, 69.7%; neratinib plus trametinib, 77.7%; $P < 0.0001$). **Conclusion**: Combining neratinib with everolimus or with trametinib enhanced the antitumor effects of these drugs in TNBC regardless of *PIK3CA* mutation status, and clinical investigations evaluating these combination regimens for the treatment of TNBC are warranted.

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# Endocrine therapy non-persistence and recurrence in young women with early stage breast cancer

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**Background:** Young age at diagnosis is an independent risk factor for recurrence and death from breast cancer (BC), with the greatest impact of young age demonstrated in hormone receptor positive (HR+) disease. Younger women are less likely to be adherent to endocrine therapy (ET), which may contribute to disparate outcomes. **Methods:** As part of a prospective cohort that enrolled women with BC diagnosed at age ≤40 between 2006-2016, we identified women with HR+, Stage I-III BC. Serial surveys with items assessing socio-demographic and treatment information including medication use are administered 1-2 times per year. Medical record review was used to ascertain stage and HR status and to confirm recurrent disease (locoregional, distant, or new primary breast cancer). Women who initiated ET but discontinued it <5-years post-diagnosis without resumption were classified as non-persistent. Univariable and multivariable regression models were fit to identify predictors of non-persistence and recurrence.**Results:** Among 607 women who initiated ET (median age at diagnosis: 36, range:17-40; 38%, 45%, 17% were Stage 1, 2, and 3, respectively).16% (99/607) were non-persistent, of whom 30% (30/99) discontinued ET ≤2 years post-diagnosis and over half had discontinued (54%, 54/99) by 3 years. In multivariable regression, those who were younger at diagnosis (age ≤30 vs. 36-40: OR: 3.39, 95% CI: 1.84-6.24; age 31-36 vs. 36-40: OR: 2.81 95% CI: 1.70-4.64) were more likely to discontinue ET while those with a higher stage at diagnosis were less likely to discontinue ET (Stage 2 vs. 1: OR: 0.46, 95% CI: 0.29-0.74; Stage 3 vs 1: OR: 0.32, 95% CI: 0.15-0.68). At a median follow-up time from diagnosis of 7.8 years (range 1-13 years), 15% of women (88/607) recurred or developed a new primary BC at a median time from diagnosis of 3.5 years (range 1-12 years). Of these, 66% (58/88) were distant recurrences, 32% (28/88) loco-regional, and 2% (2/88) new primary BCs. Rates of recurrence were higher among women who were persistent (81/508, 16%) vs. non-persistent (7/99, 7%, p=0.02). In multivariable regression, those who were non-persistent were less likely to recur (OR: 0.43, 95% CI: 0.19-0.98) while those with a higher stage were more likely to recur (Stage 3 vs. 1: OR: 2.36, 95% CI: 1.03-5.41). Sociodemographic, patient, and other treatment factors did not predict recurrence. **Conclusions:** Approximately 16% of young women with HR+ BC stop ET earlier than indicated, however non-persistence was not a risk factor for BC recurrence a median of 8 years following diagnosis in our cohort. Importantly, women with higher risk disease who are likely to benefit most from adherence to ET were less likely to discontinue treatment. Extended follow-up will further inform the impact of non-persistence on the incidence of late recurrences for which women with HR+ BC are at increased risk.

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Pathologic complete response and 3-year survival with or without pertuzumab using real-world data of stage II and III HER2-positive breast cancer

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**Background** Pertuzumab greatly improves pathologic complete response (pCR) rates in early stage HER2-positive breast cancer. Long-term benefit of pertuzumab, however, is less well established, as follow-up of the NEOSPHERE and APHINITY trials did not show clear improvement in overall survival, although patients with high risk of recurrence (e.g. node positive) appeared to benefit. Since its long-term benefit remains uncertain, we compared outcome of patients treated with or without pertuzumab in a quasi-random experiment using real-world data.
**Methods** We identified all patients with stage II-III HER2-positive breast cancer in the Netherlands treated with neoadjuvant trastuzumab containing chemotherapy between November 2013 and January 2016 from the nationwide Netherlands Cancer Registry. During this period, reimbursement of pertuzumab in the Netherlands was pending and pertuzumab was only available as trial medication for patients in 37 hospitals that participated in the TRAIN-2 study. This setting created a unique opportunity to compare two quasi-random cohorts of patients treated with or without pertuzumab. We used logistic regression analysis to evaluate the association between pertuzumab use and pCR (ypT0/is, ypN0) and Kaplan-Meier estimates and Cox regression analysis for the association with overall survival (OS). Multivariate analyses included age, cT-status, cN-status, hormone receptor (HR) status and grade. Multiple imputation was used to impute missing data for multivariate analysis.
**Results** We identified 1,124 eligible patients of whom 453 (40%) had received pertuzumab. Baseline characteristics were comparable with and without pertuzumab: 61% of tumors were cT2, 22% cT3, 66% were node positive and 62% ER and/or PR-positive. Grade was missing for 17% in patients treated with and 46% in patients treated without pertuzumab and therefor imputed. PCR in breast and axilla could be determined in 1,091 patients. Pertuzumab use improved pCR rates (65% vs 41%, adjusted odds ratio [aOR] 3.01; 95% confidence interval [CI] 2.29-3.97; p<0.001). At a median follow-up of 59 months (IQR 53-66) 23 deaths had occurred in the pertuzumab group and 68 in the non-pertuzumab group (3-year OS 98% vs 95%; adjusted hazard ratio [aHR]: 0.61; 95% CI:0.38-1.00, p=0.048). Pertuzumab benefit appeared largest in ER/PR negative and cN+ tumors, although the number of events in each subgroup was too small for formal comparisons. Complete-case analysis showed similar aHRs, but with broader 95% confident intervals.

| | pCR (%) | | 3-yr OS (%) | | |
|---|---|---|---|---|---|
| | Ptz | no Ptz | Ptz | no Ptz | aHR (95%CI) |
| Overall | 65% | 41% | 98% | 95% | 0.61 (0.38-1.00) |
| HR-positive | 51% | 32% | 98% | 97% | 0.70 (0.36-1.33) |
| HR-negative | 86% | 55% | 97% | 92% | 0.54 (0.26-1.13) |
| cN0 | 71% | 46% | 99% | 100% | 0.54 (0.14-2.00) |
| cN+ | 62% | 38% | 97% | 93% | 0.65 (0.39-1.09) |

**Conclusion** This real-world quasi-experiment confirms the efficacy of pertuzumab to achieve a pCR in stage II and III HER2-positive breast cancer. In addition, these data suggest a small absolute overall survival benefit with pertuzumab, most prominently in hormone receptor negative and node positive tumors. Despite the unique setting of two quasi-random cohorts treated with or without pertuzumab and very similar baseline characteristics, residual confounding cannot be fully excluded. Breast cancer specific evaluation and translational work including central revision of tumor grade for missing cases is pending.

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# Predictors of 10-year overall survival in patients with breast cancer

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**Background:** The combination of mass screening programs and improved, targeted therapies have led to a substantial increase in the number of breast cancer (BC) survivors. Despite a growing majority of patients surviving beyond 5 years, few studies have examined prognostic factors associated with 10-year overall survival (OS) in breast cancer.
**Methods:** We conducted a retrospective analysis of patients with BC using the *National Cancer Database* (NCDB). Our dataset documents survival leading up to and including the year 2016. Thus, to evaluate factors associated with 10-year OS, we included patients diagnosed between 2004-2006. We described sociodemographic and clinicopathologic characteristics of this cohort using frequencies/percentages. Variables were included in a multiple logistic regression model predicting 10-year OS, and considered statistically significant to a p-value <0.001, due to the large sample size.
**Results:** A total of n=515,610 patients with BC were analyzed. The age distribution included n=125,657 (24.4%) <50 years, n=256,003 (49.7%) between 50-70 years, and n=133,950 (26.0%) >70 years. N=440,048 (87.6%) were White, n=52,220 (10.4%) were Black, and n=9872 (2.0%) were Asian. 10-year OS by AJCC clinical stage was: 54.5% for patients diagnosed at stage 0, 50.0% at stage I, 42.4% at stage II, 29.7% at stage III, and 6.1% at stage IV. Sociodemographic variables significantly associated with 10-year OS were: age, race, income, insurance status, and facility type (Table 1). Black patients were less likely to exhibit 10-year OS compared to White patients (40.7% compared to 48.0%, OR 0.821, 95% CI 0.786-0.858, p<0.001). Patients with an estimated annual income >$46,000 were more likely to experience 10-year OS compared to those with an annual income <$30,000 (50.5% compared to 41.8%, OR 1.126, 95% CI 1.076-1.178, p<0.001). Compared to patients treated at community cancer programs (CPs), those treated at comprehensive community CPs were more likely to experience long-term survival (47.7% versus 43.8%, OR 1.125, 95% CI 1.077-1.175, p<0.001). Clinicopathologic factors significantly associated with 10-year OS were: Charlson/Deyo comorbidity index, AJCC clinical staging, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, the use of surgery, radiation, chemotherapy, hormonal therapy, and immunotherapy (Table 1). Compared to patients with well-differentiated tumors, those with moderately-differentiated (OR 0.889, 95% CI 0.860-0.919, p<0.001) and poorly-differentiated tumors (OR 0.782, 95% CI 752-0.812, p<0.001) had lower long-term survival. ER positivity was associated with a lower likelihood of 10-year OS, while PR positivity was associated with a higher likelihood of 10-year OS. However, effect sizes for receptor status are small (ORs between 0.90-1.10), and thus may not have clinical relevance despite statistical significance. HER2 status was not documented in the NCDB before 2010, so its prognostic value could not be evaluated. Tumor histology was not significantly associated with 10-year OS.
**Conclusions:** 10-year OS data for BC is scarce. We found high rates of 10-year OS, particularly in patients diagnosed at early stages. This is welcomed news; emphasizing the real-world impact of population screening. As anticipated, racial disparities and social determinants of health remain relevant prognosticators of long-term survival.

**Table 1:** Multiple logistic regression model predicting 10-year OS in patients with breast cancer.

| Variable | No. (%) | 10-year OS | | | | |
|---|---|---|---|---|---|---|
| | | % | OR | 95% CI | | p-value |
| Age | | | | | | <.001 |
| *<50 (ref)* | 125,657 (24.4%) | 54.1% | 1.000 | - | - | - |
| *50-70* | 256,003 (49.7%) | 53.0% | .946 | .916 | .978 | .001 |
| *>70* | 133,950 (26.0%) | 30.1% | .427 | .407 | .448 | <.001 |
| Race | | | | | | <.001 |
| *White (ref)* | 440,048 (87.6%) | 48.0% | 1.000 | - | - | - |
| *Black* | 52,220 (10.4%) | 40.7% | .821 | .786 | .858 | <.001 |
| *Asian* | 9872 (2.0%) | 51.9% | 1.166 | 1.067 | 1.275 | .001 |
| Ethnicity | | | | | | |
| *Hispanic (ref)* | 445,220 (95.6%) | 47.7% | 1.000 | - | - | - |
| *Non-Hispanic* | 20,481 (4.4%) | 44.4% | .936 | .878 | .998 | .042 |
| Income | | | | | | <.001 |
| *<$30,000 (ref)* | 55,038 (11.0%) | 41.8% | 1.000 | - | - | - |
| *$30,000-$34,999* | 79,054 (15.8%) | 44.9% | 1.026 | .977 | 1.078 | .296 |
| *$35,000-$45,999* | 133,171 (26.6%) | 46.7% | 1.065 | 1.017 | 1.115 | .008 |
| *>$46,000* | 233,078 (46.6%) | 50.5% | 1.126 | 1.076 | 1.178 | <.001 |
| Insurance status | | | | | | <.001 |
| *Uninsured (ref)* | 10,440 (2.1%) | 36.8% | 1.000 | - | - | - |
| *Private insurance* | 284,063 (56.5%) | 55.4% | 1.552 | 1.417 | 1.701 | <.001 |
| *Medicare* | 181,088 (36.0%) | 36.5% | 1.264 | 1.150 | 1.390 | <.001 |
| *Medicaid/other governmental insurance* | 26,766 (5.3%) | 41.8% | 1.211 | 1.092 | 1.343 | <.001 |
| Facility type | | | | | | <.001 |
| *Community cancer program (ref)* | 46,176 (9.4%) | 43.8% | 1.000 | - | - | - |
| *Comprehensive community cancer program* | 227,815 (46.5%) | 47.7% | 1.125 | 1.077 | 1.175 | <.001 |
| *Academic/research program* | 142,123 (29.0%) | 49.0% | 1.063 | 1.015 | 1.113 | .010 |
| *Integrated network cancer program* | 73,703 (15.0%) | 44.6% | .819 | .776 | .865 | <.001 |
| Setting | | | | | | .001 |
| *Metro (ref)* | 427,832 (85.6%) | 47.6% | 1.000 | - | - | - |
| *Urban* | 63,288 (12.7%) | 47.4% | 1.076 | 1.034 | 1.120 | <.001 |
| *Rural* | 8534 (1.7%) | 47.4% | 1.091 | .984 | 1.209 | .099 |
| Charlson/Deyo comorbidity index | | | | | | .000 |
| *0 (ref)* | 450,329 (87.3%) | 49.1% | 1.000 | - | - | - |
| *1* | 52,983 (10.3%) | 38.3% | .746 | .717 | .777 | <.001 |
| *2* | 9425 (1.8%) | 25.1% | .506 | .459 | .557 | <.001 |
| *3* | 2873 (0.6%) | 16.4% | .343 | .280 | .421 | <.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| AJCC clinical staging | | | | | | <.001 |
| *0 (ref)* | 59,736 (25.7%) | 54.5% | 1.000 | - | - | - |
| *1* | 87,698 (37.7%) | 50.0% | .731 | .703 | .760 | <.001 |
| *2* | 51,604 (22.2%) | 42.4% | .526 | .503 | .551 | <.001 |
| *3* | 18,871 (8.1%) | 29.7% | .281 | .264 | .299 | <.001 |
| *4* | 14,620 (6.3%) | 6.1% | .073 | .065 | .082 | <.001 |
| Grade | | | | | | <.001 |
| *Well-differentiated (ref)* | 94,046 (21.2%) | 51.6% | 1.000 | - | - | - |
| *Moderately-differentiated* | 184,976 (41.7%) | 48.5% | .889 | .860 | .919 | <.001 |
| *Poorly differentiated* | 164,490 (37.1%) | 44.9% | .782 | .752 | .812 | <.001 |
| Histology | | | | | | .007 |
| *Ductal carcinoma (ref)* | 367,409 (72.7%) | 47.7% | 1.000 | - | - | - |
| *Lobular carcinoma* | 79,387 (15.7%) | 47.3% | .993 | .957 | 1.031 | .720 |
| *Other carcinoma* | 47,959 (9.5%) | 49.1% | 1.013 | .966 | 1.061 | .598 |
| *Epithelial-myoepithelial* | 1861 (0.4%) | 42.1% | .898 | .703 | 1.146 | .385 |
| *Papillary* | 6005 (1.2%) | 30.8% | 1.054 | .883 | 1.260 | .559 |
| *Fibroepithelial* | 2058 (0.4%) | 34.9% | .937 | .755 | 1.162 | .552 |
| *Mesenchymal* | 402 (0.1%) | 21.4% | .713 | 0.309 | 1.645 | 427 |
| Estrogen receptor status | | | | | | |
| *Negative (ref)* | 97,628 (21.9%) | 43.9% | 1.000 | - | - | - |
| *Positive* | 348,611 (78.1%) | 48.6% | .908 | .868 | .949 | <.001 |
| Progesterone receptor status | | | | | | |
| *Negative (ref)* | 147,951 (33.6%) | 44.0% | 1.000 | - | - | - |
| *Positive* | 292,529 (66.4%) | 49.3% | 1.095 | 1.057 | 1.134 | <.001 |
| Type of surgery | | | | | | .000 |
| *None (ref)* | 30,799 (6.0%) | 15.8% | 1.000 | - | - | - |
| *Lumpectomy* | 294,554 (57.3%) | 52.6% | 2.300 | 2.112 | 2.506 | <.001 |
| *Mastectomy* | 188,531 (36.7%) | 44.3% | 2.320 | 2.134 | 2.523 | <.001 |
| Radiation | | | | | | |
| *No (ref)* | 239,355 (47.5%) | 40.4% | 1.000 | - | - | - |
| *Yes* | 264,681 (52.5%) | 53.3% | 1.385 | 1.341 | 1.430 | <.001 |
| Chemotherapy | | | | | | |
| *No (ref)* | 309,000 (62.9%) | 46.0% | 1.000 | - | - | - |
| *Yes* | 182,510 (37.1%) | 49.2% | 1.375 | 1.331 | 1.420 | <.001 |
| Hormonal therapy | | | | | | |
| *No (ref)* | 245,859 (51.0%) | 42.3% | 1.000 | - | - | - |
| *Yes* | 236,454 (49.0%) | 51.9% | 1.207 | 1.167 | 1.248 | <.001 |
| Immunotherapy | | | | | | |
| *No (ref)* | 497,793 (99.6%) | 47.2% | 1.000 | - | - | - |
| *Yes* | 1862 (0.4%) | 43.3% | 1.273 | 1.236 | 1.311 | <.001 |

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# Trastuzumab deruxtecan (T-DXd; DS-8201) combinations in patients with HER2-positive advanced or metastatic breast cancer: A phase 1b/2 open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast07)

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**Background**
HER2-targeted therapies have substantially improved survival in patients with HER2-positive (immunohistochemistry [IHC] 3+ or IHC2+/in situ hybridization-positive) advanced or metastatic breast cancer. Despite significant advancements, patients ultimately develop resistance to standard-of-care HER2-targeted therapies. Therefore, a need remains for regimens that prolong disease control and survival in these patients. T-DXd is a HER2-targeted antibody-drug conjugate containing a linker selectively cleaved in tumor cells and a topoisomerase I inhibitor payload with high cell-membrane permeability. T-DXd has been approved by the FDA for use in adult patients with unresectable or metastatic HER2-positive breast cancer who have received ≥ 2 prior anti-HER2-based regimens in the metastatic setting and by Japan's Ministry of Health, Labour and Welfare for use in patients with HER2-positive unresectable or recurrent breast cancer after prior chemotherapy (use limited to patients refractory to or intolerant of standard treatments). Results from the phase 2 DESTINY-Breast01 trial demonstrated an objective response rate (ORR) of 60.9% per independent central review and a median progression-free survival (PFS) of 16.4 months in a heavily pretreated population (median of 6 prior lines of therapy) of patients with HER2-positive advanced or metastatic breast cancer treated with T-DXd (Modi S, et al. *N Engl J Med*. 2020;382:610-621). Here, we describe a phase 1b/2 trial evaluating the safety and preliminary antitumor activity of T-DXd combinations in patients with HER2-positive advanced or metastatic breast cancer.

**Study Description**
DESTINY-Breast07 is a global, multicenter, open-label, phase 1b/2 dose-finding and dose-expansion trial designed to evaluate the safety, tolerability, and preliminary antitumor activity of T-DXd in combination with other therapies in patients with HER2-positive advanced or metastatic breast cancer. Patients will be enrolled globally at ≈ 110 sites in ≈ 10 countries. The study will initially consist of 4 combination modules, each with 2 parts: dose finding (part 1) and dose expansion (part 2), and a T-DXd monotherapy module (part 2 only). The 4 combination modules will enroll patients for treatment with (1) T-DXd + durvalumab, (2) T-DXd + pertuzumab, (3) T-DXd + paclitaxel, or (4) T-DXd + durvalumab + paclitaxel. New combination treatment modules may be added via protocol amendment. Part 1 of each combination module will enroll patients who have had disease progression on ≥ 1 prior line of therapy in the metastatic setting. In part 2, patients who have received no prior therapy for metastatic disease will be randomized to receive a combination regimen or T-DXd monotherapy. Antitumor activity will be evaluated based on investigator assessment according to RECIST 1.1. The primary endpoint is to assess the safety and tolerability of T-DXd combinations and determine the recommended phase 2 doses. Secondary endpoints include ORR, PFS, duration of response, overall survival, pharmacokinetics, and immunogenicity.

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# Metastatic breast cancer patients' preferences and expectations for oral chemotherapy

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**Introduction:** As options for cancer treatment continue to expand, there is a growing need to understand patients' preferences for treatment options and their tolerance for related side effects. The aims of the present analysis were to 1) describe metastatic breast cancer (MBC) patient and survivor perceptions of intravenous (IV) and oral chemotherapy modalities, and 2) explore the relationship between modality perceptions, tolerance for side effects, and current levels of physical and social functioning.

**Methods**: 129 MBC patients were recruited to participate in an online research survey about expectations and preferences for oral and IV chemotherapy treatments. Respondents were also asked to report their willingness to tolerate various chemotherapy side effects using multi-item Likert scales. Quality of life was assessed using two Patient-Reported Outcomes Measurement Information System (PROMIS-29v2.0) subscales, Physical Function and Ability to Participate in Social Roles and Activities, with transformed T scores used for purposes of interpretation.

**Results**: Respondents were 91% White and 6% Black with ages ranging from 28 to 77 years old ($M$= 58.0, $SD$=10.1). Time since diagnosis ranged from <1 to 32 years ($M$=11.2, $SD$=6.4). Almost half of respondents (46%) reported having received both oral and IV chemotherapy at some point during their treatment history, while 36% reported having received only IV and 11% reported having received only oral chemotherapy. When assuming equal effectiveness of the two treatments, the majority of respondents stated a preference for oral chemotherapy (72%) versus IV chemotherapy (11%), while 17% stated no preference. The most frequently expected benefits of oral chemotherapy included ease of managing medication at home (76%), less need to travel to treatment center (81%), and freedom to travel or work while on treatment (73%). The severe (grade III/IV) side effects participants were least willing to tolerate (*not at all* or *not very willing*) included hand-foot syndrome (58%), diarrhea (58%), neuropathy (61%), and nausea (57%).

Controlling for treatment history, participants who indicated a preference for oral chemotherapy were more likely to have higher expectations for oral chemo ($t$=-2.69, $p$<.01) and better physical ($t$=-2.06, $p$<.05) and social functioning ($t$=-2.27, $p$<.05). Additionally, they reported less willingness to tolerate key side effects: nausea ($t$=2.40, $p$<.05) and neuropathy ($t$=2.10, $p$<.05)

**Conclusion:** Many MBC patients report a preference for oral chemotherapy and believe it will confer benefits including fewer disruptions to work and life. Those who prefer oral chemotherapy are less willing to tolerate side effects and report better social and physical functioning. As options for treatment continue to expand, it is important to understand the shifting perceptions of available treatments among patients. Patients' attitudes, beliefs, and behaviors can and do influence treatment decision-making and adherence. Additionally, when patients have a better understanding of the treatments they are being offered, they are more likely to have a proactive role in the treatment decision-making process and are less likely to experience decision regret. Therefore, it is key to not only ensure patients are involved in treatment decision-making, it is imperative to ensure that they are prepared with the tools to engage in shared decision-making.

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# Elderly breast cancer patients benefit from surgery according to guidelines

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Background: With a globally increasing population of otherwise healthy people above 70 years, more knowledge on treatment and prognosis of breast cancer patients in this group is needed. In Denmark, the Danish Breast Cancer Group describes national treatment guidelines for diagnostic work-up and surgical and oncological treatment of all patients with primary invasive breast cancer with no upper age limit. Still, many patients ≥70 years, regardless of comorbidity, do not adhere to treatment guidelines, often receiving less imaging and less treatment than recommended. The aims of the present study were to examine, among patients ≥70 years with primary invasive breast cancer, whether endocrine treatment only, resulted in an inferior breast cancer related survival compared to standard surgical and oncological treatment, to examine whether patients treated with breast conserving surgery (BCS) with no preoperative imaging had a higher risk of local recurrence than patients receiving preoperative imaging, and finally to examine whether clinically node negative patients had a higher risk of regional recurrence if they did not receive axillary staging. Methods: All women, ≥70 years, diagnosed with primary invasive breast cancer and treated at the Department of Breast Surgery at Herlev Hospital, Denmark, from 2000-2007 were included. Patients were prospectively registered in a hospital-based database. Differences in standardized mortality ratios (SMR) between patients treated by surgery, endocrine therapy only, or endocrine therapy followed by surgery were estimated by Poisson regression and evaluated by rate ratios. Differences in local recurrence between patients with and without preoperative imaging before BCS, and in regional recurrence between surgically treated patients with and without a sentinel lymph node biopsy, with axillary clearance in case of a positive sentinel node, excluding clinically node positive patients directly treated with an axillary clearance, were estimated by Cause Specific Hazards Models and evaluated by cause specific hazard ratios (HR). Adjustments were made for age, comorbidity, adjuvant radiotherapy, tumor size, time since diagnosis, and time period. Results: In total 1,142 patients were included in the study. The median age was 77 years. For overall mortality, median follow-up was 7.80 years, with 795 (69.6%) dying during follow-up, and for recurrence 6.25 years. 52 were registered with local recurrence and 39 with regional recurrence. Patients who received only endocrine therapy had a significantly higher SMR than patients treated with primary surgery (adj. RR=2.57; 95% CI: 2.01-3.30), while patients who received endocrine therapy followed by later surgery did not (RR=1.23; 95% CI: 0.91-1.66). 253 out of 580 patients with BCS (43.6%) did not have preoperative imaging. Patients without imaging did not have a higher risk of local recurrence compared to patients with preoperative imaging (adj. HR=1.14; 95% CI: 0.36-3.67). 13 out of 197 surgically treated patients without axillary surgery (6,8%) had regional recurrence, while only 7 out of 428 patients (1.6%) with axillary staging by sentinel node biopsy had regional recurrence. This difference was significant (adj. HR 4.68 95% CI=1.53-14.37).
Conclusions: In the present study we have shown that women ≥70 years, diagnosed with primary invasive breast cancer, have a higher mortality if they are not surgically treated, and they have a higher risk of regional recurrence if they are not offered axillary staging. The study emphasizes that unless elderly patients have comorbidity contraindicating surgery, they should be treated according to guidelines.

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# Outcomes associated with disseminated tumor cells at surgery after neoadjuvant chemotherapy in high-risk early stage breast cancer: The I-SPY SURMOUNT study

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**Background:** Disseminated tumor cells (DTCs) in bone marrow detected after treatment may represent occult residual disease. We enumerated DTCs after neoadjuvant chemotherapy (NACT) in patients (pts) diagnosed with high-risk early stage breast cancer and examined the relationship of these cells with response and survival. **Methods:** I-SPY SURMOUNT is a sub-study of the I-SPY 2 TRIAL (NCT01042379). Pts enrolled on I-SPY 2, who signed consent for this sub-study, had bone marrow aspirates (BMA) collected after NACT at the time of surgery. DTCs were isolated and enumerated from BMA using immunomagnetic enrichment/flow cytometry (IE/FC). DTCs were defined as EPCAM-positive and CD45-negative nucleated cells. Samples were considered positive using a predetermined threshold of >4 DTCs per mL (Magbanua et al, unpublished data). Pathologic response was assessed using the residual cancer burden (RCB) method at local sites, and pts underwent standard adjuvant therapy if indicated and follow up for recurrence events and death. Relationship of DTCs with clinicopathologic variables was examined using Chi-squared test. Group means were compared using t tests. The log-rank test was used to compare survival curves. **Results:** A total of 73 patients were enrolled, 51 of whom had successful DTC assessment. The median DTC per mL was 4 (interquartile range 1.2-11.6). 24/51 (47%) were DTC-positive. Clinical characteristics by DTC status are shown in the table. DTC-positive pts were significantly younger (p=0.02) and had larger pretreatment tumors (longest diameter by magnetic resonance imaging) compared to DTC-negative pts (p=0.032). DTCs were not associated with receptor subtype. Thirty pts (41%) achieved a pathologic complete response (pCR). DTCs were not associated with pCR (p= 0.166); however, DTC-positive patients were significantly more likely to have residual cancer (RCB-II/III) after NACT compared to DTC-negative patients (OR 3.3, p=0.037). Median follow up of this cohort was 2.8 years (range: 0.9-4.8). Interim survival analysis showed that DTCs were not significantly correlated with EFS (p=0.6) or DRFS (p=0.41). **Conclusions:** Detection of DTCs at surgery after NACT is significantly more common in young patients, those with larger tumors, and those with residual disease at surgery. While these associations suggest higher risk for later recurrence, larger studies and longer follow up are necessary to determine if DTCs add prognostic value over pathologic evaluation alone for pts receiving NACT.

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# Pharmacodynamic analysis from a phase 1 study of rintodestrant (G1T48), an oral selective estrogen receptor degrader, in ER+/HER2- locally advanced or metastatic breast cancer

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**Background**: Rintodestrant is an orally bioavailable, potent and selective estrogen receptor degrader (SERD) that inhibits estrogen receptor (ER) gene transcription, degrades the ER, and delays tumor proliferation in preclinical models. Preliminary results from Part 1 dose escalation (200-1000 mg once daily) demonstrated that rintodestrant has a favorable safety profile and encouraging antitumor activity in patients (pts) with heavily pretreated ER+/HER2- advanced breast cancer (ABC) (Dees et al., ESMO 2019 [abstract #3587]). Here, we report the pharmacodynamic (PD) analysis in peripheral blood and tumor biopsies from pts who received rintodestrant in Part 1 and 2 (600 and 1000 mg dose expansion) to characterize the pt population and mechanisms of response. **Methods**: This Phase 1, first-in-human, open-label study evaluated rintodestrant in women with ER+/HER- ABC after progression on endocrine therapy. PD analysis included inhibition of ER target engagement with $^{18}$F-fluoroestradiol positron emission tomography (FES-PET), mutational profiling (cell-free DNA [cfDNA]), and circulating tumor cell (CTC) enumeration. Tumor biopsies sampled at baseline and 6 weeks on treatment were evaluated for ER degradation (immunohistochemistry [IHC]) and proliferation (Ki67, IHC) to understand the on-target effects of rintodestrant. **Results**: As of May 13, 2020, 67 pts had been treated. FES-PET data were obtained in 14 pts and showed a decrease in all pts, with maximum standard uptake values (SUVmax) ranging from 70% to 98% after 4 weeks of rintodestrant monotherapy across all doses. Fifty-nine pts were tested for cfDNA at baseline; 95% (n = 56) harbored ≥1 somatic variant (median = 3 mutations per pt). Among pts with somatic variants, 41% had *ESR1* mutations, with *D538G* being the most common (58%). Additionally, 46% and 42% of pts harbored mutations in *TP53* and *PIK3CA,* respectively, and 10% had mutations in both *ESR1* and *PIK3CA*. Similar clinical benefit rates were observed in wild-type vs *ESR1* and/or *PIK3CA* mutant tumors. An analysis of change of variant allele fraction (VAF) in 55 pts between baseline and 2 weeks of treatment revealed that 58% had a decrease in mean VAF, with a decrease in *ESR1* VAF in 16/20 pts that had *ESR1* mutations at baseline. Furthermore, of 24 pts who had samples collected at baseline and progression, 16 (67%) developed additional variants (median [range]: 2 [1, 15]), including *EGFR, ERBB2, TP53,* and *ESR1*. CTC analysis (n = 45) showed the mean value of Epi+CD45- CTCs decreased from 2.8 cells/mL to 1.8 cells/mL after 8 weeks of treatment. Tumor biopsies were collected in 9 pts (5 received 600 mg and 4 received 1000 mg) at baseline and 6 weeks on treatment. Of the 7/9 pts that had a decrease in the ER H-score (median [range]: -27.8% [-33.8%, -3.4%]), 4 had ≥1 variant in *ESR1* at baseline. Overall, 4 pts had a decrease in Ki67, with reductions mostly observed in pts who received 600 mg rintodestrant. Additional analyses, including correlations with clinical response, are ongoing and will be presented. **Conclusions**: Rintodestrant demonstrated robust ER target engagement on FES-PET, as well as substantial decreases in ER H-score, cfDNA VAF, and Epi+CD45- CTCs. These data, along with promising clinical benefit in pts with heavily pretreated ER+/HER2- ABC, regardless of *ESR1* or *PIK3CA* mutation status, warrant additional investigation of rintodestrant (NCT03455270).

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# Ribociclib + letrozole in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2−) advanced breast cancer (ABC) and central nervous system metastases: Subgroup analysis of the phase IIIb CompLEEment-1 trial

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**Background:** Approximately 10-30% of patients (pts) with metastatic breast cancer (BC) are diagnosed with central nervous system (CNS) metastases, which are a major cause of morbidity and mortality, and are associated with a poor prognosis. Due to improving diagnostics and treatments in BC, and therefore longer pt survival, more CNS metastases in breast cancer pts are readily detected. However, pts with CNS metastases are often excluded from clinical trials. Ribociclib (RIB), an oral, selective cyclin-dependent kinase 4/6 inhibitor, is approved for use in combination with endocrine therapy (ET) in women with HR+, HER2- ABC. Here, we present a subgroup analysis of pts with CNS metastases at baseline from the Core Phase of CompLEEment-1 (NCT02941926), a Phase IIIb trial of RIB in combination with letrozole (LET) in pts with HR+, HER2- ABC. The eligibility criteria for this study allowed a broader and more diverse pt population than those of previous Phase III trials of RIB + LET, to reflect a typical real-world clinical setting. **Methods:** CompLEEment-1 included women of any menopausal status and men with HR+, HER2- ABC treated with ≤1 line of prior chemotherapy and no prior hormonal therapy for advanced disease. Pts received RIB (600 mg QD, 3 weeks on/1 week off) in combination with LET (2.5 mg QD, continuous). Men and premenopausal women received a luteinizing hormone-releasing hormone agonist (3.6 mg goserelin or 7.5 mg leuprolide, Q28D). This subgroup analysis assessed the primary outcomes (safety and tolerability) and secondary outcomes of time to progression (TTP), overall response rate (ORR), and clinical benefit rate (CBR) in pts with CNS metastases. **Results:** At the data cutoff date (November 8, 2019), 51 pts with CNS metastases (1.57%; total pt population N = 3,246) had been evaluated: median age was 56.0 years, 30 (58.8%) pts were postmenopausal, and ECOG PS <2 was observed in 49 (96.1%) pts. Median duration of exposure to RIB was 16.8 months. Adverse events (AEs) were reported in 49 (96.1%) pts; with all but one experiencing a treatment-related AE. Grade ≥ 3 AEs were reported in 38 (74.5%) pts; serious AEs were reported in 8 pts. There was 1 treatment-related fatal AE (sepsis). The most common all-grade AEs were neutropenia (66.7%), nausea (39.2%), and vomiting (29.4%). The most common grade ≥ 3 AEs were neutropenia (51.0%), leukopenia (13.7%), and increased alanine aminotransferase (5.9%), aspartate aminotransferase (5.9%), and gamma-glutamyltransferase (5.9%). Overall, 19 pts (37.3%) had ≥ 1 dose reduction of RIB, 12 (23.5%) due to AEs, and 32 pts (62.7%) permanently discontinued treatment, 6 (11.8%) due to AEs. Median TTP was not estimable (NE) (95% CI, 15.5-NE) in this subgroup analysis; with an event-free probability of 56.1% (95% CI, 39.3-69.8) at 30 months. For the 35 pts with measurable disease and CNS metastases at baseline, ORR was 42.9% (95% CI, 26.3-60.6%) and CBR was 62.9% (95% CI, 44.9-78.5). **Conclusions:** This subgroup analysis from CompLEEment-1 supports the use of RIB + LET in pts with CNS metastases, who typically have poor outcomes and are frequently excluded from clinical trials. Efficacy results support the use of RIB + LET in HR+, HER2- ABC in a close to real-world setting. The safety profile associated with RIB + LET was manageable, with few pts discontinuing treatment due to AEs, consistent with previous Phase III trials of RIB + LET.

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# Blocking H3K27me3 methyltransferase or demethylase activity impacts epithelial-mesenchymal plasticity, suppressing tumor growth and metastasis

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Background: Epithelial-mesenchymal plasticity (EMP) is key feature driving breast cancer metastasis. Induction of epithelial-mesenchymal transition (EMT) increases the migratory and invasive capabilities associated with metastatic competence and endows tumors with stem cell properties necessary for initiating tumor growth in the metastatic site. Mesenchymal-epithelial transition (MET) has been increasingly recognized as an integral part of the latter stages of the metastatic cascade as it is required for re-epithelialization, proliferation, and expansion of micro-metastases into macro-metastases with a histopathology similar to that of the primary tumor. Interconversion between epithelial and mesenchymal states requires remodeling of the epigenome--including addition and erasure of H3K27me3, especially near gene promoter and enhancers. Deposited by EZH1 or EZH2, members of the PRC2 complex, H3K27me3 is associated with gene silencing. However, gene activation occurs upon H3K27me3 demethylation to H3K27me1, mediated by KDM6A or KDM6B, members of the Compass-like complex. Results: Based upon our prior work, which showed EMT-driven re-distribution of H3K27me3 onto and off of genes that are critical regulators of cell fate and differentiation, we asked whether inhibition of H3K27me3-directed methyltransferases and demethylases could impact breast cancer. We found that the EZH2 inhibitor, EPZ011989, reduced EMP by preventing recovery of epithelial trails in cells exposed to TGFβ, but did not, on its own, induce EMT. However, we found that either inhibition of the H3K27me3-directed demethylases, KDM6A and KDM6B, using GSK-J4 or shRNA knockdown, induced EMT and promoted cellular migration. Thus, manipulation of either EZH2 or KDM6A/B affected the capacity of cells to repress or activate expression of genes known to exhibit dynamic gain or loss of H3K27me3 during EMT. Given the effects of inhibitors of H3K27-targeted enzymes on EMP, we sought to ascertain their impact on tumor growth and metastasis. Using a GFP-expressing patient-derived xenograft (PDX) model of ER-positive breast cancer, we observed a dose-dependent suppression of primary tumor growth and fewer disseminated tumor cells (DTCs) in response to small molecules targeting H3K27me3 regulators. Conclusions: These results indicate that addition and removal of H3K27me3 is critical for maintenance of cell fate and plasticity. Furthermore, targeting this pathway suppresses breast cancer growth and metastasis in a mouse model of ER-positive breast cancer.

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Neoadjuvant adriamycin plus cyclophosphamide followed by docetaxel (AC4-D4) vs 5-fluorouracil, epirubicin plus cyclophosphamide followed by docetaxel (FEC3-D3) in stage II or III operable breast cancer : Randomized phase III neo-shorter trial (NCT02001506)

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**Background:** Two neoadjuvant anthracycline and taxane containing chemotherapy regimens have been widely used. The objective of the study was shorter duration of 6 cycles of FEC3-D3 is comparable to 8 cycles of AC4-D4 **Method:** Enrolled patients (pts) were diagnosed clinically stage II or III breast cancer between November 2012 and December 2015 at Asan Medical Center, Seoul, Korea. Pts were stratified according to hormone receptor and HER2 expression status and randomized 1:1 to AC4-D4 and FEC3-D3 arm. The primary endpoint was pathologic complete response (pCR) and the secondary end points were 3 year disease-free survival (3Y DFS) and toxicities.**Result:** Among 252 pts enrolled, 1pt ineligible for screening; 10 pts discontinued treatment due to progressive disease (7 pts in AC4-D4 arm and 3 pts in FEC3-D3), 17 pts dropped out due to withdrawal of written consent and 2 pts unable to complete study. Two hundred twenty two pts receiving surgery were included for this analysis. Baseline characteristics are well balanced between two arms- median age (47 vs 48), % of TNBC (24% vs 26%) in AC4-D4 (N=126) vs FEC3-D3 arm (N=125) respectively. Baseline median Ki-67 labeling index was 50% (range, 10%-90%). By ITT analysis, pCR was achieved in 18/126 (14.3%) pts of AC4-D4 arm and 15/125 (12.0%) pts in FEC3-D3 arm, respectively ($p$=0.17). According to per protocol, in AC4-D4 arm, 95/103 pts achieved clinical response (6 complete response [CR] and 89 partial response [PR]) and among them 18 pts (17.5%) achieved pCR. In FEC3-D3 arm, 97/119 pts achieved clinical response (4 CR and 93 PR) and among them 15 pts (12.6%) achieved pCR. With a median follow up of 64.1 months, 3Y DFS (77.0% in AC4-D4 vs. 74.9% in FEC3-D3) was comparable between two arms ($p$=0.79). The most common adverse event (AE) was Grade 3/4 neutropenia. 44/126 (34.9%) pts in AC4-D4 arm vs 39/125 (31.2%) pts in FEC3-D3 arm. The most common Grade 3/4 non-hematologic AE was hyperglycemia (3.2%). Dose modification was done in 37/126 (29.4%) pts in AC4-D4 arm and 25/125 (20.0%) pts in FEC3-D3 arm, respectively ($p$=0.09). Multivariate analyses showed that ≥50% of baseline Ki-67 labeling index [hazard ratio (HR) 2.1 (95% confidence interval (CI),1.20-3.72; $p$=0.009)], ≥40% of pre-treatment Ki-67 labeling index reduction after neoadjuvant chemotherapy(NACT) [HR 2.1 (95% CI,1.20-3.66; $p$=0.01)], and ≥4 lymph node metastases at surgery [HR 2.2 (95% CI,1.24-3.80; $p$=0.07)] were independent predictive factors for 3Y DFS. Of note, in patients with non-pCR, ≥ 40% reduction of Ki-67 after NACT was associated with better 3Y DFS in luminal type [HR 2.9 (95% CI,1.51-5.65; $p$=0.001)]. **Conclusion:** Both NACT AC4-D4 and FEC3-D3 showed comparable outcomes in terms of pCR, 3 year DFS and toxicities. ≥50% of baseline Ki-67 labeling index and ≥40% reduction of Ki-67 labeling index after NACT were independent for 3Y DFS. Shorter neo-adjuvant FEC3-D3 could be an alternative to AC4-D4 in stage II or III operable breast cancer.**Keywards:** Neoadjuvant, AC followed by docetaxel, FEC followed by docetaxel, operable breast cancer

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# A retrospective analysis of association of *MYC* and *RAD21* amplification with final overall survival (OS) data in the phase 3 EMBRACA study with talazoparib

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**Background:** Loss-of-function mutations in genes encoding components of the homologous recombination DNA damage response (DDR) machinery, notably *BRCA1/2*, are associated with tumor sensitivity to poly(ADP-ribose) polymerase inhibitors (PARPi). Little is known about the potential contribution of tumor alterations in non-DDR genes to modulating sensitivity to PARP inhibitors in the clinic. In EMBRACA, the PARPi TALA improved progression-free survival (PFS) (HR [95% CI] 0.54 [0.41-0.71], *P*<0.001) vs chemotherapy (CT) in germline *BRCA1/2*-mutated HER2-negative locally advanced/metastatic breast cancer.

**Methods:** Baseline tumor tissue from 308 pts (71%; intent-to-treat) was tested by FoundationOne®. To support exploratory identification of tumor gene alterations associated with best vs worst outcomes, pts were mapped into 2 groups: [1] BEST: Pts in TALA arm with OS ≥ 30 mo and duration of treatment ≥ 24 mo, Pts in CT arm with OS ≥ 30 mo; [2] WORST: Pts in TALA or CT arm with a PFS event (PD by Independent Radiological Facility or death) ≤ 12 wks. 2 pts had short PFS but long OS and were initially mapped to both groups but then assigned to BEST and excluded from WORST.

**Results:** Exploratory heat map visualizations of known/likely pathogenic genetic alterations defined by the FoundationOne® gene panel were used to assess differences in genetic alterations between BEST and WORST in TNBC and non-TNBC subpopulations, leading to the identification of *MYC* and *RAD21* as commonly altered genes of high interest. Based on these results showing imbalances in tumor amplification events between BEST and WORST outcome pts, Cox regression analysis was used to explore potential associations of *MYC* or *RAD21* amplification with OS across the evaluable ITT population. In TNBC pts receiving TALA, OS was shorter with *MYC* amplification than without [HR (95% CI) 1.877 (1.102, 3.196)]. No such association was evident in TNBC pts receiving CT [HR (95% CI) 0.706 (0.303, 1.643)]. In contrast, for non-TNBC pts receiving TALA, no association with OS was evident for *MYC* amplification versus without [HR (95% CI) 0.603 (0.310, 1.173)], while for pts receiving CT OS was shorter with *MYC* amplification than without [HR (95% CI) 1.917 (1.037, 3.544)]. *RAD21* amplification status was not associated with OS in either TNBC or non-TNBC patients for either treatment arm, although it should be noted that two *RAD21* subgroups were very small (n=7 and 11; others had n ≥ 21).

**Conclusions:** Based on these exploratory, retrospective analyses *MYC* amplification was associated with shorter OS in TNBC pts receiving TALA. This may reflect the role of *MYC* in positive regulation of genes involved in homologous recombination such as *RAD51* (Carey et al, Cancer Res 2018;78(3):742-757). *MYC* and *RAD21* are both located at 8q24 and frequently coamplified in breast cancer (eg, Annunziato et al, Nat Commun. 2019;10(1):397), hence the lack of association of *RAD21* amplification with outcome in TNBC suggests that the association of *MYC* amplification with shorter OS seen in pts receiving TALA may be gene-specific. Further investigation is warranted.

**Funding:** Pfizer

| | | **TNBC** | | | | **Non-TNBC** | | |
|---|---|---|---|---|---|---|---|---|
| | TALA | | CT | | TALA | | CT | |
| **Gene Alteration** | Best n=10 | Worst n=15 | Best n=7 | Worst n=16 | Best n=17 | Worst n=11 | Best n=20 | Worst n=11 |
| *MYC* amplification | 0 (0%) | 7 (47%) | 2 (29%) | 6 (38%) | 5 (29%) | 1 (9%) | 3 (15%) | 5 (46%) |
| *RAD21* amplification | 1 (10%) | 2 (13%) | 3 (43%) | 5 (31%) | 5 (29%) | 1 (9%) | 7 (35%) | 4 (36%) |

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# Gene expression profiles of Ghanaian and Ethiopian triple-negative breast tumors

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**Background:** Triple-negative breast cancer (TNBC) remains the most aggressive molecular subtype of breast cancer, with worse survival outcomes compared to other breast cancer subtypes. TNBC prevalence is highest among women of African descent worldwide, and through our previous work we have established a connection between West African ancestry (WAa) and higher rates of TNBC. Specifically, we have shown that prevalence rates of TNBC among West African and African American women are similar and higher than that of East African and White American women. We have also shown that quantified African ancestry is higher among TNBC cases compared to non-TNBC cases. To determine the influence African ancestry on the TNBC tumor environment, we sought to determine any differences in gene expression profiles of Ghanaian (West African) compared to Ethiopian (East African) women. **Methods:** RNA was extracted and sequenced from a pilot cohort of archival FFPE tumor tissue among Ghanaian ($n$ = 19) and Ethiopian ($n$ = 20) women. RNAseq reads were aligned, and quality of alignments were assessed, where de-duplicated samples with counts above 10M reads were included in the final analysis. Genetic ancestry was quantified by obtaining SNVs called from the RNAseq alignments, using GATK best practices. Differentially expressed genes lists were determined comparing Ghanaian vs. Ethiopian TNBC tumors, and also by identifying genes that were associated with increasing African ancestry. These gene lists, and log-fold change between comparison groups, were used as input for Ingenuity Pathway Analysis (IPA), to identify canonical pathways and *de novo* networks that are specific to Ghanaian or Ethiopian TNBC tumors. **Results:** Using 1KG populations as our reference to quantify genetic ancestry, we show that Ghanaian samples have >94% AFR ancestry, specifically matching population groups representative of WAa. The Ethiopian samples showed between 37-48% AFR ancestry, primarily represented by East African groups. Interestingly, there seems to be a significant proportion of EUR ancestry among the Ethiopians samples (30-49%), primarily represented by Italian ancestry. We have conducted the differential gene expression analysis in two ways. First, we have compared gene expression profiles between Ghanaian and Ethiopian tumors. In our preliminary analysis, we identified >600 genes ($p < 0.01$) that were differentially expressed between Ghanaian and Ethiopian TNBC tumors. Second, we used AFR ancestry as a continuous variable, where we conducted a linear regression analysis to identify genes associated with AFR ancestry. We identified >900 genes associated with AFR ancestry ($p < 0.01$), and this gene signature distinguished Ghanaian from Ethiopian tumors in an unsupervised hierarchical clustering. In comparing the differentially expressed gene lists from these two approaches, approximately 200 genes were shared, indicating the distinct value of both analyses. Using these gene lists as input for IPA analysis, we have begun to identify canonical pathways that have been altered by our differentially expressed genes, alongside *de novo* networks that differ between our Ghanaian and Ethiopian tumors. In our overlapping gene list, we see predicted differences in functions such as quantity of T lymphocytes, where genes downregulated in Ethiopian tumors may indicated reduced presence of these immune cells. Using CIBERSORT and xCell deconvolution methods, validation of these findings are ongoing. **Conclusions and Ongoing work:** This work highlights how ancestry-specific gene regulation can delineate differences in the tumor microenvironment among a cohort of African tumors. We are currently evaluating distribution of TNBC subtypes and estimation of immune cell populations in these tumors, to determine ancestry-specific differences in tumor heterogeneity and immune response.

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# Deep inspiration breath-hold in right-sided breast irradiation: Quantifying the benefit

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**Background:** Deep inspiration breath-hold (DIBH) in left-sided breast radiation therapy (RT) is proven to reduce ipsilateral lung and heart doses. The potential benefit of this technique in right-sided breast RT has not been fully explored. We describe the differences in organs at risk (OAR) dosimetry between DIBH and free-breathing (FB) plans in 15 patients who received right-sided breast RT.
**Materials and methods:** Fifteen consecutive patients with right-sided breast cancer who received RT with DIBH between January 1, 2016 and August 31, 2019 were enrolled in this study. All patients initially underwent RT planning with FB scans, and subsequently required DIBH rescanning due to concerns related to exposure of OAR. Dose volume histograms (DVH) for the target volume and OAR coverage were compared between both plans on RayStation Treatment Planning System to quantify the benefit of DIBH. The median value of relative reduction (MRR) and interquartile range in dosimetric parameters were calculated when comparing DIBH to FB. Two-sided Wilcoxon signed-rank test was performed, and a p-value $< 0.05$ was considered statistically significant.
**Results:** The median age of patients was 64 (38-78). None of the patients had cardiac, respiratory or hepatic comorbidities. The majority of patients (10/15) received locoregional RT (50 Gy in 25 fractions); the remaining 5 patients received breast RT (42.4 Gy in 16 fractions). Tumor bed boost was delivered in 9 of 15 patients. DIBH was delivered throughout RT to 14/15 patients and the clinical goal(s) for which DIBH was introduced was achieved in all cases. DIBH was most commonly used to minimize liver exposure (11/15 patients); in 3 of these 11 patients, reduction in heart or lung exposure was also required. Statistically significant reductions in the imaged liver V5Gy [MRR 89.8% (99 to 71.6, $p<0.001$)], V10Gy [MRR 94.7% (100 to 77.9, $p<0.001$)], V20Gy [MRR 97.2% (100 to 84.7, $p<0.001$)], maximum dose [MRR 15.5% (73.2 to 8, $p<0.001$)] and average dose [MRR 68.7% (79.4 to 58.6, $p<0.001$)] were observed with DIBH. Compared to FB, the use of DIBH led to statistically significant reductions in right lung V20 [Median Relative Reduction 20.8% (27.1 to 15.9, $p<0.001$)], as well as the maximum dose received by the heart and left lung. The target volume coverage was not compromised by DIBH, with at least 99% of the target volume receiving 95% dose in all 15 cases.
**Conclusion**: DIBH for right-sided breast irradiation effectively reduces exposure to liver, lung and heart while maintaining target volume coverage. It can be employed to achieve specific dosimetric goals in the clinical setting.

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# Subgroup analysis of patients with brain metastases from the phase 3 ASCENT study of sacituzumab govitecan versus chemotherapy in metastatic triple-negative breast cancer

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**Background:** Patients (pts) with metastatic triple-negative breast cancer (mTNBC) who have brain metastases represent a poor prognosis cohort with a high unmet clinical need. Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to SN-38, an active metabolite of irinotecan, via a unique hydrolyzable linker that allows for SN-38 release intracellularly and in the tumor microenvironment (bystander effect). SN-38 can cross the blood-brain barrier and is a drug partner in central nervous system (CNS) disease regimens (PMID: 18784279; PMID: 26080460). Although antibody-based therapy raises concerns regarding CNS penetration, activity with SG has been seen in intracranial xenograft models (Brenner *Neurooncol Adv* 2019). In a subgroup analysis from ASCENT, the efficacy and safety of SG were evaluated in pts with stable brain metastases.
**Methods:** In the phase 3 ASCENT study (NCT02574455), 529 pts with mTNBC refractory to or relapsing after at least 2 prior chemotherapies were randomized 1:1 to receive SG (10 mg/kg IV on days 1 and 8 every 21 days) or single-agent treatment of physician's choice (TPC; capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. Brain MRIs were required in pts with known brain metastases who were eligible if they had stable CNS disease for ≥4 wk by MRI. Per protocol, stable disease was defined as ≥2 wk from discontinuation of antiseizure medication and corticosteroid dose (≤20 mg prednisone equivalent) that was stable or decreasing for ≥2 wk before randomization. In these pts, brain MRIs were required throughout the study. The primary endpoint was progression-free survival (PFS) per independent central review (RECIST v1.1) in brain metastases-negative pts. Secondary endpoints included PFS per investigator assessment, PFS in the full population (in pts with/without brain metastases) by central review, objective response rate (ORR), overall survival (OS), and safety.
**Results:** Overall, 61 of 529 (12%) enrolled pts had stable brain metastases at screening and were randomized to SG (n=32) or TPC (n=29). Median age was 53 y for SG and 51 y for TPC; all pts were female and had a median of 5 prior anticancer regimens. In this subset, median PFS was 2.8 mo (95% CI, 1.5-3.9) for SG vs 1.6 mo (95% CI, 1.3-2.9) for TPC by central review, and median OS was 6.8 mo (95% CI, 4.7-14.1) for SG vs 7.5 mo (95% CI, 4.7-11.1) for TPC. ORR for SG vs TPC, respectively, was 3% (1/32) vs 0% by central review, with a clinical benefit rate of 9.4% vs. 3.4%. Stable disease was achieved in 15 (47%) pts with SG vs 9 (31%) pts with TPC. In 53 pts who received at least 1 dose of treatment (SG, n=30; TPC, n=23), any-grade treatment-emergent adverse events (>20% with SG) for SG vs TPC were fatigue (63% vs 52%), diarrhea (50% vs 13%), neutropenia (43% vs 35%), nausea (43% vs 26%), decreased appetite (30% vs 17%), decreased neutrophil count (33% vs 22%), anemia (23% vs 35%), alopecia (23% vs 13%), and constipation (23% vs 22%). There were no treatment-related deaths. Two pts treated with SG are continuing study treatment for 16.2 and 6.3 mo as of the data cutoff date.
**Conclusions:** Data interpretation in this population with poor prognosis is limited by the small sample size. In this exploratory analysis of pts with brain metastases from the phase 3 ASCENT study, SG was numerically better than TPC for tumor response and PFS but not OS. The safety profile was similar to that of the population without brain metastases for both study arms. SG is currently under clinical investigation for pts undergoing elective craniotomy for breast cancer with brain metastases or recurrent glioblastoma (NCT03995706) based on promising preclinical and intracranial clinical data.

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# Intratumoral activation and phase 1/2 clinical activity of CX-2009, a probody drug conjugate (PDC) targeting CD166

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**Background:** Probody® therapeutics (Pb-Tx) are masked antibodies designed to be selectively activated in the tumor microenvironment by tumor-associated proteases, while remaining largely inactive in normal tissue and in circulation. This allows Pb-Tx to address previously undruggable targets that are highly expressed in both tumor and normal tissue, such as the adhesion molecule CD166 (ALCAM). CX-2009, an investigational PDC consisting of an anti-CD166 monoclonal antibody conjugated to the microtubule inhibitor DM4, is being evaluated in a Phase 1/2 clinical trial for patients with advanced solid tumors (NCT03149549). Clinical data have been previously presented (Boni V, et al. *J Clin Oncol*. 2020; 38 [15 suppl]: abstract 526); here we present translation data assessing tumoral CX-2009 activation and DM4 accumulation in patients receiving ≥4 mg/kg every 2 or 3 weeks (Q2W or Q3W), alongside clinical results from breast cancer (BC) patients.
**Methods:** Eligible patients with metastatic cancer after ≥2 prior standard treatments were required to submit tumor tissue for CD166 IHC analysis. CX-2009 was administered at escalating doses Q3W (0.25-10 mg/kg) or Q2W (4 or 6 mg/kg) until discontinuation criteria were met. Tumor response was assessed Q8W. On-treatment tumor biopsies in consenting patients were collected 3-5 days after the first dose. Levels of CD166 and of intact and activated CX-2009 in patient biopsies were measured by capillary immunoelectrophoresis; levels of DM4 were evaluated by a competitive ELISA, following depletion of the majority of CX-2009 from the sample.
**Results:** 99 patients, including 45 with HR+/Her2- BC, HER2+ BC, or TNBC, were enrolled from 27 sites. The median number of prior therapies was 5.5 (range, 1-10) in all patients and 7 (3-16) in BC patients. Patients received a median of 2 (range, 1-16) CX-2009 doses. 92 patients discontinued treatment; the majority for disease progression/symptomatic deterioration (n=65) or adverse events (n=11). In 26 evaluable BC patients treated at ≥4 mg/kg, ORR was 11% (HR+/HER2-; n=18) and 38% (TNBC; n=8) including confirmed and unconfirmed responses, with a Clinical Benefit Rate at 24 weeks (CBR24) of 35%. CX-2009 remained predominantly (median >95%) in the inactive form in circulation (Stroh M, et al. *J Clin Oncol*. 2020; 38 [15 suppl]: abstract 3599). Over the dose range of 4-10 mg/kg, activated CX-2009 was quantifiable in 18 out of 22 biopsy samples, including 6 of 7 samples from the BC subset. The intratumoral concentrations of activated CX-2009 and CD166 were significantly correlated ($r^2$=0.59, p=0.004). DM4 was measured in 12 evaluable biopsy samples. Levels of normalized intratumoral DM4 were significantly correlated with the relative change in target lesions ($r^2$=0.34, p=0.045).
**Conclusions:** CX-2009 behaved as designed, with activated drug in tumor and predominantly intact drug in plasma, leading to clinically meaningful disease control in patients with advanced BC. The relationship between normalized intratumoral DM4 and tumor volume changes support the premise that accumulation of payload toxin is related to anti-tumor activity. The correlation between activated CX-2009 and target expression suggests a role for CD166 in intratumoral accumulation of activated CX-2009. Taken together, the data support continued development of CX-2009 in patients with HR+/HER2- BC and TNBC.
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# Contemporary practice patterns for the use of regional nodal irradiation during post-lumpectomy radiotherapy for patients with N0/N1 breast cancer

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BACKGROUND: Current national guidelines encourage consideration for treating the at-risk regional nodes (axillary, supraclavicular, and/or internal mammary) with directed regional nodal irradiation (RNI) during post-lumpectomy radiotherapy for high risk N0 (node negative) and N1 (1-3 nodes positive) breast cancer patients. This recommendation is based on the results of several randomized trials published over the last decade. Evidence regarding translation of these trials into clinical practice in the United States has been limited to date. In this study, we sought to characterize the temporal changes in and clinical factors associated with the utilization of RNI during post-lumpectomy radiotherapy for N0-N1 breast cancer across a contemporary, statewide consortium of radiation oncology practices.
METHODS: Within a statewide radiation oncology quality consortium, 12,170 breast cancer patients were consecutively enrolled between 1/1/2013 and 10/31/2019 in both academic (teaching) and community (non-teaching) facilities. Data on receptor status, adjuvant systemic therapy, age, TNM stage, extent of axillary surgery, race, body mass index (BMI), type of treating facility, and year completing radiotherapy (RT) were collected. Eligibility for the present analysis was limited to patients with N0 and N1 disease not receiving neoadjuvant systemic therapy and receiving adjuvant radiotherapy after lumpectomy for non-metastatic breast cancer. Multiple variable logistic regression models were separately fit to explain the use of directed RNI (to the axilla, supraclavicular region, and/or internal mammary region) for the N0 and N1 populations separately and described using odds ratios (OR), with significant ORs ($p<0.05$) reported.
RESULTS: A total of 8,468 patients from 29 treating facilities met the inclusion criteria: 6,929 (81.8%) with N0 and 1,539 (18.2%) N1 disease. RNI was performed in addition to whole breast radiation in 95 (1.4%) and 908 (59%) patients in the N0 and N1 cohorts respectively. For the N0 cohort, significant correlates of RNI on multivariable analysis (MVA) were receipt of adjuvant chemotherapy (OR 2.7), higher T-stage (OR 1.9 for T2 vs T1 and 27.3 for T3/T4 vs T1), axillary surgery [compared to sentinel node biopsy (SLN) alone : no axillary surgery (OR 14.5), axillary lymph node dissection (ALND) with 10+ nodes removed (OR 15.1) ALND after SLN (OR 2.7)], and underweight BMI (OR 4.9 compared to overweight, which was the reference as the largest BMI category). For the N1 cohort, MVA suggested adjuvant chemotherapy (OR 1.8) and larger tumors (OR 1.6 [T2 vs T1]) were significantly associated with use of RNI. The year completing RT was also significantly associated with RNI use, with 22% and 15% increases per year from 2013 to 2019 in the N0 and N1 cohorts, respectively. Lastly, receiving treatment in an academic facility compared to a community facility was significantly associated with receipt of RNI in both the N0 (OR 1.8) and N1 (OR 2.2) cohorts.
CONCLUSION: In this large cohort, selective use of RNI added to post-lumpectomy whole breast radiotherapy is estimated to have increased over time, suggesting growing implementation of recent trial data and current clinical practice guidelines. Patient, treatment, and tumor characteristics appear to factor into the decision to treat with RNI, but differences in use between academic and community practices suggest opportunities for improving the consistency of care across care delivery settings. Ongoing trials seeking to identify subgroups of N1 patients in whom RNI can safely be omitted may be especially important to inform decisions, given the almost even split (59% receiving, 41% not) in practice observed in this large American cohort.

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Mapping the tumor and microenvironmental evolution underlying DCIS progression throughmultiplexed ion beam imaging

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Ductal Carcinoma in Situ (DCIS) is a pre-invasive lesion that accounts for nearly 20% of new breast cancer diagnoses. Of these cases, about half will progress to invasive breast cancer (IBC) within ten years. However, because diagnostic criteria for delineating low risk lesions from those likely to progress to IBC have not been identified, many patients are receiving unnecessary chemotherapy and surgery that can result in therapy-related morbidity and death. With this in mind, we used Multiplexed Ion Beam Imaging by time of flight (MIBI-TOF) and RNA-seq laser-capture microdissection (SMART-3SEQ) to construct a comprehensive spatial atlas describing the structure, function, and cellular composition of DCIS. MIBI-TOF and SMART-3SEQ were used to compare lesions from patients that later developed IBC with those from age- and history matched DCIS controls without recurrence. Using a 37-marker staining panel to interrogate 137 lesions, we identified 17 distinct cell populations of epithelial, stromal, and immune cells that were arranged in recurrent cellular microenvironments specific for DCIS or invasive disease. We observe a coordinated shift in the immune and stromal compartments as invasive disease arises, including a robust influx of lymphocytes and expansion reactive stromal phenotypes in synchronous DCIS + IBC, which was distinct from the macrophage-dominant, highly vascularized microenvironment of recurrent IBC. Further, single cell segmentation using a deep learning model was combined with pixel-level coexpression analysis to extensively evaluate how the thickness, continuity, and phenotype of ductal myoepithelium changes as tumors progress from a pre-invasive state. These data were incorporated into a comprehensive model which was subsequently used to identify a subset of features that correlate with disease-free survival following DCIS tumor resection. Taken together, these features represent important prognostic metrics that can be used to separate pre-invasive from indolent DCIS tumors, and allow for tailored therapy that improves patient outcomes and quality of life in this disease.

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# Volumetric changes on longitudinal dynamic contrast enhanced MR imaging (DCE-MRI) as an early treatment response predictor to neoadjuvant systemic therapy (NAST) in triple negative breast cancer (TNBC) patients

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Background and Purpose:There is currently a lack of recognized imaging criteria for prediction of treatment response to NAST in breast cancer patients with recent reports showing that breast MRI is the most accurate modality for evaluation of NAST response. DCE-MRI evaluates tumor perfusion that influences tumor enhancement at the post-contrast subtraction images and allows for more accurate measurement of changes in tumor volume during NAST. In this study, we evaluated the ability of tumor volumetric changes after 2 and 4 cycles of NAST by longitudinal ultrafast DCE-MRI to predict pathologic complete response (pCR) in TNBC undergoing NAST. Materials and Methods: Stage I-III TNBC patients enrolled in an IRB approved prospective clinical trial (ARTEMIS, NCT02276433) who had ultrafast DCE-MRI at baseline (BL, N=103), post 2 cycles (C2, N=59), and post 4 cycles (C4, N=103) of anthracycline-based NAST,and had surgery, were included in this analysis. Tumor volume was calculated using 3D measurements of the index lesion at BL, C2, and C4. Percent change of tumor volume (%TV) between BL, C2, and C4 was calculated at early (9-12 sec) and delayed (360-480 sec) phases of DCE-MRI. The largest lesion was used for analysis in patients with multicentric or multifocal disease. Demographic, clinical, and pathologic data and treatment response at surgery (pCR versus non-pCR) were documented. Receiver operating characteristics curve (ROC) analysis was performed for prediction of pCR status. Positive predictive value (PPV), negative predictive value (NPV) and Youden Index were used to select %TV cut-off thresholds for pCR prediction.Results: 103 patients (median age, 53 years; range, 24-79 years) were included, 48 (47%) had pCR, and 55 (53%) had non-pCR at surgical pathology. The %TV reduction at C2 DCE-MRI was predictive of pCR on both early phase DCE MRI (AUC, 0.873; CI:0.779-0.968, $p < .0001$) and delayed phase DCE MRI (AUC, 0.844; CI:0.742-0.947, $p < .0001$). Optimal thresholds were as follows: 70% TV reduction on early phase DCE MRI with Youden's index of 1.58 was able to predict pCR correctly for 79% of patients with PPV of 81%; 75% TV reduction on delayed phase with Youden's Index of 1.44 was able to predict pCR correctly for 71% of patients with PPV of 85%.%TV reduction was also predictive of pCR at the C4 time point on both early phase DCE MRI (AUC, 0.761; CI:0.665-0.856, $p < .0001$) and delayed phase DCE MRI (AUC, 0.737; CI:0.641-0.833, $p < .0001$). Optimal thresholds were as follows: 90% TV reduction on early phase DCE MRI with Youden's index of 1.43 was able to correctly predict pCR in 72% of patients with PPV of 70%; and 90% TV reduction on delayed phase with Youden's Index of 1.34 was able to predict pCR correctly in 68% of patients with PPV of 71%.Conclusion: Our data shows that percent tumor volume reduction by DCE-MRI after 2 and 4 cycles of NAST was able to predict pCR in TNBC with high accuracy and can be used as an early imaging biomarker of NAST response prediction. Volumetric changes by longitudinal DCE-MRI can be used to differentiate chemoresistant and chemosensitive TNBC patients as early as after 2 cycles of NAST, and can help to triage patients for treatment de-escalation or targeted therapy.

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# The MYC oncogene suppresses tumor immune infiltration and function which is reversible with combinatorial immunotherapies

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Immunotherapy has great potential to improve outcomes for breast cancer patients. Yet, deciding on how to rationally combine therapeutic agents and predict patient populations who would benefit remains challenging. Less than 20% of patients with metastatic breast cancer respond to current immunotherapy regiments, further demonstrating the need for research in this area. We postulate that oncogene activation leads to immune-related vulnerabilities which can be exploited to discover new immunotherapy combinations with improved efficacy. MYC is an oncogene that is frequently overexpressed in the majority of triple negative breast cancers (TNBCs), and is frequently found in disease recurrence, metastasis, and chemotherapy resistance. Despite the association of MYC with poor patient outcome, little is known about how MYC facilitates immune evasion in TNBC. Using TNBC patient datasets from the TCGA, we discovered that the MYC gene signature is anti-correlated with T-cell activation signatures and a subset of genes that regulate antigen processing and presentation with MHC-I. We further examined the effects of MYC using a MYC-driven mammary tumor mouse model (MTB-TOM). MYC activation leads to downregulation of MHC-I expression on tumor cells, poor CD8+ T cell infiltration and consequently poor response to anti-PD-L1 monotherapy. We demonstrate three methods to improve response to immunotherapy—by inactivation of MYC, by inducing an interferon response within the breast tumor, or by inducing MYC tumor synthetic lethality with a small molecule inhibitor of PIM kinases. Using these combination immunotherapy strategies, we observed that a majority of animals eradicated their breast tumors and demonstrated a durable anti-tumor response following subsequent tumor re-challenge. Our data suggest MYC is an indicator of whether a breast cancer patient will respond to immunotherapy. Analysis of the MYC gene signature as a predictor of patient response to pembrolizumab in combination with paclitaxel followed by AC in the neoadjuvant I-SPY 2 trial is on-going and will be presented. Our study is the first to describe oncogenic MYC downregulation of MHC-I in a TNBC model of breast cancer and to demonstrate translatable approaches to overcome MYC orchestrated immune evasion.

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# Comparison of breast cancer staging models in patients after neoadjuvant chemotherapy

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**Background:** Neoadjuvant chemotherapy (NAC) is commonly utilized for breast cancer, however no consensus exists on the best way to stage these patients following treatment. Importantly, the American Joint Commission on Cancer (AJCC) 8$^{th}$ edition staging system did not specifically address staging after NAC. However, previous work by our group has shown that the pathologic prognostic stage does stratify patients with respect to outcomes. Our objective was to compare performance of the AJCC pathologic prognostic staging system to a second staging model, the Residual Cancer Burden (RCB) Index which takes into account residual tumor size, cellularity, lymph node status and size of any lymph node metastases.
**Methods:** A retrospective review identified patients with stage I-III invasive breast cancer treated with NAC from 2004-2014 at Dana-Farber Cancer Institute. Patients were excluded if they did not have RCB reported on final pathology. Disease-free survival (DFS) was defined as any recurrence or death from any cause, and overall survival (OS) as death from any cause. DFS and OS were calculated using the Kaplan-Meier method for each staging model. Receiver operator characteristic (ROC) curves were used to assess model fit using the c-statistic and the Hanley method to compare c-statistics.
**Results:** A total of 802 patients underwent NAC for stage I-III breast cancer. The median age was 48 years (range 22-86). Most patients presented with cT2 (n=470, 58.6%) or cT3 (n=188, 23.4%) and cN1 (n=422, 52.6%) disease. The majority (n=563, 70.2%) presented with grade 3 disease. In terms of subtype, 296 (36.9%) patients had hormone receptor-positive, HER2 negative, 261 (32.5%) HER2+, and 245 (30.5%) triple negative disease. Median follow up was 79.5 months (range 4-169). There were 176 recurrences including 32 local, 25 regional, and 145 distant recurrences. 676 (76.8%) patients were alive at last follow-up. The **Table** depicts the 7-year DFS and OS estimates for each of the staging models. The ROC c-statistics for DFS model fit were statistically similar, 0.72 for AJCC pathologic prognostic stage and 0.71 for RCB (p=NS). The c-statistics for OS were 0.74 and 0.71 respectively (p=NS).
**Conclusions:** Our results provide additional external validation of the AJCC pathologic prognostic stage and RCB's ability to stratify patients after NAC with respect to survival outcomes. These data can be used to inform subsequent revisions of the AJCC breast cancer staging system.

Estimated 7-year DFS and OS in Potential Staging Models for Breast Cancer Patients after NAC (n=802)

| | 7yr-DFS | 7yr-OS |
|---|---|---|
| Pathologic Prognostic Stage | | |
| Stage 0 (n=228) | 92.9% | 94.8% |
| Stage IA (n=193) | 81.7% | 90.2% |
| Stage IB (n=173) | 74.5% | 86.6% |
| Stage IIA (n=105) | 62.2% | 71.5% |
| Stage IIB (n=11) | 70.2% | 57.3% |
| Stage IIIA (n=40) | 62.2% | 75.4% |
| Stage IIIB (n=27) | 56.7% | 83.0% |
| Stage IIIC (n=25) | 27.8% | 28.2% |
| C-statistic (95% CI) | 0.72 (0.68-0.76) | 0.74 (0.69-0.79) |
| RCB | | |
| 0 (n=226) | 93.5% | 94.8% |
| I (n=118) | 83.0% | 90.0% |
| II (n=278) | 75.9% | 85.0% |
| III (n=180) | 55.1% | 69.9% |
| C-statistic (95% CI) | 0.71 (0.67-0.75) | 0.71 (0.66-0.75) |

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# Impact of chemotherapy (chemo) on t-cell maturation and clonal proliferation in early-stage and metastatic breast cancer

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**Background** Adaptive immunity is initiated by T-cell receptor (TCR) engagement with cognate tumor antigen, leading to T-cell maturation (i.e. conversion from naïve to effector state), clonal proliferation, and potentially tumor elimination. Therefore, broad T-cell repertoire diversity could be an important determinant of anti-tumor immunity. In breast cancer, chemo may facilitate adaptive immunity, but conversely may also be lymphotoxic. We characterize the impacts of curative-intent chemo and palliative combination chemo/immune checkpoint inhibition (ICI) on lymphocyte quantity, maturation, and clonal proliferation. **Methods** Peripheral blood mononuclear cells (PBMCs) were collected at baseline and serially in stage I-III subjects receiving curative-intent chemo (dose-dense doxorubicin, cyclophosphamide, paclitaxel, n=20), and in stage IV subjects receiving palliative ICI (pembrolizumab) plus chemo (paclitaxel, n=15; or capecitabine, n=14). Flow cytometry was conducted on fresh PBMCs to minimize cellular losses related to cryopreservation. DNA was extracted for T-cell clonality analysis using the immunoSEQ Assay (Adaptive Biotechnologies) at deep resolution. T-cell richness, calculated using the iChao1 richness estimator was used to assess overall T-cell diversity. **Results** Both dose-dense chemo and palliative chemo/ICI were lymphodepleting, however dose-dense chemo was associated with greater reductions in CD4+ naïve T cell count (week 8 counts 34% vs. 96% of baseline, p<.001) and T-cell richness (week 8 richness 57% vs 90% of baseline, p<.001). These effects were durable, with reductions in lymphocyte subsets (ALC, CD4, CD8, naïve, effector, and central memory subsets) and T-cell richness (estimated rearrangements 4.37 vs 3.29 x $10^5$/sample) sustained at metastatic relapse. T-cell richness correlated with CD4+ naïve cell proportion ($R^2$=0.52), suggesting a major contribution of CD4+ naïve cells to overall T-cell diversity. In this dataset, acute memory T-cell expansions were observed following initiation of chemo, but only among younger patients (age<60). **Conclusions** Curative-intent cytotoxic chemotherapy durably alters the quantity and diversity of peripheral T-cells, particularly of naïve cells, contributing to lymphopenia and reduced T-cell richness at metastatic relapse. Acute expansions of EM subsets were also observed but only in younger individuals. These contrasting immunologic effects highlight the potential importance of sequencing of ICI relative to chemo, and raise concerns regarding age-related thymic involution and immunosenescence. Ongoing research is warranted to investigate the predictive/prognostic utility of T-cell diversity/quantity in breast cancer, and whether thymic T-cell regeneration can be targeted therapeutically to enhance immunotherapy response, for example with cytokine therapies (IL-12 or IL-7, NCT04095689) or sex steroid inhibition (NCT03650894).

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# Predictors for fear of cancer recurrence in breast cancer patients referred for radiation therapy during the COVID-19 pandemic: A multi-center cross-section survey

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**Background** The outbreak of COVID-19 pandemic in China has greatly impacted the radiotherapy (RT) strategy for breast cancer (BC) patients, which might lead to an increased distressing psychological symptom. Thus, we perform a multi-center cross-section survey aiming to investigate the prevalence of fears of cancer recurrence (FCR) and explore predictors for FCR in BC patients referred for RT during pandemic. **Methods:** 542 BC patients who referred for RT between 24$^{th}$ Jan and 30$^{th}$ April 2020 during pandemic were consecutively enrolled from 14 hospitals around China including Yangtze Delta River Region, Guangdong and Shanxi province. Patients' sociodemographic, treatment information as well as psychological characteristics were collected using an information sheet, Fear of progression questionnaire-short form (FoP-Q-SF), Hospital Anxiety and Depression Scale (*HADS)* and EORTC QLQ-C30. The influence of pandemic on RT schedule was divided into four categories: "delay" was defined as >12 weeks from surgery to RT in patients without chemotherapy or >8 weeks from last time of anti-tumor therapy (including chemotherapy and surgery) to RT in patients with chemotherapy; "Special normal" was defined that patients themselves believed to have delayed RT initiation but actually not; "Interruption" was defined as any unplanned gaps in original RT regime and all other would be classified into "normal". Another type of influence on RT strategy was that patients had to shift planned RT hospital from Grade-A tertiary hospital to local hospitals. Univariable analyses of FCR were performed in a one-way analysis of variance (ANOVA) or student t-test or Pearson correlation analyses and candidate variables with $P<0.2$ were included Hierarchical multiple regression models to investigate predictors for FCR. Guangdong province was chosen as reference in models. **Results** 488 patients with complete data were eligible for the present analysis and none of patients and their family members had been diagnosed as COVID-19. The RT strategy was affected in 265 (54.3%) patients, including 143 with delayed RT initiation, 66 with "special normal" schedule, 24 (4.9%) with RT interruptions, 19 shifting to local hospitals for RT, and the remaining 13 being influenced on both RT schedule and planned RT hospitals. Most of patients with affected RT strategy occurred in late January and February, when was peak of COVID-19 pandemic in China. The mean FCR scores was 24.83 (SD=8.554) and 84 patients (17.3%) were classified as dysfunctional level of FCR (sum score ≥34). In univariable analyses, FCR were significantly higher in patients who received RT in Guangdong province and in hospitals with < 100 BC cases per year. In term of during pandemic, a significant difference in FCR was observed in terms of influence on RT schedule ($p<0.001$). and changes of hospital levels($p=0.009$). There were significant correlations between FCR and anxiety/depressive in HADS or all five function scales (physical, role, emotional, cognitive and social) and global QoL in QLQ-C30 ($p<0.001$). Finally, the model explained 59.7% of observed variances in FCR and showed that influence of RT strategy during pandemic had significantly impacted on FCR ($\Delta R2=0.01$, $\Delta F=2.966$, $p=0.019$). Hospitals in Shanxi province ($\beta=-0.117$, $p=0.001$), emotional function ($\beta=-0.19$, $p<0.001$), social function ($\beta=-0.111$, $p=0.006$), anxiety ($\beta=0.434$, $p<0.001$) and RT interruption ($\beta=0.071$, $p=0.035$) were independent predictors for FCR. **Conclusions** RT strategy for BC patients was greatly influenced during pandemic. RT interruption is an independent predictor for high FCR. Our findings emphasize the necessity to ensure the continuum of RT in BC patients, and efforts should be taken to alleviate the FCR through psychological interventions.

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Patient perception of telehealth services for breast and gynecologic cancer care during the SARS-CoV-2 (COVID-19) pandemic in NYC: A single center survey-based study

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**Background:** Prior to the COVID-19 pandemic, telehealth was rarely utilized in providing oncologic care. At our large NYC based outpatient clinic, telehealth services were quickly adapted for utilization for visits that could be completed outside of the clinic, in order to limit patient exposure to the novel coronavirus. This survey-based study aimed to assess patient perceptions of the utility of telehealth in their oncologic care during a time of national crisis. **Methods:** A 34-question survey was administered to all patients receiving care at our outpatient center between March 1, 2020 and June 30, 2020 including those who had visits delayed or cancelled during this time period. Of the 622 patients who received the survey via RedCap online or physical copy in clinic, 211 (34%) completed the survey. For evaluation of the Telehealth provided during the pandemic, we have adapted the validated SUTAQ (Service User Technology Acceptability Questionnaire) which assesses patient acceptability of telehealth via measures of accessibility, comfort, usability, privacy and security, confidentiality, satisfaction, convenience and health benefits with in-home telemonitoring. **Results:** All patients who completed the survey had a history of DCIS/ADH/LCIS, invasive breast cancer or gynecologic malignancy. Of the total survey respondents, 72 (35%) participated in a telehealth visit during the four month evaluation period. For all survey questions, “agreement” was considered if the patient selected mildly, moderately or strongly agreed on the SUTAQ scale. Of patients who participated in telehealth visits, 66 (92%) felt that the telehealth saved them time, 52 (72%) felt it increased their access to care and 56 (81%) felt it helped improve their health. Only 8 (12%) of patients felt that telehealth made them feel uncomfortable and 4 (6%) worried about confidentiality related to telehealth usage. Overall, 65 (92%) of patients were satisfied with the telehealth services they received and 64 (89%) would recommend these services to people with similar health conditions. Twenty-five (35%) felt that telehealth can be a replacement for their normal health care and 67 (93%) reported it could be a good addition to their care. Fifty-four (76%) would be interested in participating in telehealth visits in the future. **Conclusions:** Overall, patients expressed satisfaction with the use of telehealth services for oncologic care during the COVID pandemic. Although most patients do not feel that this is a suitable replacement for their in person care, they expressed that it was certainly a good addition to their care. A large majority of patients expressed interest in continuing to participate in telehealth visits in the future. Telehealth services should be carefully adapted as a long term addition to the in person clinical care of patients with cancer. These services should be utilized to optimize patient satisfaction, save time and increase access to care, especially among high risk patients.

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DCE-MRI derived imaging features for characterizing invasive lobular breast cancer and predicting recurrence-free survival after neoadjuvant therapy

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**Background** With current imaging technologies, assessing response to neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET) remains a challenge for patients with invasive lobular carcinoma (ILC). Therefore, we evaluated imaging features from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) before and after neoadjuvant therapy in a cohort of patients with ILC, including the longest tumor diameter (LD), functional tumor volume (FTV), and peak signal enhancement ratio (SER). FTV is the sum of all image voxels enhancing above a set threshold within a defined region, and has been validated as a predictor of recurrence-free survival (RFS) for breast cancer. SER is a measure of contrast wash-in and wash-out and reflects neovascularity of tumors. We determined whether baseline and post-treatment imaging features differed by type of neoadjuvant therapy and if they were associated with RFS in neoadjuvantly treated ILC regardless of treatment type.
**Methods** With institutional review board approval, a retrospective analysis of pre- and post-treatment breast DCE-MRI was performed on a cohort of ILC patients receiving neoadjuvant therapy between 1998 and 2017. We compared pre-treatment, post-treatment, and percent reduction (α) in LD, FTV, and peak SER by neoadjuvant treatment type (i.e. NAC or NET) using the Wilcoxon rank-sum test. Univariate t-tests, Chi-squared tests, analysis of variance, and Spearmen's correlation were used to evaluate associations of clinicopathologic features and treatment type. Univariate and multivariate associations with RFS in the entire neoadjuvantly treated cohort adjusting for treatment type were evaluated using the log-rank test and Cox proportional hazards models.
**Results** A cohort of 76 patients with pre- and post-treatment MRI were included in this study, of whom 42 (55.3%) received NAC and 34 (44.7%) received NET. The NAC group was significantly younger (55 *vs.* 60 years, $p$=0.013), less likely to have stage 1 disease (26.2% *vs.* 73.5%, $p$<0.001), and showed a trend of having more human epidermal growth factor 2 receptor-positive (HER2) tumors. The mean follow up time was 4.9 years with no difference between treatment groups. Patients in the NAC group had significantly larger pre-treatment LD and FTV but no difference was found in pre-treatment peak SER between groups. Post-treatment LD, FTV, and peak SER did not differ between treatment groups (**Table 1**). Those receiving NAC had significantly greater reduction in FTV compared to those receiving NET; αLD and α peak SER did not differ. In a multivariate Cox proportional hazards model including all patients in the cohort, higher pre-treatment peak SER was significantly associated with worse RFS regardless of neoadjuvant treatment type when adjusting for age, stage, receptor subtype, and tumor grade (hazard ratio 1.3, $p$=0.005, 95% CI 1.1-1.6). Neither LD nor FTV were associated with RFS on multivariate analysis.
**Conclusion**Pre-treatment peak SER measured by MRI may provide prognostic information beyond standard clinicopathologic variables in patients with ILC receiving either neoadjuvant
chemotherapy or endocrine therapy. Further evaluation in a larger ILC cohort is needed to validate our initial findings.
**Table 1.** Comparison of MR imaging features of ILC patients receiving neoadjuvant chemotherapy and neoadjuvant endocrine therapy.

| | **Overall(n=76)** | **NAC(n=42)** | **NET(n=34)** | **P-value** |
|---|---|---|---|---|
| **Pre-treatment (median, IQR)** | | | | |
| **LD (cm)** | 2.7, 1.6-5.4 | 4.6, 2.5-7 | 1.8, 1.4-3.2 | **0.0006** |
| **FTV (cc)** | 5.8, 2.2-16.4 | 8.7, 4.1-24.2 | 3.0, 0.9-8 | **0.0004** |
| **SER** | 0.9, 0.8-1.0 | 0.9, 0.9-1.0 | 0.9, 0.8-1.1 | 0.8335 |
| **Post-treatment (median, IQR)** | | | | |
| **LD (cm)** | 1.1, 0-1.9 | 1.0, 0-1.8 | 1.3, 0-1.9 | 0.6071 |
| **FTV (cc)** | 0.5, 0.1-1.8 | 0.3, 0.1-1.8 | 0.7, 0.3-1.8 | 0.2196 |
| **SER** | 0.9, 0.8-1.0 | 0.8, 0.8-1.0 | 0.9, 0.8-1.1 | 0.2321 |
| **Percent reduction (%)** | | | | |
| **LD** | 44.6, 15.1-100 | 79.6, 33.8-100 | 33.8, 10.1-100 | 0.0958 |
| **FTV** | 93, 72.5-97.4 | 95.8, 90.7-99.1 | 72.6, 43.1-94.5 | **<0.0001** |
| **SER** | 8.5, -11.1-19.7 | 10.7, -6.0-21.8 | 1.9, -15.1-17.9 | 0.3041 |

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# The role of CYP2D6 mediated tamoxifen metabolism in the suppression of ovarian function trial (SOFT)

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Tamoxifen (T) is a pro-drug that undergoes CYP2D6-mediated metabolic activation to metabolites that more potently inhibit estrogen stimulated growth compared to the parent drug. While many studies have examined the role of *CYP2D6* genotype in T-treated postmenopausal women, the role of CYP2D6 metabolism in premenopausal women (pre-MW) receiving T, with or without ovarian function suppression (OFS) or exemestane (E) and OFS is unknown. Methods: SOFT randomized 3066 (pre-MW) from 2003-2011 in 27 countries, stratified according to prior receipt or nonreceipt of chemotherapy and nodal status, to receive 5 years of T, T+OFS, or E+OFS. We designed a pharmacogenetics substudy (activated October 2010) to collect blood DNA from North American (NA) patients (pts) or to extract non-tumor DNA from available formalin fixed paraffin embedded (FFPE) tissue blocks. For pts with a blood sample, CYP2D6 was genotyped beginning with the Luminex Tag-It Mutation Detection Kit and when needed, with a copy number variation assay and/or sequencing assays. For pts with FFPE-derived DNA, *CYP2D6* genotyping for *3, *4, *6, *9, *10, *17 and *41 was performed using a Taqman Allelic Discrimination Assay. CYP2D6 phenotypes were called by classifying pts on the basis of a combination of poor (PM: *3, *4, *5, *6, *7, *8), slow (SM: *10), intermediate (IM: *9, *17, *29, *41) and extensive metabolizer alleles (EM; all others). Activity scores (AS) from phenotypes assigned for each allele: 0 if PM, 0.25 if SM, 0.5 if IM and 1 if EM allele, and multiplied x2 or x3 if duplicate or triplicate. With concomitant use of potent CYP2D6 inhibitor, AS=0; use of weak inhibitor subtracted 0.5. Metabolizer status was defined by *CYP2D6* genotype alone or in combination with CYP2D6 inhibitor use at randomization from the AS: extensive (AS 1.25 to 3), intermediate (AS >0.5 to <1.25), slow/poor (AS 0 to 0.5) metabolizer status. The laboratory was blinded to all clinical data. The substudy primary objective was to assess the association between disease-free survival (DFS) and CYP2D6 metabolizer status in the T arm, and secondarily in the T + OFS, and E + OFS arms. A Cox model estimated hazard ratios comparing status according to treatment assignment, with prespecified prognostic factors. Results: 1200/3047 (39%) randomized pts in the intention-to-treat (ITT) population had successful *CYP2D6* genotyping and 50% received prior chemotherapy. Following randomization, 435/1023 (42%) NA pts provided a blood sample and *CYP2D6* genotypes were derived in 435/435. Non-tumor tissue was macrodissected from 1277 available FFPE blocks, resulting in DNA concentrations of > 0.3 ng/ml in 1053, and successfully derived *CYP2D6* genotypes for 765/3047 pts (25%). 182 (15%) pts had DFS events after 8 yrs median follow-up. Metabolizer status from genotype was 57% extensive, 29% intermediate, 15% slow/poor. Metabolizer status was not associated with DFS in pts assigned T alone (P=0.60; Table), nor in pts assigned T+OFS (P=0.41) or E+OFS (P=0.30). 11% of pts used CYP2D6 inhibitors concomitantly at randomization; for 8% it changed the metabolizer status. The results using this definition were consistent. Conclusion: This retrospective-prospective SOFT pharmacogenetics substudy found no relation of CYP2D6 metabolizer status with DFS in premenopausal pts receiving T, T + OFS, or E + OFS. Given that 50% were pretreated with chemotherapy, further study is needed regarding the role of CYP2D6 metabolism in patients treated with T monotherapy.

Table

| Treatment Group | N pts (N events) | Comparison (N pts) | Hazard Ratio | 95% CI |
|---|---|---|---|---|
| Tamoxifen | 324 (56) | Intermediate (114) vs Extensive (210) | 0.78 | 0.43-1.39 |
| Tamoxifen | 265 (52) | Slow/Poor (55) vs Extensive (210) | 1.11 | 0.58-2.13 |
| Tamoxifen + OFS | 357 (46) | Intermediate (122) vs Extensive (235) | 0.73 | 0.38-1.40 |
| Tamoxifen + OFS | 299 (45) | Slow/Poor (64) vs Extensive (235) | 1.25 | 0.64-2.43 |
| Exemestane + OFS | 344 (46) | Intermediate (107) vs Extensive (237) | 0.59 | 0.28-1.22 |
| Exemestane + OFS | 293 (47) | Slow/Poor (56) vs Extensive (237) | 1.13 | 0.56-2.27 |

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# Germline mutation landscape in Chinese breast cancer patients

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**Background:** Genetic testing for patients with breast cancer (BCa) patients may change the routine patient care and shift the paradigm towards more personalized managing and treatment strategies. In particular, testing germline mutations in BRCA1/2 has become a part of the standard clinical practice for patients with BCa. However, our understanding of genetic epidemiology of BCa is mainly driven by data from Caucasian populations and it has been evident that gene alterations may be ethnic specific in breast cancer.
**Methods:** Aiming to delineate the landscape of germline mutations in Chinese patients with BCa to breast cancer, we collected blood samples from in 356 BCa patients at stage I-IV in Beijing Cancer Hospital between Jan. 2013 to Dec. 2019. Peripheral blood mononuclear cells were isolated from blood samples and genomic DNA were extracted for capture-based NGS sequencing. A large comprehensive 600 gene panel (PredicineATLAS, Huidu Medical Science Techonology, Inc.) was used to detect germline mutations in the covered genes with average 300x sequencing depth.
**Results:** A total of 356 BCa patients were included in our study, with the median age at first diagnosis of 49 years (Range: 21-87). Among all cases, 21.9% (78/356, 95% confidence interval [CI]: 17.7-26.6%) carried pathogenic or likely pathogenic mutations in 48 cancer related genes. Twenty-seven patients (7.6%, 95% CI: 5.1-10.8%) harbored BRCA1/2 mutations, followed by 5 patients carrying ATM mutations and RAD50 mutations respectively. Other commonly mutated genes include BARD1 (1.1%), FANCD2 (1.1%), CHEK2 (0.6%), FANCC (0.6%), FANCM (0.6%), PMS2 (0.6%), and TP53 (0.6%), most of which are related to DNA damage repair pathway. Moreover, BRCA1/2 carriers were more likely to appear among those with breast or ovarian cancer family history than those without (OR=3.41, 95% CI: 1.14-9.12, P=0.01). Compared with patients that aged older than 50 years at first diagnosis, those aged 30 years or younger were 6 times more likely to detect germline mutations in BRCA1/2 (95% CI: 1.18-26.1, P=0.02). In addition, mutations in BRCA1/2 were differentially associated with breast cancer subtypes. BRCA1 mutations were strongly enriched in triple-negative breast cancer (TNBC) (OR=6.7, 95% CI: 1.54-33.13, P=0.005). There is no strong significant survival difference observed between BRCA1/2 carriers and non-carriers, however, patients carrying ATM or RAD50 mutations tend to have lower disease-free survival.
**Conclusions:** This is a comprehensive analysis of germline mutation spectrum in a large Chinese patient cohort with breast cancer. Collectively, a substantial proportion of patients with breast cancer had hereditary risk factors. Distinct distribution of pathogenic mutations in breast cancer subtypes and differential associations between mutation status and clinical features were further observed. All these findings will advance our understanding regarding the pathologies and heterogeneity of breast cancer.

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Radioactive Iodine Seed placement in the Axilla with Sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer: Results of the prospective multicenter RISAS trial

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**Rationale and research objective:** As a result of neoadjuvant chemotherapy (NAC), approximately 1/3 of clinically node positive (cN+) breast cancer patients convert to a pathologic complete response (pCR) of the axilla. Targeted Axillary Dissection appears to be most accurate to evaluate axillary treatment-response, but evidence to support this is limited. The RISAS trial was set up to determine the accuracy of sentinel lymph node biopsy (SLNB) combined with excision of the pretreatment marked positive lymph node for axillary staging after NAC in cN+ patients.
**Methods:** This prospective, multicenter trial included cT1-4N1,2,3b patients treated with NAC. Prior to NAC, an iodine seed was placed in the pathologically confirmed positive lymph node. After NAC, all patients underwent SLNB together with excision of the marked lymph node (RISAS-procedure) followed by axillary lymph node dissection (ALND). The identification rate and the accuracy (i.e. false negative rate (FNR) and negative predictive value (NPV)) were calculated for the RISAS procedure. Assuming an FNR of 2%, a prevalence of a positive ALND of 64% and a 10% drop-out rate, a sample size of 248 patients was needed to determine non-inferiority. The NULL hypothesis of inferiority would be rejected at a significance level of 5% if the upper bound of the two-sided 90% Clopper-Pearson confidence interval of the observed FNR would be below the non-inferiority margin of 6.25%. Secondary objectives included the accuracy of the SLNB and excision of the marked lymph node separately.
**Results:** A total of 252 pathologically proven cN+ patients provided informed consent of whom 227 underwent the RISAS procedure/Targeted Axillary Dissection (SLNB combined with excision of the marked positive lymph node). The identification rate of the RISAS procedure is 98% (223/227). Preliminary analysis shows a false negative rate of approximately 5% and a negative predictive value of approximately 91%. Furthermore, by combining SLNB with excision of the marked lymph node, both the identification rate and the accuracy are improved compared to either the SLNB alone or the excision of the marked lymph node alone.
**Conclusion:** This prospective multicenter validation trial shows that the RISAS procedure/Targeted Axillary Dissection is most suitable in terms of identification rate and accuracy to replace ALND for axillary staging after NAC in cN+ patients.
The trial was funded by the Dutch Cancer Society (KWF, grant number 2015-8023).

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Definition of a high risk cardiac zone on non-contrast computed tomography (CT) scans for indirect optimization of left anterior descending coronary artery (LADCA) dosimetry for breast radiotherapy

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**Background :** Breast radiotherapy is associated with a cardiotoxicity risk which could be decreased by optimizing radiation dose to the left anterior descending coronary artery (LADCA). However, precise delineation of the LADCA on non-contrast computed tomography (CT) scans is complex and poorly reproducible.
**Purpose :** This study aimed to define a reproducible “high risk cardiac zone” (HRCZ) which could straightforwardly replace LADCA delineation on non-contrast CT scans for treatment planning optimization. Additionally, we compared standard dosimetric parameters (mean and maximum doses) of the proposed HRCZ and of the LADCA.
**Materials/methods :** Forty breast cancer patients treated with intensity-modulated radiation therapy (IMRT) were randomly selected from our institutional database. The LADCA was manually delineated on the non-contrast simulation CT scans according to ESTRO guidelines (Duane et al., 2017), to ensure reproducibility, and each contour was validated by a staff of three radiation oncologists. “High risk cardiac zones” (HRCZ) were defined as segments of the anterior cardiac wall, geometrically centered around the inter-ventricular groove where the LADCA anatomically lies (from top to bottom) with a constant 1cm-thickness and a symmetrical lateral expansion on both sides of the groove (HRCZ width). For each patient, eight “high risk cardiac zones” (HRCZ) were delineated differing by their width, ranging between 1 cm and 8 cm (by steps of 1cm). Mean and maximum doses to the LADCA and to the HRCZ were retrieved, and relative variations were calculated as follows, as a function of the HRCZ width:
*Mean dose relative variation = [mean dose (HRCZ) - mean dose (LADCA)]/mean dose (LADCA)*
*Max. dose relative variation = [max. dose (HRCZ) - max. dose (LADCA)]/max. dose (LADCA)*
**Results :** Mean and maximum dose relative variations between HRCZ and LADCA are reported in **table 1** as a function of HRCZ width, for left-sided and right-sided irradiation. For a given HRCZ width, LADCA radiation exposure can be straightforwardly deducted from HRCZ dosimetric parameters, by applying the corresponding dose adjustments. HRCZ had higher maximum doses than LADCA, independently of the width. However, for a HRCZ width larger than 4 cm, dosimetric adjustments for the maximum doses drastically increased for right-sided irradiation with a potential risk of non-representativeness.

Table 1: maximum and mean dose relative variation between the LADCA and the proposed HRCZ

| **HRCZ width (cm)** | **Max. dose var. (left-sided RT)** | **Mean dose var. (left-sided RT)** | **Max. dose var.(right-sided RT)** | **Mean dose var. (right-sided RT)** |
|---|---|---|---|---|
| **1** | 5.3% | -13.0% | 7.8% | -1.4% |
| **2** | 12.6% | -19.1% | 16.3% | -2.4% |
| **3** | 19.1% | -22.6% | 26.4% | -2.8% |
| **4** | 24.8% | -26.0% | 38.6% | -2.8% |
| **5** | 29.0% | -28.5% | 52.2% | -2.2% |
| **6** | 29.0% | -32.3% | 71.3% | -1.1% |
| **7** | 29.9% | -36.0% | 92.4% | 0.5% |
| **8** | 29.9% | -38.8% | 118.3% | 2.8% |

*Table 1: maximum and mean dose relative variation between the LADCA and the proposed HRCZ, as a function of the HRCZ width. HRCZ: “high risk cardiac zone”. LADCA: Left anterior descending coronary artery.*

**Conclusion :** When planning breast radiotherapy on non-contrast CT scans, delineating a segment of the anterior cardiac wall centered on the inter-ventricular groove from top to bottom, with a 1cm thickness and a 3-4cm width, can replace LADCA uncertain contouring and can be conveniently used for indirect coronary sparing.

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# The psychosocial impact of caregiving on partners of young women with breast cancer in treatment

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**Background**Cancer diagnosis and early treatment may have wide-ranging consequences for a woman'spartner (ie. spouse or significant other). In general, younger caregivers have been found to havegreater unmet needs and higher levels of distress compared to those who are older. To date,there is little known about the unmet needs and experiences of partners who care for youngwomen with breast cancer during active treatment.**Trial Design:** Cross-sectional survey of partners of young women with breast cancer.**Eligibility Criteria:** The current analysis focuses on a subset of respondent partners of womenwith breast cancer participating in the Young Womens Breast Cancer Study (NCT01468246)who met the following criteria: diagnosed at age < 40 years; time since diagnosis <12 months;and/or Stage IV disease (at diagnosis or in metastatic setting); and/or local recurrent disease< 12 months.**Specific Aims:** To explore the experience of partners of women in active treatment or havingvery recently completed treatment for breast cancer.**Statistical Methods:** We employed descriptive statistics to present sample characteristics,including means or medians for continuous variables and proportions for categorical variables.We assessed partners' responses re: sociodemographics, perceived social support (MOS-Social Support Survey, Cancer Perceived Agents of Social Support), quality of life (QOL)(Caregiver QOL Index-Cancer), coping (Brief COPE), perceived financial security, perceivedparenting concerns (Parenting Concerns Questionnaire), anxiety and depression symptoms(Hospital Anxiety and Depression Scale), sexual satisfaction (Global Measure of SexualSatisfaction), posttraumatic growth (Posttraumatic Growth Inventory-Short Form), and an open-ended question to explore their experiences and needs.**Accrual:** 25 participants were included.**Results:** All partners were male (25/25; 100%), and most were white (n=23/25; 92%), workingfull-time (n=21/25; 91%); and college educated (n=19/25; 86%). Eighteen partners (n=18/25;72%) were parenting children <18 years old and 40% (n=10/25) were partnered with womenwith Stage 4 breast cancer. At the time of the survey, the median age of partners was 44 years(range, 28-69) and of patients was 38 years (range, 25-40). Many partners (57%) reportedsymptoms of anxiety (>8 on the HADS anxiety subscale), fewer (22%) were categorized ashaving symptoms of depression (>8 on the HADS depression subscale). Additionally, 39%reported not being sexually active; 41% reported maladaptive coping; 30% reported financialstrain;30% reported relationship strain. Reported caregiver QOL ranged from 22-116, with amean score of 52.5 (SD, 23.9), similar to population norms, with higher scores indicating lowerquality of life. Parenting concerns scores were generally low indicating less concern, with arange of 12-35, and mean of 20.5 (SD, 7.6). Post-traumatic growth ranged from 4-33, with amean score of 20.7 (SD, 7.4), with higher scores indicating greater personal growthexperienced. 44% (11/25) responded to the open-ended experiences and needs question.Common responses included feeling a lack of support, need for tailored and titrated information,and desire to connect with other men who faced similar experiences. Partners also reportedtheir struggles with uncertainty about the future.
**Discussion:** A subset of partners of young women in active treatment for breast cancerexpressed concerns related to relationship strain, sexuality, need for support, and finances.Future work designed to meet the needs of partners of breast cancer patients includinginformational and psychosocial supports may benefit them and the patients as they manage theprocess of ongoing treatment and challenges about the future.

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Primary efficacy results from AIPAC: A double-blinded, placebo controlled, randomized multinational phase IIb trial comparing weekly paclitaxel plus eftilagimod alpha (soluble LAG-3 protein) vs. weekly paclitaxel plus placebo in HR-positive metastatic breast cancer patients

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**Background:**Eftilagimod alpha (efti, IMP321),a soluble LAG-3 protein (LAG-3Ig) that binds to a subset of MHC class II molecules, mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. AIPAC (Active Immunotherapy PAClitaxel; NCT02614833) investigatedcombinations of the APC activator efti + weekly paclitaxel compared to paclitaxel + placebo in metastatic breast carcinoma (MBC) patients (pts).
**Methods:**The placebo-controlled, double-blinded, 1:1 randomized, multinational, phase IIb trial enrolled pts with measurable disease, hormone receptor-positive (HR+) MBC with indications for first line weekly paclitaxel without indication for HER2/neu targeted therapy. Pts received paclitaxel (80 mg/m² IV at D1, D8, D15 plus efti (30 mg) or placebo at D2, D16 (injected SC every 2 weeks) for 6 cycles (1 cycle = 4 weeks). Maintenance phase followed in which pts benefitting from treatment received efti or placebo for an additional 52 weeks. Primary endpoint was progression-free survival (PFS) (RECIST1.1) determined by blinded independent central read (BICR). Secondary endpoints included local read PFS, RECIST 1.1 tumor response, pharmacodynamic effects, quality of life and overall survival. The study was powered (80 %) to detect 0.667 hazard ratio (HR) based on 5% one-sided alpha and planned to enroll 226 pts.
**Results:** From Jan 2017-Jul 2019, 227 pts were randomized. All except 1 received ≥ 1 treatment and were included in the full analysis set [(efti (n = 114); placebo (n = 112)]. Data cut-off was 10th Jan 2020 with 12 month median follow-up. HR for PFS assessed by BICR was 0.93 [95 % CI 0.67-1.30], p =0.341. In the efti group 63 % (95% CI 52- 71%) were progression free at 6 months compared to 54 % (95% CI 43-63%) in the placebo group. ORR was 48.3 % in the efti group compared to 38.4 % in the placebo group as assessed by BICR (p=0.118). Efti increased numbers of PBMCs and T cells (CD4 and CD8) significantly compared to placebo. In predefined subgroups such as pts with low monocytes at baseline, luminal B subtype or age <65 years, clinically meaningful improvement in PFS was observed. TEAE rates leading to death (or discontinuation) in the two groups were similar, at 1.8 % (5.3 %) and 2.7 % (6.3 %) for the efti and placebo groups, respectively. Three pts (1.3 %) were withdrawn from treatment due to grade 3-4 immediate hypersensitivity reactions to efti, while 4 pts (1 in efti group vs. 3 in placebo group) were withdrawn from the study due to grade 2-3 hypersensitivity to paclitaxel. The most frequent (≥10%) TEAEs ≥ grade 3 were gamma-glutamyl transferase increase (19.3% vs 29.5%), aspartate aminotransferase increase (8.8% vs 10.7%) and neutropenia (15.8% vs 14.3%) reported in the efti and placebo group, respectively. Injection site reaction (34.2% vs 3.6%) and injection site erythema (30.7% vs 1.8%) were more frequent in efti versus placebo arms.

| | **BICR** | | **Investigator** | |
|---|---|---|---|---|
| | **Efti+paclitaxel(N= 114)** | **Placebo+paclitaxel(N= 112)** | **Efti+paclitaxel(N= 114)** | **Placebo+paclitaxel(N= 112)** |
| Median PFS, months (95% CI) | 7.29 (6.64-7.46) | 7.29 (5.52-7.46) | 7.16 (5.65-7.39) | 6.70 (5.52-7.33) |
| HR (95% CI) | 0.93 (0.67-1.30) | | 0.92 (0.69-1.23) | |
| P value | 0.341 | | 0.305 | |
| Mean PFS [SE], months | 7.12 [0.37] | 6.64 [0.38] | 6.81 [0.33] | 6.30 [0.31] |

**Conclusion:** Efti did not prolong overall median PFS in women with HR+ MBC receiving first line chemotherapy. Tested in a randomized setting against placebo in pts receiving paclitaxel, efti is well tolerated and did not add clinically significant toxicity while inducing a sustained, significant increase in CD8 T cells in blood and clinical benefits in some predefined subgroups. Relevant subgroups and overall survival will be investigated.

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# Igf1r mediates cdk4/6 inhibitor (cdk4/6i) resistance in tumor samples and in cellular models

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**Background**: Deciphering the molecular landscape of resistance to the CDK4/6 inhibitors represents a critically important question for patients with hormone-receptor positive (HR+) metastatic breast cancer (MBC). Emerging insights from sequencing efforts suggest that inactivating alterations in the RB1 tumor suppressor occur in a small minority of patients and that a variety of heterogeneous mediators provoke resistance in patient samples. Proteins implicated in CDK4/6i resistance include cell cycle regulators such as cyclin E1/2, CDK6, and aurora kinase as well as known oncogenic signal transduction mediators involved in activation of the RAS-MEK and AKT-mTOR pathways. The insulin-like growth factor 1 receptor (IGF1R) has been implicated in modulating anti-estrogen resistance, and IGF1R inhibitors are currently in various stages of pre-clinical and clinical development.
**Methods**: We identified patients with amplification events in IGF1R from a database containing targeted sequencing of solid tumor samples obtained from patients with HR+ MBC enrolled on a research biopsy protocol. Tumor biopsies may have been obtained at various points during each patient's clinical treatment course. HR+ T47D cells were modified to over-express IGF1R via lentiviral infection and selection. Derivative cell lines were treated with IGF-1 ligand and downstream activation of the PI3K/AKT and RAS/MEK pathways were assessed via western blotting. Control cells (expressing GFP) were mixed with IGF1R-expressing cells 1:1 and cultured in the presence of IGF-1 ligand and palbociclib or other drugs, for 1-3 weeks. At the timepoint of interest, cells were harvested and the relative proportion of GFP or IGF1R-expressing cells were interrogated via flow cytometry.
**Results**: We identified seven patients with HR+ MBC and IGF1R amplifications via targeted sequencing of tumor biopsies. Five of these patients had exposure to CDK4/6i-based therapy in the metastatic setting. Three patients demonstrated intrinsic resistance to CDK4/6i treatment (with duration <6 months) and biopsies were obtained prior to CDK4/6i exposure or, in one case, while on treatment. In an additional patient, after nine months of CDK4/6i-based therapy, an IGF1R amplification was present at the time of progression. In one counter-example, a baseline biopsy revealed IGF1R amplification and subsequent clinical benefit with CDK4/6i, exceeding 10 months, was noted. T47D cells over-expressing IGF1R demonstrated increased pERK and pAKT activation following introduction of IGF-1 ligand. Control GFP and IGF1R-expressing cells were plated 1:1 and cultured in the presence of IGF-1 ligand and palbociclib. In a flow cytometry-based competition assay, an IGF-1 dose-dependent increase in the relative proportion of IGF1R-expressing cells was noted after one, two, and three weeks of palbociclib treatment. The extent of IGF1R-expressing cell enrichment was attenuated in the presence of either a MEK inhibitor or an IGF1R inhibitor.
**Conclusions**: IGF1R amplification events were identified in tumor biopsy samples that reflect either intrinsic or acquired resistance to CDK4/6i-based therapy. HR+ breast cancer cells which over-express IGF1R demonstrate enrichment under palbociclib drug selection in a flow cytometry-based competition assay, which was abrogated by concurrent use of a MEK or IGF1R inhibitor. These results suggest that IGF1R may join the increasingly heterogeneous landscape of CDK4/6i resistance mediators. Further exploration of this possibility is warranted. A subset of patients with IGF1R-mediated CDK4/6i resistance could benefit from therapeutic strategies designed to downregulate MEK or IGF1R activity.

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The role of purinergic signaling in the chemotherapy response of triple negative breast cancer

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Triple negative breast cancer (TNBC) affects women worldwide with a higher incidence in minority populations. Patients with TNBCs often have poorer prognoses in comparison to other breast cancer sub-types due to a lack of effective therapeutic options. Chemotherapy and immunotherapy are the only effective treatments, but these modalities generally result in short-term response. Therefore, there is a need to identify additional therapies to intensify the chemotherapeutic response in TNBC. When cancer cells are exposed to chemotherapy, they release adenosine triphosphate (ATP) into the extracellular space. Extracellular ATP is degraded by CD39 (E-NTPDase) to adenosine diphosphate (ADP) and then adenosine monophosphate (AMP), and AMP is broken down to adenosine by CD73. We examined the potential role of extracellular ATP in chemotherapy- induced cancer cell death. We hypothesized that extracellular ATP sensitizes TNBC cells to chemotherapy and that ATP degrading enzymes such as CD39 and CD73 attenuate this effect. TNBC MDA-MB 231, MDA-MB 468, and Hs 578t cell lines were treated with the chemotherapeutic agent paclitaxel for different time courses. Extracellular ATP was measured via the ATPlite 1step luminescence assay, and cell viability was assessed by applying PrestoBlue HS cell viability reagent. Paclitaxel-treated TNBC cell lines revealed a dose-dependent increase in extracellular ATP release in the presence of an inhibitor of CD39 (POM-1), accompanied by a dose-dependent decrease in cell viability. In addition, the general P2X receptor (P2RX) inhibitor iso-PPADS and the P2RX7 specific inhibitor (A438079) were added separately to observe if the P2X receptors are necessary for the release of ATP upon paclitaxel treatment. After paclitaxel treatment, TNBC cell lines showed a decline in the amount of ATP released with the addition of the inhibitors iso-PPADS and A438079. Treatment of non-tumorigenic immortalized MCF-10A mammary epithelial cells with paclitaxel in the presence and absence of the inhibitors iso-PPADS and A438079 did not result in a significant increase in extracellular ATP or a decrease in cell viability. These results indicate that P2RX7 is necessary for ATP release in TNBC cell lines exposed to chemotherapy. Furthermore, when TNBC cell lines were treated with increasing concentrations of ATP, there was a dose-dependent decrease in cell viability. Overall, these findings suggest that extracellular ATP may impact the chemotherapeutic response in TNBC cell lines through the activation of the ATP-gated channel P2RX7.

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# The human tumor atlas network (HTAN) breast pre cancer atlas: A multi-omic integrative analysis of ductal carcinoma in situ (DCIS) and correlation with clinical outcomes

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**Introduction.** As nonobligate precursors of invasive disease, pre-cancers provide a unique vantage point from which to study the molecular pathways and evolutionary dynamics that lead to the development of life-threatening cancers. Ductal carcinoma *in situ* (DCIS) is the most commonly diagnosed precursor of breast cancer, with variable propensity for invasive progression. In order to address the problems of over- and under-treatment, we performed a multimodal, integrated profile of DCIS with clinical outcomes with which to develop and validate predictors of invasive progression. **Methods.** We present observations on DNA, RNA, and protein expression on two independent patient cohorts of DCIS, diagnosed from 1981 to 2014, from the Translational Breast Cancer Research Consortium (TBCRC 038) and the Washington University Repository of Archival Human Breast Tissue (RAHBT). Patients initially diagnosed with DCIS, with either DCIS or invasive recurrence (cases; mean follow up 5.8 years) were matched to those without recurrence (controls; mean follow up 10.3 years), based upon age at diagnosis and year of diagnosis. **Results.** We present genomic and cellular changes that correlate with both disease states and patient outcomes in DCIS. DCIS can be clustered by classification systems developed for IBC. Specific immune cell types and pathways correlate with longitudinal outcome. Luminal cell adhesion and metabolism pathways are upregulated in controls and cases, respectively. Highly multiplexed ion beam imaging (MIBI) was used to validate RNA seq findings, and to provide single cell-level spatial context for molecular alterations.**Conclusion.** We have performed an integrated multi-omic analysis of DCIS and associated tumor micorenvironment. Our multi-scale approach employs in situ methods to generate a spatially resolved atlas of breast precancers where different modalities can be directly compared to each other, and correlated with conventional pathology findings and clinical outcome. The PreCancer Atlas represents a complex multi-modal database for DCIS study, whose design allows for future discovery and hypothesis generation.

**Table 1. Breast Pre-cancer Atlas Multi-scale Characterization Assays**

| Assay | Scale | Type of Data | Integration and validation with other assays |
|---|---|---|---|
| RNA-seq (Single duct, single cell, TME) | Cell, duct, organ, normal tissue | 1. Whole transcriptome gene expression profiling per single duct (also enabling CNV and cell type prediction)2. Whole transcriptome gene expression profiling per single duct | 1. Prediction of CNV confirmed by DNA-seq (single duct) and FISH (single cell)2. Prediction of cell type composition (Cibersort) confirmed by multiplex IHC and multicolor flow cytometry |
| Low-pass whole genome DNA-seq | Duct and adjacent normal | CNV profiling per single duct | Analysis of CNV supported by RNA-seq (single duct) and MIBI (single cell) |
| Whole genome sequencing | Duct and adjacent normal | Mutation status per single duct | Mutational analysis confirmed by RNA-seq |
| Multiplex IHC (MIBI & Cyclic multicolor) | Cell | 1. Cell type2. Proteomic analysis | Analysis of cell type supported by RNA-seq of ducts (Cibersort) and single cells |
| H&E Morphometrics | Cell, duct, organ | Spatial location of cell types, organization of ducts | Analysis of H&E images correlated with FISH data |

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A phase 1/2 study of SAR439859, an oral selective estrogen receptor (ER) degrader (SERD), as monotherapy and in combination with other anti-cancer therapies in postmenopausal women with ER-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC): AMEERA-1

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**Background** SERDs belong to a class of ER-targeted therapies that antagonize and degrade ERs, including in ER-dependent tumors resistant to other endocrine therapies (ET). This study (AMEERA-1; NCT03284957) investigates SAR439859, an oral SERD, as monotherapy and (in ongoing cohorts) in combination with targeted therapies in patients (pts) with ER+/HER2- mBC. Here we report updated safety and antitumor activity with SAR439859 monotherapy, including exploratory analyses by prior therapy and *ESR1* status. **Methods** This open-label, phase 1/2, first-in-human study assessed SAR439859 as monotherapy in Parts A (dose escalation 20-600 mg once daily [QD]) and B (dose expansion with recommended dose at 400 mg QD). Eligible pts were heavily pre-treated, postmenopausal women with ER+/HER2- mBC and measurable disease who received ≥6 months of prior ET in the advanced setting. Prior chemotherapy, mammalian target of rapamycin inhibitors (mTORi) and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) for advanced disease were allowed. This analysis pooled data from pts receiving SAR439859 ≥150 mg (Part A) and 400 mg (Part B), administered in 28-day cycles. Antitumor activity was assessed by the objective response rate and clinical benefit rate (CBR: complete response [CR], partial response [PR] and stable disease [SD] ≥24 weeks) per RECIST v1.1, determined by investigators. Analyses by prior therapy and baseline *ESR1* mutation status were performed. Safety was also evaluated. **Results** Pts (n = 62; Part A: 13; Part B: 49) had a median age of 63 (range 37-88) years and ECOG PS 0 (59.7%) or 1 (40.3%); 93.5% had visceral metastases. Pts had a median of 2 (range 1-8) prior lines of therapy in the advanced setting (48.4% had ≥3 prior lines): all had prior ET and 72.6% had prior targeted therapy. SAR439859 monotherapy showed antitumor activity in the response-evaluable population (n = 59) and in subset populations with ≤3 prior lines (n = 33) or without prior mTORi, CDK4/6i, or SERD (n = 14) (Table 1). For pts with *ESR1* status (n = 58), CBR with SAR439859 was comparable in *ESR1* wild-type (36.7%) and mutant mBC (32.1%), with similar results in subpopulations. Treatment-related adverse events (TRAEs) occurred in 62.9% of pts (all grade 1-2); none resulted in SAR439859 discontinuation. Most frequent TRAEs were hot flush (16.1%); constipation and arthralgia (each 9.7%); decreased appetite, vomiting, diarrhea and nausea (each 8.1%); and fatigue (6.5%). **Conclusions** Among heavily pre-treated pts, SAR439859 demonstrated antitumor activity, similar to historical single-agent fulvestrant activity in less heavily pre-treated pts with advanced/mBC (2L+ setting; no prior targeted agents) (indirect comparison). In both subsets of pts with fewer prior advanced lines of therapy, SAR439859 showed trends of greater clinical activity versus historical fulvestrant activity. SAR439859 had a favorable safety profile with limited TRAEs. No safety signals of cardiac or ocular toxicities were observed. Ongoing parts of the study are investigating SAR439859 in combination with targeted therapies. Based on the monotherapy results, a randomized phase 2 study is investigating SAR439859 compared with physician's choice in a 2L+ setting (AMEERA-3; NCT04059484). Funding: Sanofi.

Antitumor activity overall and in subpopulations by prior lines of therapy (Parts A+B)

| | Overall population (A+B) (n = 59)[a] | ≤3 Prior advanced lines (n = 33)[b] | Without prior targeted therapy (n = 14)[c] |
|---|---|---|---|
| BOR, n (%) | | | |
| --CR | 0 | 0 | 0 |
| --PR | 5 (8.5) | 5 (15.2) | 3 (21.4) |
| --SD | 24 (40.7) | 15 (45.5) | 8 (57.1) |
| --PD | 30 (50.8) | 13 (39.4) | 3 (21.4) |
| ORR, n (%) | 5 (8.5) | 5 (15.2) | 3 (21.4) |
| CBR, n (%) | 20 (33.9) | 14 (42.4) | 9 (64.3) |

[a]Pooled cohort (A ≥150 mg QD + B); [b]Subset of pooled cohort with ≤3 prior lines in the metastatic setting, including ≤1 of either prior chemotherapy or CDK4/6i and no prior mTORi; [c]Subset of pooled cohort with no prior mTORi, CDK4/6i, or fulvestrant.

BOR, best overall response; CBR, clinical benefit rate; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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# Biomarker analysis of paclitaxel, ganitumab, and metformin (PGM) therapy in the I-SPY2 neoadjuvant clinical trial

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I-SPY2 is a neoadjuvant trial evaluating experimental therapies in combination with cytotoxic chemotherapy compared to chemotherapy alone with the primary endpoint of pathologic complete response (pCR). Abundant preclinical evidence suggested the type I insulin-like growth factor receptor (IGF-1R) regulated breast cancer growth, although multiple clinical trials did not show benefit. We were the first to report the results of a monoclonal IGF-1R antibody ganitumab (G) in combination with chemotherapy. PGM followed by doxorubicin/cyclophosphamide (AC) did not result in substantial increases in pCR when compared to P followed by AC. In this report, we examined several potential predictive biomarkers.

IGF-1R inhibitors induce hyperglycemia and we examined hemoglobin A1C (HgbA1c) as a measure of glucose control in patients before and after PGM therapy. 106 patients received PGM and 104 patients had baseline HgbA1c with a median of 5.4%. However, 27% (28/104) had levels greater than 5.7% the upper limit of normal as defined by the NIDDK. 4 of 104 had HgbA1c greater than 6.5%, a level associated with type 2 diabetes. pCR rates are similar between patients with baseline HgbA1c ≤5.7% (21%) vs. >5.7% (25%) (Fisher test p=0.79). 72 of these patients had an additional HgbA1c during the course of PGM therapy. For patients with HgbA1c ≤5.7%, 27% (14/52) had subsequent elevation above 5.7% after PGM. For patients with a baseline HgbA1C >5.7%, all 20 patients continued to have elevated levels through PGM.

We also examined pre-treatment tumor gene expression profiles derived from custom Agilent 44K full-genome microarrays. We studied 11 genes associated with the IGF-1R signaling (IGF1, IGF2, IGF1R, INSR, IGFBP2, IRS1, IRS2, IGFBP3, IGFBP4, IGFBP5, CDH1), the IGFBP5/IGFBP4 ratio, and two IGFR expression signatures (Creighton, et al. J Clin Oncol 26:4078 2008 PMID: 18757322; Mu, et al. Breast Cancer Res Treat 133:321 2012 PMID: 22297468). The 2 signatures evaluated: the IGF1 ligand score and the IGF1-R signature are anti-correlated (Rp= - 0.79). In the population as a whole, lower levels of IRS1 and IGFBP5 significantly associated with response to PGM (likelihood ratio test (LR) p< 0.05), as do lower levels of the IGF1 ligand score and higher levels of the IGF-1R signature. However, levels of IRS1 and the two expression signatures also trend toward or are significantly associated with response in the control arm; and treatment interactions for all four biomarkers are non-significant (LR p>0.05). Therefore, none of these biomarkers qualify as specific predictors of response to PGM. Similarly, high MammaPrint scores (MP2) were associated with higher pCR scores in both PGM and Control arms. Previous gene expression profiles were divided into tertiles (low, intermediate, high). Similar to the continuous case, IGF1Rsig-class associates with pCR in both the PGM and control arms (Fisher test p=0.033 and 0.044, respectively), and thus also fails as a specific predictor of response to PGM.

We conclude that PGM therapy results in worsening of glucose control and likely increases serum insulin levels. While IGF gene expression profiling associated with treatment response, they were not specific for PGM. Further, biomarker analysis and strategies to control glucose will be needed to optimize anti-IGF-1R therapies.

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Young, empowered & strong (YES): A web-based education and supportive care intervention for young women with breast cancer across the care continuum

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Background: Young women diagnosed with breast cancer have unique physical and psycho-social needs that are often unaddressed. Patient-centered models of care, including eHealth strategies, can help empower young women to self-manage symptoms and psychosocial concerns, as well as support informational needs throughout the cancer care trajectory. Methods: YES (Young, Empowered and Strong) is an interactive web-based portal designed with patient-reported outcome questionnaires (PROs) that trigger delivery of young breast cancer patient-specific education and symptom management materials. Personal journal and messaging components are also available. We piloted the YES portal among young women (<45 years) with newly diagnosed early breast cancer (EBC), breast cancer survivors (BC-S) and women living with metastatic breast cancer (MBC), for whom PROs were deployed weekly (EBC, MBC) or every 4 weeks (BC-S) over 12-weeks. At study completion, the use, feasibility and acceptability of the YES portal was assessed via a survey and a structured interview. Results: Thirty women were enrolled between April and June 2019: 10 EBC, 10 BC-S and 10 MBC. Mean age at diagnosis and enrollment was 36 (range 25-44) and 39 (range 31-44) years respectively and 13% (4/30) were non-white. Nearly all participants were receiving treatment (96%, 27/28) including 54% (15/28), endocrine therapy and 43% (12/28), chemotherapy. Overall, 61% (180/296) of PROs deployed were completed, with completion rates highest for EBC patients (EBC: 70%, BC-S: 63%, MBC: 52%). Of 37 PROs domains, the most frequently triggered were sexual health (EBC: 90%, BC-S: 90%, MBC: 90%), anxiety (EBC: 80%, BC-S: 90%, MBC: 90%) and fatigue (EBC: 90%, BC-S: 80%, MBC: 90%). Physical domains and young breast cancer specific domains commonly addressed in clinic (i.e., fertility, genetic testing) were less frequently triggered. The post-pilot survey was answered by 15 participants: 8/15 reported the information shared through YES was helpful, 6/14 felt the portal helped monitor side effects and 8/14 felt the portal helped manage side-effects. Nineteen women completed post-pilot interviews: most women with EBC and MBC said the portal increased symptom awareness and complemented information communicated by providers; the BC-S group more frequently commented that features of the YES portal focusing on symptom monitoring/management would have been more useful when they were earlier in their care (newly diagnosed or undergoing more active treatment). Conclusions: YES, a novel eHealth intervention designed to support young women with breast cancer, is feasible and acceptable to young women across the breast cancer care continuum. The nearly universal triggering of information and support for sexual and mental health suggests sub-optimal management of these issues in the clinical setting and the potential role for self-management through an eHealth platform for this population. Future efforts will aim to evaluate whether provision of information through the YES portal reduces symptom burden and unaddressed needs and concerns in young women with breast cancer.

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**Publication Number:** PD9-08

# Modeling clonal structure over narrow time frames via circulating tumor DNA in metastatic breast cancer

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**Introduction:** Circulating tumor DNA (ctDNA) offers the ability to repeatedly interrogate tumor genomic information, providing an opportunity for real-time monitoring of tumor genomic dynamics. In this study, we deeply analyzed multiple ctDNA samples collected over narrow time frames (days-to-weeks) from seven patients with metastatic triple-negative breast cancer (mTNBC), a cancer type known to have high ctDNA content. **Methods:** Patients with mTNBC were enrolled in a clinical trial of multi-kinase inhibitor cabozantinib, providing uniform and targeted treatment, and samples were collected day 1, day 8, then every 21 to 42 days on study. ctDNA was extracted from each plasma sample and underwent ultra-low pass whole genome sequencing (ULP-WGS; average depth 0.1x; n=42 samples), deep targeted panel sequencing (TPS) of 402 cancer-related genes with unique molecular identifier indexing (depth 10,000x; n=42 samples), and samples with tumor fraction (TFx) >10% underwent whole exome sequencing (WES; depth 200x; n=31 samples), with whole blood germline sequencing of both TPS and WES for subsequent analyses. Somatic copy number alterations (SCNAs) were identified from ULP-WGS and WES. PyClone with TPS was employed for clonal dynamic analyses. Predicted neoantigens were determined from WES using HLAthena. **Results:** A total of 42 total plasma samples from 7 patients (range 4-8 samples per patient) were collected at narrow time intervals, median 21 days (range 6 to 42 days) between samples. The median TFx across all samples was 18.1% (range 2.5% to 44.3%). TFx estimates were concordant when comparing orthogonal sequencing approaches (ULP-WGS, WES) and tumor fraction estimation algorithms (ichorCNA, FACETS). Despite all seven patients having ‘stable disease’ as best objective response, TFx dynamics were widely variable with TFx declining to lower limit of detection in three of seven patients. Of all samples, 31/42 (73.8%) had tumor fraction >10% and underwent WES; each patient had at least 3 samples that underwent both WES and TPS. There was strong agreement between TPS and WES: across all 31 shared samples, mutation recall in TPS versus WES (gold standard) was 95.5%. Variant allele frequency across all mutations detected in both TPS and WES was highly concordant (Pearson’s r=0.949). Clonal mutations were consistently detected across multiple samples within patients. When comparing genome-wide copy number from last to first available sample within each patient, copy number log ratios were largely stable within patients (union Pearson’s r=0.924) and there were not recurrent shifts in SCNAs across patients. Through statistical modeling of TPS data, we tracked distinct clonal populations for each patient over their sampling windows. Modeled clonal architecture in most patients revealed stable, polyclonal profiles, with important breast cancer driver alterations (e.g. TP53 and PIK3CA) recurrently presenting at high prevalence. Infrequently, we also detected emergence and expansion of clones over narrow time frames (weeks) containing acquired alterations poorly annotated in the breast cancer literature. We successfully predicted neoantigens from ctDNA WES at multiple time points in each patient, with evidence that patients acquired new mutations predicted to be ‘strong binder’ neoantigens over time on therapy. **Conclusions:** Analysis of serial ctDNA samples collected at narrow time intervals (days-to-weeks) provides unique insight into the dynamics of ctDNA. We demonstrate strong concordance across ctDNA sequencing appraoches. Evolving genomic features of tumor populations can be identified via ctDNA while on treatment, potentially providing real time insight for clinical decision-making.

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# Population pharmacokinetic and exposure-response modeling of the oral selective estrogen receptor degrader, rintodestrant (G1T48), in patients with ER+/HER2- advanced breast cancer

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**Background:** Rintodestrant is an orally bioavailable, potent and selective estrogen receptor degrader (SERD) that competitively binds to the estrogen receptor (ER) and blocks ER signaling in tumors resistant to other endocrine therapies. Clinical trials have been conducted to evaluate the safety and efficacy of rintodestrant in healthy volunteers and patients with ER+/HER2- locally advanced or metastatic breast cancer (ABC). Population pharmacokinetic (PK) and exposure-response (Ex/Re) analyses were performed to further characterize the PK profile of rintodestrant and identify potential Ex/Re relationships. **Methods:** The present analyses include data from two studies: (1) G1T48-01, a Phase 1 first-in-human study of rintodestrant monotherapy (200-1000 mg once daily [QD]) in women with ER+/HER2- ABC after progression on endocrine therapy (NCT03455270), and (2) G1T48-10, a study in healthy volunteers investigating potential drug-drug interactions between rintodestrant (200 mg QD) and palbociclib (125 mg QD). A PK model was developed using nonlinear mixed effects methodology to estimate PK parameters for individual patients. A tumor dynamic model was built to characterize the relationship between rintodestrant concentrations and the longitudinal tumor sizes according to RECIST v1.1. Ex/Re for key pharmacodynamic markers, including ER target engagement ($^{18}$F-fluoroestradiol positron emission tomography [FES-PET]), dynamics of cell-free DNA mutational burden, ER degradation and proliferation (Ki67) in tumors, and enumeration of circulating tumor cells are being evaluated. Relationships between model-predicted exposures and study endpoints (objective response rate, clinical benefit rate) are also being evaluated. **Results:** Rintodestrant PK was best described using a linear two-compartment model with a mixed absorption model. The predicted population mean trough concentration of rintodestrant at the recommended Phase 2 dose (800 mg QD) exceeded the $IC_{90}$ value for ER degradation established *in vitro*. A positive Ex/Re relationship was identified between total exposure and target ER engagement as measured by FES-PET. A clear Ex/Re relationship was not identified between any PK parameters and ER degradation or proliferation, potentially due to confounding effects from covariates in the model (eg, prior SERD treatment, *ESR1* mutations, etc). Additional exploration of these covariates is ongoing. The final PK, Ex/Re and PK/tumor dynamics model results will be presented. **Conclusions:** A population PK model was developed and Ex/Re relationship analyses were performed to support the development of rintodestrant for the treatment of patients with ER+ breast cancer. Initial results identified an Ex/Re relationship with target ER engagement via FES-PET analysis.

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# Tucatinib potentiates the activity of the antibody-drug conjugate T-DM1 in preclinical models of HER2-positive breast cancer

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**Background:** Tucatinib is an orally administered, reversible, highly specific HER2 tyrosine kinase inhibitor recently approved by the FDA in combination with trastuzumab and capecitabine for adult patients with advanced unresectable or metastatic HER2-positive breast cancer (mBC), including patients with brain metastases, that have failed at least one anti-HER2 regimen in the metastatic setting. In a phase IB clinical trial, tucatinib in combination with the HER2-targeted antibody-drug conjugate (ADC) ado-trastuzumab emtansine (T-DM1) was well tolerated and demonstrated activity in heavily pre-pretreated patients with HER2-positive mBC (NCT01983501; Borges VF et al., 2018). We previously presented preclinical data that tucatinib increases the activity of trastuzumab-derived ADCs in HER2-positive breast cancer models. Here, we provide mechanistic insight that tucatinib potentiates the activity of T-DM1 by modulating HER2 protein dynamics and facilitating increased cytotoxic maytansinoid drug delivery. **Methods:** To assess changes to HER2 protein levels upon treatment with tucatinib, HER2-amplified breast cancer cell lines were analyzed by Western blot and quantitative FACS (qFACS). To probe the dynamics of HER2 at the cell surface upon binding to antibody therapeutics, SK-BR-3 cells were incubated with fluorescently labeled trastuzumab to mark HER2 at the cell surface. Cells were imaged over 72 hours to observe the internalization of surface-bound antibody. Concurrent experiments were conducted with trastuzumab labeled with QF01, a quenched fluor which fluoresces only upon lysosomal processing and can serve as a proxy for antibody catabolism. To directly measure the rates of ADC catabolism, lysates were generated from BT-474 cells treated with T-DM1 in the presence or absence of tucatinib over a 72 hour time course, and were analyzed by mass spectrometry for the T-DM1 adduct, Lys-MCC-DM1. **Results:** In HER2-amplified breast cancer cell lines, treatment with tucatinib increased overall and cell membrane-localized HER2 levels. As demonstrated by internalization assays, tucatinib had an initial effect that increased the dwell time of HER2 at the cell surface of SK-BR-3 cells. At later timepoints, HER2 bound to trastuzumab was internalized and directed towards lysosomes. These data were supported by parallel intracellular Lys-MCC-DM1 measurements, which demonstrated increased concentration of the adduct when TDM-1 was administered in combination with tucatinib. These data provide a mechanistic rationale as to why the co-administration of tucatinib with T-DM1 in vitro was synergistic by isobologram analysis, and why the combination of tucatinib with T-DM1 was more effective in vivo than either single agent alone in BT-474 xenografts and in PDX models tested, producing a higher proportion of partial or complete tumor regressions. **Conclusions:** The described preclinical in vitro and in vivo data of simultaneous dual HER2 inhibition with tucatinib and T-DM1, along with the results of the phase IB/2 clinical trial demonstrating preliminary safety and efficacy of the combination, warrant further clinical development of tucatinib in combination with T-DM1. These results also support the evaluation of tucatinib in combination with other HER2-targeted ADCs in patients with HER2-positive mBC.

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# Outcomes of germline BRCA carriers versus non-carriers in the french national metastatic breast cancer ESME cohort 2008-2016

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BACKGROUND: Approximately 5% of breast cancer (BC) patients (pts) carry a deleterious germline BRCA mutation (gBRCAm). Retrospective studies suggest that overall survival (OS) is equivalent between gBRCAm carriers and non-carriers with metastatic BC (MBC). We aimed to use the large ESME multicentre national MBC database to compare outcomes of gBRCAm carriers, gBRCA wild-type (WT) and not tested (NT) pts. METHODS: We used the large ESME MBC database (NCT03275311), a unique national cohort of all consecutive pts who initiated a first-line treatment for MBC between 2008 and 2016 in one of the 18 French Comprehensive Cancer Centers. All pts with data available regarding gBRCA testing were selected for the present analysis. 26 pts with non-BRCA germline mutations were classified in the WT group. The primary endpoint was OS from date of treatment initiation in the 3 groups of patients: gBRCAm, gBRCA WT and gBRCA NT.Secondary endpoints were progression-free survival under first line treatment (PFS1), clinical and biological characteristics of the 3 groups and prognostic factors for OS. Multivariable analyses included the main known prognostic factors (age at MBC, MBC subtype, disease-free interval, presence of visceral disease, number of metastatic sites). They were conducted using Cox proportional analyses. RESULTS: 20624 pts were included in this analysis (414 gBRCAm, 1710 WT, 18500 gBRCA NT). Pts and disease characteristics are summarized in table 1. As expected, patients with gBRCAm were younger and had a higher rate of TNBC and G3 tumors.

| | **gBRCAm.<br>N = 414** | **gBRCA WT.<br>N = 1710** | **gBRCA NT<br>N = 18500** | **Pvalue (chi-2)** |
|---|---|---|---|---|
| **Age (years) median [range]** | 45 [23-82] | 48 [20- 88] | 61 [22-103] | **p<0.0001** |
| **Grade 3 N (%)<br>*Missing data*** | 202 (57.7) *64* | 598 (41.1) *254* | 5337 (34.5)<br>*3036* | **p<0.0001** |
| **Triple negative breast cancer N (%)** | 158 (38.2) | 370 (21.6) | 2331 (12.6) | **p<0.0001** |
| **De novo MBC N (%)** | 74 (17.9) | 359 (21) | 5914 (32) | **p<0.0001** |
| **Disease-free interval (months) median [range]** | 39.0 [-1.5- 425.7] | 36.3 [-2.1- 549.6] | 31.8 [-2.9- 657.8] | **p<0.0001** |
| **Metastatic sites ≥3 N (%)** | 113 (27.3) | 349 (20.4) | 3943 (21.3) | **p=0.008** |
| **Visceral metastases N (%)** | 279 (67.4) | 964 (56.4) | 10659(57.6) | **p=0.0002** |
| **Central Nervous System Metastases N (%)** | 66 (15.9) | 132 (7.7) | 1145 (6.2) | **p<0.0001** |

**Table 1: characteristics of patients and disease**

Median follow-up was 50.5 months (95%CI 49.7-51.5). Non-adjusted median OS was 30.6 months [21.9-34.3] in the gBRCAm group, 35.8 [32.2-37.8] in the WT and 39.3 [38.3-40.3] in NT groups. Median PFS1 was 7.9 months [6.6-9.3] in the gBRCAm group, 7.8 [7.3-8.5] in the WT and 9.7 months [ 9.5-10.0] in the NT groups. In multivariable analyses, OS and PFS were not significantly different between MBC patients with gBRCA and others (respective HRs 1.01 [0.88;1.17], p=0.87 and 0.94 [0.84;1.06], p=0.31). CONCLUSION: In this large scale real-life ESME MBC database analysis, outcomes of gBRCAm carriers with MBC do not differ from non carriers or not tested subgroups, when adjusted for other prognostic factors.

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# An ENT2-dependent, cell-penetrating, and DNA-damaging lupus autoantibody crosses the blood-brain barrier to target breast cancer brain metastases

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**Introduction:** Antibody-based immunotherapy has potential to change paradigms in the management of breast cancer brain metastases, if the blood-brain barrier (BBB) can be overcome. The autoimmune disease systemic lupus erythematosus offers an unexpected new approach to this problem. 3E10 is a lupus anti-DNA autoantibody that localizes to DNA at tumors, penetrates cells via the ENT2 nucleoside transporter, inhibits DNA repair, and is synthetically lethal to BRCA1/2 or PTEN-deficient cancer cells with impaired homologous recombination (HR). Breast cancer brain metastases exhibit increased HR defects and PTEN loss compared to primary breast tumors, and ENT2 expressed in brain endothelial cells (BECs) regulates nucleoside flux at the BBB. Further, 3E10 has previously delivered cargo protein to ischemic brain. We hypothesized that ENT2 may facilitate transport of 3E10 across the BBB, and that 3E10 could be used to treat breast cancer brain metastases. Deoxymab-1 (also known as PAT-DX1 or DX1) is a re-engineered and optimized fragment of 3E10 in pre-clinical development for use against HR-deficient tumors. In the present study we examined the ability of DX1 to cross the BBB and suppress breast cancer brain metastases.

**BBB study results:** ENT2-dependent transport of DX1 across the BBB was evaluated in vitro and in vivo. DX1 penetrated hCMEC/D3 BECs and crossed from apical to basolateral chambers in an hCMEC/D3 transwell model of the BBB. Integrity of the model was confirmed by measuring transendothelial electrical resistance and demonstrating the barrier prevented movement of control protein into the basolateral chamber. Expression of ENT2 in hCMEC/D3 cells was confirmed by immunostaining, and the ENT2 inhibitor dipyridamole (DP) inhibited both penetration by DX1 into the cells and its transport across the BBB transwell model. Immunodeficient mice with orthotopic GBM tumors were treated with IV and IP control buffer (n=2), IV DX1 (20 mg/kg) and IP control buffer (n=4), or IV DX1 (20 mg/kg) and IP DP (ENT2 inhibitor, 70 mg/kg) (n=4). DX1 was labeled with Alexa Fluor 750 (AF750) to allow detection by IVIS. Twenty-four hours after treatment, mice treated with DX1 in the absence of DP exhibited strong AF750 signal in the brain correlating to tumor. Co-treatment with DP reduced uptake of DX1 into the brain tumors by ~78% ($P<0.001$). These findings are consistent with DX1 crossing the BBB and localizing into brain tumors in an ENT2-dependent manner.

**Efficacy study results:** The 231-BR brain-seeking subclone of the MDA-MB-231 triple negative breast cancer cell line exhibits PTEN loss relative to parental cells. DX1 penetrated and killed 231-BR cells in vitro. For in vivo testing, brain metastases were generated in immunodeficient mice by intracardiac injection of 231-BR cells engineered for expression of luciferase. Brain metastases were confirmed by IVIS one week later, and then mice were treated with IV control buffer (PBS, n=7) or DX1 (20 mg/kg, n=7). In separate studies DX1 was delivered as a single cycle or as four consecutive cycles, with one cycle defined as control or DX1 3X/week. DX1 significantly suppressed tumor growth, evidenced by weekly IVIS. At week 5 brain radiance efficiencies ($x10^5$) in the single cycle study in control and DX1-treated mice were 264.8±72.0 and 71.9±31.3 ($P<0.04$), and 320±66 and 20.2±8.5 ($P\leq0.01$) in the four-cycle study. One cycle of DX1 yielded a non-significant increase in median survival from 30 to 35 days ($P=0.42$). Four cycles of DX1 had greater impact, with median survival increased by 14 days (from 31 to 45) ($P<0.002$). DX1 was not associated with nonspecific toxicity.

**Conclusion:** Our findings support an ENT2-mediated mechanism of BBB penetration by DX1 and establish proof of concept for use of a DNA-targeting autoantibody against breast cancer brain metastases.

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# Operational standardization and quality assurance yield high acceptance rate for breast MRI in the I-SPY 2 TRIAL

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**Background:** The I-SPY 2 TRIAL is a multi-site response adaptive clinical trial evaluating novel drug combinations for neoadjuvant treatment of breast cancer. Patients receive four or more MRI studies during treatment, and serial measurement of functional tumor volume (FTV) is used to assess response. Under FDA IDE approval, FTV plays an integral role in adjusting patient randomization and evaluating treatment efficacy. FTV is a quantitative measure that requires stringent standards for image quality and protocol adherence. The I-SPY 2 TRIAL consistently reports a high level of data quality and data acceptance for FTV measurements. We present an overview of MRI operational performance and share lessons learned about maintaining high quality MRI data in a multi-site clinical trial.
**Methods:** Over the 10-year course of the I-SPY 2 TRIAL, workflow has been improved to optimize communication between the Imaging Core Lab (ICL) and sites and to collect details about the MRI that are needed for accurate FTV measurement. A standardized imaging acquisition protocol is distributed to all sites, and new sites submit two test cases for review at site initiation. A scan verification form is required for each MRI study completed at sites to document critical information. Sites submit studies using TRIAD image transfer and de-identification software (American College of Radiology), and data is archived and processed at the ICL. All MRI studies are reviewed by the ICL for protocol adherence as soon as they are submitted, and feedback is provided to sites. Image quality factors including motion, fat suppression, and signal-to-noise ratio are qualitatively assessed. The ICL communicates with sites through a centralized email account, regular Coordinator Calls, and Imaging Working Group meetings to discuss emerging issues and offer ongoing training. The ICL contributes to revisions of study protocols and standard operating procedures.
**Results:** As of June 2020, 3020 patients had been registered in I-SPY 2, 1741 patients randomized to treatment with one of 18 experimental drugs or standard therapy (controls), and a total of 7527 MRI studies were performed. FTV could be calculated for 97% (7317/7527) of MRI studies. Of the 7317 studies where FTV could be calculated, relatively minor issues with image quality or imaging protocol adherence were documented for 28% (2030/7317). These issues included motion artifacts (32%, 659/2030), off-protocol scan duration (21%, 433/2030), off-protocol contrast injection rate (14%, 281/2030), and off-protocol imaging field of view (9%, 191/2030).
**Conclusion:** Breast MRI studies using a variety of scan protocols are well-suited for diagnostic evaluation, including BIRADS categorization, measurement of longest diameter, and assessment of lesion washout. The quantitative measures used in the I-SPY 2 trial require adherence to a specific imaging protocol that is kept consistent for all MRI studies for a single patient. Operational standardization, clear communication with sites, and streamlined workflow yield high quality MRI data across multiple sites and scanners. As a result, FTV is a robust biomarker of response to treatment, and is being used to predict patient response and guide treatment planning. We are actively investigating strategies that will improve FTV accuracy for predicting response and informing guidelines for treatment de-escalation. This will allow the ICL to further standardize and improve image quality and will provide the foundation for testing a variety of imaging biomarkers in the I-SPY 2 TRIAL.

**Publication Number:** PS2-08

# Identification of incidental putative germline variants in circulating tumor DNA

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**Background:** Circulating tumor DNA (ctDNA) has emerged as a potential tool for detecting disease recurrence, monitoring response to therapy, and identifying resistance mutations in the peripheral blood. With increased frequency of testing, there is an unmet need to recognize putative germline variants in ctDNA, and the probability that these variants are associated with inherited conditions. Here, we evaluated a large cohort of breast cancer patients who underwent ctDNA evaluation to determine the type and frequency of ctDNA mutations identified with confirmed germline testing.
**Methods:** We reviewed ctDNA testing from a single institution (Northwestern University). All breast cancer patients who had next-generation sequencing (NGS) performed by Guardant Health (Redwood City, CA) from 2015-2020 were included in this retrospective study. An allele frequency cutoff of 30% was pre-established as a threshold to review patient charts to determine whether genetic counseling and germline testing were performed, along with the timeframe of this testing (e.g. before or after ctDNA evaluation). Clinical information including demographics, pathology, tissue NGS testing, and germline testing were collected. Descriptive analyses and statistical associations were performed using STATA.
**Results:** The initial cohort consisted of 520 patients with breast cancer who underwent ctDNA testing. From this, we identified 84 patients (16.2%) who had at least one variant with allele frequency ≥30%. The most common variants identified were the following: *TP53* (34%), *PIK3CA* (27%), *BRCA1* (9%), *BRCA2* (8%), and *AKT1* (4%). Guardant360 classified 99% of these variants as pathogenic and 1% as a variant of unknown significance. Germline positivity using a separate CLIA-approved test for this indication was confirmed at the following frequencies: *BRCA1* (2 of 8 positive, 25%), *BRCA2* (2 of 5 positive, 40%), *PIK3CA* (0 of 5 positive), and *TP53* (0 of 26 positive). In total, 14% of patients with ctDNA allele frequency ≥30% had a confirmed germline mutation. Lower age at breast cancer diagnosis was significantly associated with the probability of germline testing prior to ctDNA evaluation (P=0.0001). For patients who had a variant with allele frequency ≥30%, 24.3% never received genetic counseling or germline testing.
**Conclusion:** High allele frequency ctDNA variants (≥30%) were present in 16% of patients who underwent ctDNA evaluation with 14% of these variants confirmed as true germline variants. Consenting patients for ctDNA testing should include the possibility of identifying putative germline variants, and criteria should be established to refer patients for subsequent genetic counseling and germline testing, given the potential implications for patients and their family members.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS13-08

Predictors and long-term outcome of pathologic complete response in patients receiving neoadjuvant chemotherapy for breast cancer - an NCDB analysis

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**Background:**
Among women with high-risk early stage breast cancer, neoadjuvant chemotherapy (NCT) is increasingly utilized. The Collaborative Trials in Neoadjuvant Breast Cancer working group studied 13,000 patients from 12 large trials involving NCT and concluded that pathologic complete response (pCR) resulted in significantly better outcomes with respect to both disease recurrence and mortality. This National Cancer Database (NCDB) study aims to gather patient and tumor characteristics to further identify prognosticators of pCR, and determine which subgroups achieving pCR have the greatest survival benefit.
**Methods:**
Retrospective analysis using NCDB data from 2004-2015 identified 46,836 women ≥18 years with stage I to III breast cancer who received NCT. Achievement of pCR was defined as ypT0 ypN0 or ypT0/is ypN0. Tumor and patient characteristics were evaluated, and multivariate logistic regression was used to calculate odds ratio (OR) of pCR. Kaplan-Meier curves were constructed for calculation of overall survival (OS) at 5 years. Hazard ratios (HR) were estimated from Cox models. Propensity score weighting was used to adjust for confounding effects of various factors on survival via Cox regression.
**Results:**
Patients were more likely to achieve pCR with ductal vs. lobular histology (OR 1.62 [95% CI 1.414-1.872]), grade 3 vs. 1 (OR 1.606 [95% CI 1.394-1.849]), stage 3 vs. 1 (OR 1.76 [95% CI 1.623-1.908]), ER+PR- vs. ER+PR+ (OR 2.004 [95% CI 1.855-2.165]), ER-PR- vs. ER+PR+ (OR 2.572 [95% CI 2.425-2.729]), age <60 (OR 1.43 [95% CI 1.32-1.55]), Charlson-Deyo combined comorbidity (CDCC) score of 0 vs. 2 (OR 1.27 [95% CI 1.04-1.54]), and private insurance vs. uninsured (OR 1.24 [95% CI 1.09-1.41]). HR for death adjusted by propensity score in patients attaining pCR vs. non-pCR was 0.346 (95% CI 0.325-0.368) for the overall cohort, 0.591 (95% CI 0.513-0.681) for ER+PR+ patients, 0.373 (95% CI 0.315-0.442) in the ER+PR- group, and 0.307 (95% CI 0.284-0.332) for ER-PR- patients. Achieving pCR conferred better OS in all subgroups with higher magnitude in hormone negative patients (table 1).
**Conclusions:**
This study not only highlights factors associated with achieving pCR after neoadjuvant chemotherapy for breast cancer, but also demonstrates that attaining pCR reduces the risk of death by 65.4% in all patients regardless of receptor subtype. Furthermore, the survival curve increasingly separates with time. Our study reveals an intriguing observation that ER+PR+ patients who attain pCR have 40.9% decreased mortality compared to non-pCR. Limitations of this analysis include the lack of HER2 status and that conclusions are made from non-population based observational data. Despite utilization of propensity score weighting, there may have been confounders that were not adjusted for by the multivariate model. Future analysis is needed to identify HER2 status, as HER2-positive patients may have contributed to the OS benefit in the subgroups. Nonetheless, these data are among the first to suggest that hormone-positive patients derive long-term survival benefit from achievement of pCR, albeit to a lesser extent than hormone-negative subtypes.
Table 1. 5-year survival estimates from Kaplan-Meier analysis

| | pCR | Non-pCR | Survival difference | p (95% CI) |
|---|---|---|---|---|
| All patients | 0.8850 | 0.7384 | 0.14657 | <0.0001 (0.1364-0.1567) |
| ER+PR+ | 0.9030 | 0.8117 | 0.09121 | <0.0001 (0.0744-0.1079) |
| ER+PR- | 0.8962 | 0.7074 | 0.18879 | <0.0001 (0.1609-0.2166) |
| ER-PR+ | 0.8807 | 0.6388 | 0.24198 | <0.0001 (0.1719-0.3120) |
| ER-PR- | 0.8757 | 0.6466 | 0.22913 | <0.0001 (0.2131-0.2451) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS5-08

Comparison of PD-L1 protein expression between primary tumors and metastatic lesions in triple negative breast cancers

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**Background:** Several recent studies that compared small cohorts of metastatic and primary lesions, suggested substantial heterogeneity in tumor infiltrating lymphocyte count, immune gene expression and PD-L1 protein expression across different metastatic sites and between primary breast cancers and metastasis. Understanding the frequency of PD-L1 positivity rates across different tissue sites can indicate differences in the immune microenvironment and may also guide biopsy site selection. We compared PD-L1 positivity on immune cells and tumor cells in primary and metastatic triple negative breast cancer tumors (TNBC).**Methods:** A retrospective data analysis of the Foundation Medicine PD-L1 IHC database was conducted on 340 cases of TNBC. PD-L1 positivity was determined by IHC using SP142CDx. Results are reported as percent of PD-L1 stained immune cells (IC) in the tumor area. A tumor was considered PD-L1 positive if ≥ 1% IC stained positive with PD-L1. As an exploratory analysis, PD-L1 positivity of tumor cells (TC) was also assessed. PD-L1 percent positive staining results are reported as means with 95% CI. The proportion of PD-L1 positive and negative IC and TC in primary tumors vs metastatic sites was compared using Chi-Square test. Prism 8 was used for all data analysis.**Results:** All patients were female, with median age 56 years (range 26-89); 179 samples were from primary tumors and 161 from metastatic lesions, representing 15 different tissue sites. Overall, PD-L1 expression on immune cells was statistically significantly more frequent in primary tumors compared to metastatic sites (63.7% [n=114] vs 42.9% [n=69]), p<0.0001). This was driven by the lower PD-L1 positivity rates in skin (23.8%, 95% CI: 8.22% - 47.2%), liver (17.4%, 95%CI: 5.00% - 38.8%) and bone (16.7%, 95%CI: 2.10% - 48.4%) metastases. Lung (68.8%, 95% CI: 41.3 - 90.0), soft tissues (65.2%, 95% CI: 42.7 - 83.6) and lymph nodes 51.1%, 95% CI (35.8 - 66.3) had PD-L1 % positivity rates similar to primary tumors. PD-L1 expression was rare on tumor cells in both the breast and metastatic sites (8.3% vs 4.3%, p=0.13). **Conclusion:** We observed substantial heterogeneity in PD-L1 positivity rates across metastatic sites. Lung, soft tissues and lymph node metastases had PD-L1 % positivity rates that were similar to that of primary tumors whereas skin, liver and bone metastases had significantly lower PD-L1 % positivity rates. These results raise the possibility that response to immune therapy could depend on the location and the PD-L1 positivity of the metastatic site. Limited current experience in breast cancer is not sufficient to correlate tumor response with PD-L1 expression in metastases, but as more patients receive treatment, this could be examined in the future.

1

**Table 1: Sample Characteristics and % PD-L1 positivity on immune cells**

| **Sample type** | **Total N (%)** | **N PD-L1 positive (%, 95% CI)** |
|---|---|---|
| Primary Tumor | 179 (52.6) | 114 (63.7%, 56.2% - 70.7%) |
| Metastatic Lesion | 161 (47.4) | 69 (42.9%, 35.1% - 50.9%) |
| **Sites of Metastases** | **N (% of metastatic samples)** | **N PD-L1 positive (%, 95% CI)** |
| Lung | 16 (10.0) | 11 (68.8%, 41.3% - 90.0%) |
| Soft Tissues | 23 (14.3) | 15 (65.2%, 42.7% - 83.6%) |
| Lymph Nodes | 45 (28.0) | 23 (51.1%, 35.8% - 66.3%) |
| Skin | 21 (13.0) | 5 (23.8%, 8.22% - 47.2%) |
| Liver | 23 (14.3) | 4 (17.4%, 5.00% - 38.8%) |
| Bone | 12 (7.5) | 2 (16.7%, 2.10% - 48.4%) |
| Brain | 9 (5.6) | 5 |
| Mediastinum | 4 (2.5) | 1 |
| Pleura | 2 (1.2) | 0 |
| Muscle | 1 (<1) | 0 |
| Omentum | 1 (<1) | 1 |
| Ovary | 1 (<1) | 0 |
| Pelvis | 1 (<1) | 0 |
| Retroperitoneum | 1 (<1) | 0 |
| Adrenal Gland | 1 (<1) | 1 |

**Table 2: Comparison of PD-L1 positivity in primary versus metastatic sites**

| **Tissue** | **PDL1+ Immune Cell** | **PDL1- Immune Cell** | **P value** | **PDL1+ Tumor Cell** | **PDL- Tumor Cell** | **P value** |
|---|---|---|---|---|---|---|
| Primary | 114 | 65 | 0.0001 | 15 | 164 | 0.1313 |
| Metastasis | 69 | 92 | | 7 | 154 | |

2

**2020 San Antonio Breast Cancer Symposium®**

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Low dose endoxifen represses mouse mammary tumorigenesis: A preclinical study of monotherapy and combination with ulipristal acetate

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**Background:** Endoxifen (ENX), a major active metabolite of the selective estrogen receptor (ER) modulator tamoxifen (TAM), has been shown to inhibit the growth of ER+ cancer. However, it has not been evaluated for prevention of mammary cancer. We report here the cancer prevention efficacy of ENX as monotherapy and in combination with ulipristal acetate (UPA), a selective progesterone receptor (PR) modulator. We compare these to TAM using the SV40 C3 T-antigen (C3-TAg) mouse, a well-documented mammary cancer prevention model. **Methods:** C3-TAg female virgin mice aged 7-8 weeks were randomized to no-treatment control or to drug treatment groups (TAM, ENX, UPA and ENX+UPA). Drug pellets were subcutaneously implanted on backside of mice. The doses of drug pellet were 12.5mg/30d for TAM, 9mg/90d for ENX, 10mg/30d for UPA, and combination of ENX (9mg/90d) + UPA (10mg/30d). The dose of ENX was equivalent to the exposure resulting from 20 mg/day, the lowest dose used in a recent Phase I human trial. Pellets were replaced every 30 days or 90 days. Mammary tumor formation was monitored twice weekly by palpation. Tumor latency, multiplicity, and tumor volume were recorded; animals are euthanized at 23 weeks of age, or earlier if tumors reach > 1 $cm^2$. Tumors and mammary glands were formalin fixed and paraffin embedded for histology evaluation by a rodent pathologist. The primary endpoint was a reduction in tumor incidence in drug treated versus control groups. Secondary endpoints included prolongation of latency, reduction in tumor multiplicity, and tumor burden. Statistical significance between groups was calculated with Wilcoxon log-rank test for % tumor-free survival and Mann Whitney test for tumor multiplicity and burden.**Results:** All mice in the control group developed tumors by 18 weeks of age. Tumor-free survival % of ENX, UPA, and ENX+UPA treated groups were significantly higher than control animals, with the greatest increase in the ENX group ($p=0.02$). TAM had no effect on tumor-free survival ($p=0.32$). Median tumor latencies were similar in three treated groups: ENX (112 days), UPA (114 days), and ENX+UPA (111 days) groups, and were significantly delayed compared to the control or TAM group (100 days in both) ($p<0.05$). Median tumor multiplicity (invasive adenocarcinoma) per animal was significantly lower in ENX group compared to control group (3 vs. 7, $p=0.02$). UPA and TAM did not significantly reduce tumor multiplicity (4 for TAM and 6 for UPA). We observed non-significant 32% and 23% reduction in median tumor weight of ENX+UPA group and ENX group, respectively compared to control group. Histology evaluation for ENX+UPA group and pathologic size of invasive carcinoma is ongoing, along with the expression of Ki67, ERα and PR of mammary tumors and mammary gland by immunohistochemistry.**Conclusions**: TAM showed no significant effect on delaying tumorigenesis, consistent with a previous study. However, low dose of ENX (equivalent to 24 mg/day in human) effectively repressed tumor development and growth than TAM or UPA treatment. Our data suggest that ENX is promising for prevention of ER+ mammary tumorigenesis and warrant a dose optimization study for improving efficacy.

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**Publication Number:** GS2-09

# Diabetes risk reduction diet and survival following breast cancer

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**Importance:** Type 2 diabetes (T2D) is associated with poor breast cancer prognosis. Adherence to a dietary pattern associated with lower T2D risk may improve breast cancer outcomes.
**Objective**: To evaluate the association between adherence to a diabetes risk reduction diet (DRRD) after diagnosis and survival outcomes following breast cancer.
**Method:** We followed 8,320 women diagnosed with stage I-III breast cancer from two large prospective cohort studies, the Nurses' Health Study (NHS; 1980-2014) and the NHSII (1991-2015). Information on diet and other covariates was repeatedly measured in validated follow-up questionnaires every two to four years. The DRRD adherence score includes 9 dietary components: higher intakes of cereal fiber, coffee, nuts, whole fruits and polyunsaturated:saturated fat ratio; and lower glycemic index of diet, lower intakes of trans fat, sugar-sweetened beverages/fruit juices, and red meat. Cumulative average DRRD score was calculated using repeated measures of diet after breast cancer diagnosis. Deaths were reported by family members or via the search of National Death Index, and cause of death was assigned by reviewing death certificates/medical records. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between DRRD score and breast cancer-specific and all-cause mortality were estimated using Cox proportional hazards models.
**Results:** During a median of 16 years of follow-up after diagnosis, we ascertained 2,146 deaths, of which 948 were due to breast cancer. In the multivariable-adjusted models, women with higher post-diagnostic DRRD scores had a 17% lower risk of breast cancer-specific mortality (top vs. bottom quintile HR =0.83; 95%CI=0.67-1.02; p-trend=0.03) and 33% lower risk of all-cause mortality (HR =0.67; 95%CI=0.58-0.78; p-trend <0.0001). Associations were slightly attenuated after further adjusting for neighborhood socioeconomic status index (breast cancer mortality: HR =0.86; 95%CI=0.70-1.07; p-trend=0.06; overall mortality: HR =0.69; 95%CI=0.60-0.80; p-trend <0.0001). Compared with women who consistently had lower DRRD score (≤median) before and after diagnosis, those who improved their score from low to high had a significantly lower risk of breast cancer mortality (HR =0.81; 95%CI=0.65-1.00).
**Conclusion:** We found that greater adherence to the DRRD after breast cancer diagnosis was associated with better survival, suggesting dietary modification after diagnosis consistent with T2D prevention may be important to breast cancer survivors.

**Table 1.** Multivariable HRs and 95% CIs for the association between post-diagnostic diabetes risk reduction diet score and mortality among breast cancer survivors using pooled data from NHS abd NHSII (N=8,320)

| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | p-trend |
|---|---|---|---|---|---|---|
| Median (IQR) | 20 (18-21) | 24 (23-25) | 27 (26-28) | 30 (29-31) | 34 (33-37) | |
| **Breast cancer-specific mortality** | | | | | | |
| No. of events (n=948), 589,953 py | 207 | 205 | 184 | 176 | 176 | |
| Model 1 | 1 (referent) | 0.97 (0.80-1.18) | 0.80 (0.65-0.97) | 0.79 (0.64-0.96) | 0.75 (0.61-0.92) | 0.0008 |
| Model 2 | 1 (referent) | 0.88 (0.72-1.07) | 0.76 (0.62-0.93) | 0.77 (0.63-0.95) | 0.83 (0.67-1.02) | 0.03 |
| Model 3 | 1 (referent) | 0.99 (0.81-1.20) | 0.82 (0.67-1.00) | 0.85 (0.69-1.04) | 0.86 (0.70-1.07) | 0.06 |
| **All-cause mortality** | | | | | | |
| No. of events (n=2,146), 589,953 py | 506 | 447 | 476 | 383 | 334 | |
| Model 1 | 1 (referent) | 0.83 (0.73-0.94) | 0.80 (0.71-0.91) | 0.67 (0.59-0.76) | 0.57 (0.50-0.65) | <.0001 |
| Model 2 | 1 (referent) | 0.81 (0.71-0.92) | 0.87 (0.76-0.98) | 0.74 (0.65-0.85) | 0.67 (0.58-0.78) | <.0001 |
| Model 3 | 1 (referent) | 0.89 (0.78-1.01) | 0.91 (0.80-1.04) | 0.78 (0.68-0.90) | 0.69 (0.60-0.80) | <.0001 |

**Table 2.** Multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between changes of diabetes risk reduction diet score before or after diagnosis and mortality among breast cancer survivors using pooled data from NHS abd NHSII (N=8,320)

| Characteristics | HR (95% CI) |
|---|---|
| ***Breast cancer-specific mortality*** | |
| **Cross classified changes** | |
| No. of events (n=948), 589,953 py | |
| Low to Low | 1 (referent) |
| Low to High | 0.81 (0.65-1.00) |
| High to Low | 0.97 (0.79-1.19) |
| High to High | 0.87 (0.74-1.02) |
| ***All-cause mortality*** | |
| **Cross classified changes** | |
| No. of events (n=2,306), 589,953 py | |
| Low to Low | 1 (referent) |
| Low to High | 0.88 (0.76-1.02) |
| High to Low | 0.99 (0.87-1.12) |
| High to High | 0.80 (0.72-0.89) |

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**Publication Number:** PS19-08

Intratumoral heterogeneity of second-harmonic generation scattering from tumor collagen and its effects on metastatic risk prediction

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Second harmonic generation (SHG) is an intrinsic optical signal that can be generated from fibrillar collagen. The directionality of SHG emission is influenced by the diameter and spacing of collagen fibrils, and the disorder in their packing within collagen fibers. One measure of SHG directionality is the ratio of forward- to backward-scattered SHG, or “F/B”. F/B has been used to assess healthy vs diseased tissue in breast, ovarian, and lung cancer, and is an independent prognostic indicator of metastasis free survival time in ER+, lymph node-negative (N0), invasive ductal carcinoma (IDC). Here we assess the heterogeneity in F/B within tumor sections from ER+ N0 IDC, and its effect on the use of F/B for metastatic risk prediction. We find that F/B of tumor collagen varies between the tumor/host interface and the more cellular tumor bulk ($p<0.0001$, Student’s t-test), and that F/B from the tumor/host interface, but not tumor bulk, is prognostic of metastasis free survival in 95 IDC ER+ N0 patients ($p=0.0020$ and 0.10, respectively, log rank test for trend). This result was repeated with two additional image analysis procedures to generate F/B with reduced user input and hence reduced possibility of bias. Using Random Survival Forests to generate a data-driven predictive model, we find that F/B from the tumor/host interface, but not bulk, as well as a 21-gene prognostic score inferred from Affymetrix data, both contribute to predicting metastasis-free survival in this cohort. Any tool to help predict metastasis and assist with treatment decisions is likely to be applied in combination with the now well-established genomic scores. To understand how F/B can support genomic methods for guiding treatment decisions we divided our patient samples into two cohorts based upon the value of their 21-gene score relative to the TAILORx cutoff of 26 (separating low-intermediate and high-risk groups). The F/B value from tumor-host interface identifies a subgroup of patients in the low-intermediate risk group with poor clinical outcome ($p=0.045$, log rank test for trend). Overall, this data reveals that intratumor heterogeneity can impact the ability of F/B to predict patient outcome, and that F/B specifically from the tumor-host interface may provide a tool to better identify patients in need of adjuvant treatment or enrollment in clinical trials.

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**Publication Number:** PS12-08

A window-of-opportunity study with atezolizumab and the oncolytic virus pelareorep in early breast cancer (REO-027, AWARE-1)

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**Background**: A previous phase 2 study in metastatic breast cancer compared treatment with intravenously delivered oncolytic reovirus, pelareorep (pela), in combination with paclitaxel (PTX) versus PTX alone. This study demonstrated a statistically significant improvement in overall survival (OS), without differences in objective response or progression-free survival. We hypothesized that the OS benefit from pela + PTX may be attributed to an adaptive immune response triggered by pela. To test this hypothesis, and examine if pela can mediate the priming of an anti-tumor immune response, we designed a study called AWARE-1 (A window-of-opportunity study of pela in Early Breast Cancer), which is currently enrolling and for which initial translational research results are presented.
**Methods**: AWARE-1 is evaluating the safety and effect of pela ± atezolizumab on the tumor microenvironment (TME) in 38 women with early breast cancer. Patients are treated with pela on days 1, 2, 8, and 9, while atezolizumab is administered on day 3. Tumor biopsies are collected at diagnosis, day 3, and day ~21. Five cohorts will be examined: Cohort 1: Hormone Receptor-positive/HER2-negative (HR+/HER2-neg) (10 patients), pelareorep + letrozole. Cohort 2: HR+/HER2-neg (10 patients), pelareorep + letrozole + atezolizumab. Cohort 3: Triple Negative Breast Cancer (TNBC) (6 patients), pelareorep + atezolizumab. Cohort 4: Hormone Receptor-positive/HER2-positive (HR+/HER2+) (6 patients), pelareorep + trastuzumab + atezolizumab. Cohort 5: Hormone Receptor-negative/HER2-positive (HR-/HER2+) (6 patients), pelareorep + trastuzumab + atezolizumab. The primary endpoint of the study is CelTIL score, a metric for quantifying the changes in tumor cellularity and infiltration of TILs, where an increase in CelTIL is associated with a favorable response to treatment. Tumor tissue was examined for pela replication, and changes to the TME were assessed by imaging mass cytometry (IMC), immunohistochemistry, and T cell receptor sequencing (TCR-seq). Peripheral blood was also examined by TCR-seq.
**Results**: Detailed translational research results will be presented from patients in cohort 1, who received just pelareorep and letrozole. CelTIL score increased in 5/10 patients at day 3 biopsies and 6/10 patients at day 21 biopsies. Preliminary results show high levels of viral replication (>50% of tumor cells) while immunohistochemistry and IMC analysis revealed changes to the TME, with increases in CD8+ T cells and upregulation of PD-L1 at both day 3 and day 21 biopsies. Overall, preliminary data from cohort 1 of AWARE-1 demonstrate pela-mediated priming of an adaptive immune response. (NCT04102618)

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**Publication Number:** SS1-08

Did Medicaid expansion under the Affordable Care Act narrow the gap between American Indians and Whites on breast cancer management and prognosis?

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Prior studies have shown that over a span of 20 years (1990-2009), breast cancer death rates in the U.S. have not significantly declined for American Indians (AIs) in comparison to the White population. Health insurance coverage contributes independently and positively to the health of individuals through the receipt of adequate preventive services and care for diseases such as breast cancer. To this end, the 2010 Medicaid Expansion as part of the Affordable Care Act (ACA) has extended the health insurance coverage eligibility to adults with incomes up to 133 percent of the federal poverty level. In this study, we examined whether Medicaid expansion resulted in the improvement of breast cancer management and prognosis for AIs relative to the White population. Methods: We abstracted information from the National Cancer Data Base (NCDB) for AI and White breast cancer patients diagnosed between the years 2004-2016 who lived in states that expanded Medicaid in January 2014, and those that did not expand Medicaid. Data on age, race, stage at diagnosis, insurance status, definitive treatment initiation within 30 days of diagnosis, and 3-year mortality was analyzed. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multiple logistic regression to determine the impact of race (White vs. AI), Medicaid expansion status, and pre- vs. post-expansion periods on breast cancer management and prognosis. All p-values are two-sided. Analyses were performed using SPSS software V25. Results: There were 1,465,103 newly diagnosed White and AI breast cancers between the years 2004-2016; 99.7% were Whites and 0.3% were AIs. Of these, 46.9% resided in states that expanded Medicaid in January 2014 and 53.1% in states that did not expand Medicaid; 73.8% were diagnosed in the pre-expansion period (January 2004-December 2013) and 26.2% were diagnosed in the post-expansion period (January 2014-December 2016). There was an increase in the proportion of early stage (0, 1) breast cancer diagnosis in the period 2014-2016 as compared to the period 2004-2013 (OR=1.434, 95% CI:1.159- 1.775; p = 0.001), and this increase was significantly greater for AIs than for Whites (6% vs 3%; p=0.027) in both expansion and non-expansion states. An independent chi-square analysis of AIs found that there was a significant increase of the early stage diagnosis in the expansion states during the post-expansion period (p=0.001). The proportion of uninsured declined in the period 2014-2016 as compared to the period prior (OR=0.331, 95% CI: 0.129- 0.850; p=0.022), more so in the expansion states (decrease from 1.4% to 0.8%), vs. non expansion states (decrease from 2.3% to 2.2%) (p=0.019); no difference in decline was found between Whites and AIs. The probability of getting first definitive treatment within 30 days of diagnosis declined more in states without Medicaid expansion (decrease from 54% to 43%) than in states with Medicaid expansion (decrease from 50% to 43%) (p=0.028) for both AIs and Whites; and the decline was more in Whites ( decrease from 55% to 44%) than in AIs (decrease from 49% to 42%) from pre-expansion period to post-expansion period (p=0.018). The 3-year mortality rates did not show any significant relationship to race, expansion status, or the pre- or post-expansion periods. Conclusion: In patients newly diagnosed with breast cancer, the proportion of uninsured declined significantly with Medicaid expansion and the proportion of patients who received first definitive treatment within 30 days of diagnosis decreased significantly less in AIs and in states that expanded Medicaid under the Affordable Care Act. Medicaid expansion increased early breast cancer diagnosis in AIs; this effect was not seen in non-expansion states. Medicaid expansion did not affect 3-year mortality rate.

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# Impact of genetic testing for hereditary breast cancer on screening and risk-reducing surgeries among multi-ethnic breast cancer survivors

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**Introduction** Current guidelines for cancer risk management for hereditary breast cancer focus on individuals with pathogenic/likely pathogenic variants (P/LP) in high penetrance genes. There is little consensus on prophylactic mastectomy for low/moderate penetrance genes or variants of uncertain significance (VUS). Furthermore, many guidelines for enhanced breast cancer screening are targeted to unaffected carriers, but not breast cancer survivors. Given the increasing use of multigene panel testing, more patients are receiving results of P/LP in low/moderate penetrance genes or VUSs. We aimed to investigate how multigene panel results impacted surgical and screening decisions among breast cancer patients. **Methods** We conducted a retrospective analysis of women diagnosed with stage 0-III breast cancer at Columbia University Irving Medical Center in 2013 or later, who received germline genetic testing. Clinical data were extracted from the electronic health record (EHR), tumor registry, and genetic testing portals. Patients were excluded if they had stage IV disease at diagnosis, had bilateral mastectomy before 2013, or had missing genetic test results or surgical reports. For the screening analysis, patients were excluded if they had bilateral mastectomy or did not have breast imaging in the EHR. Surgery type was defined by the most advanced breast surgery received. Enhanced screening was defined as use of breast ultrasound or MRI in the absence of breast symptoms and in the setting of a normal mammogram. Univariable and multivariable analyses were performed to assess the association between clinical factors and receipt of bilateral mastectomy or enhanced screening. **Results** Among 715 evaluable women, about two-thirds were 50 years or younger, with 45% white, 12% black, 27% Hispanic, 11% Asian, and 4% other. Most patients (69.5%) had benign/likely benign (B/LB) genetic test results, while 91 (12.7%) had P/LP and 127 (17.8%) had VUS. VUS rates were higher among racial/ethnic minorities (27% Asian, 25% Hispanic, 19% black) compared to white women (10%). About 31% of women underwent bilateral mastectomy, 25% unilateral mastectomy, and 45% lumpectomy. Bilateral mastectomy rates among patients with P/LP variants were higher compared to those with VUS or B/LB results (66% vs. 27% vs. 26%), particularly P/LP in high-penetrance genes (76%) compared to other genes (45%). On multivariable analysis, compared to patients with B/LB genetic results, P/LP was significantly associated with bilateral mastectomy (odds ratio [OR]=5.72, 95% confidence interval [CI]=3.43-9.53). Younger age at diagnosis and family history of breast cancer were also associated with bilateral mastectomy. Among patients with breast cancer screening data, almost half (43%) received enhanced screening (59% ultrasound, 25% MRI, 16% both). On multivariable analysis, patients with P/LP variants and age of diagnosis under 50 were more likely to receive enhanced screening (OR=4.43, 95% CI=1.59-12.33 and OR=1.92, 95% CI=1.09-3.38, respectively). Hispanic women compared to non-Hispanic whites and those with Medicaid rather than private health insurance were less likely to undergo enhanced screening. **Conclusions** We demonstrated that detection of P/LP variants on multigene panel testing influences surgical and screening decisions among breast cancer patients. Patients with VUS, a group enriched for racial/ethnic minorities, appropriately have similar surgical and screening decisions as those with B/LB results. Our findings suggest adequate genetic counseling and communication of cancer risk to multi-ethnic breast cancer survivors.

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# Correlative studies of the breast cancer index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine benefit: A trans-aTTom study

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**Background:** Several biomarkers such as estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR) and Ki67 have been implicated in the pathogenesis and/or as prognostic biomarkers of breast cancer, and are utilized to determine treatment. Given the heterogeneity of response to endocrine therapy, however, predictive biomarkers are critical to better individualize patient care. Previous results from the Trans-aTTom study demonstrated that the Breast Cancer Index HOXB13/IL17BR [BCI (H/I)] biomarker significantly predicts extended endocrine benefit from 10 vs 5y of tamoxifen. In this correlative study, the predictive activity of BCI (H/I) was compared with ER, PR, AR and Ki67 protein expression in node positive patients treated in the aTTom trial. **Methods:** Patients with available tumor tissue and biomarker analyses were included. ER, PR, AR and Ki67 were centrally assessed by immunohistochemistry (IHC) utilizing tissue microarrays. BCI gene expression analysis by RT-PCR was performed blinded to clinical outcome. Multivariate Cox models adjusting for age, tumor size, tumor grade and HER2 status were used to assess the significance of the interaction between treatment and each biomarker as continuous variables. 17-year risk of recurrence, as a function of each continuous biomarker, was estimated from Cox models in each of the 2 treatment arms. **Results:** Analysis of 789 HR+, N+ patients showed a weak negative correlation between BCI (H/I) and ER, PR, and AR expression whereas Ki67 and the AR/ER ratio showed no correlation (ER, cor=−0.18; PR, cor=−0.25; AR, cor=−0.14; Ki67, cor=0.04; AR/ER ratio, cor=0.02). The interaction between BCI (H/I) and extended tamoxifen treatment was significant (p=0.014). In addition, analysis of risk of recurrence as a function of continuous BCI (H/I) demonstrated that the magnitude in the reduction in recurrence risk with extended tamoxifen correlated with increasing H/I levels. In contrast, interaction P values were nonsignificant (ER, p=0.829; PR, p=0.659; AR, p=0.783; Ki67, p=0.865; AR/ER ratio, p=0.835) and the magnitude of endocrine benefit did not correlate with expression levels of any of other biomarkers.
**Conclusion:** Results from this post-hoc analysis of the Trans-aTTom study demonstrated that whereas BCI(H/I) is a significant predictive biomarker of endocrine response, analysis of ER, PR, AR, Ki67 and AR/ER expression showed no interaction with treatment, and lacked the ability to predict benefit of extended tamoxifen in HR+ early stage breast cancer. These results add to the growing body of evidence that BCI (H/I) is distinct in its ability to predict benefit from therapy and interrogates distinct tumor biology that is not captured by other traditional biomarkers.

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# Assessment of early response to neoadjuvant systemic therapy (NAST) of triple-negative breast cancer (TNBC) using chemical exchange saturation transfer (CEST) MRI: A pilot study

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**Introduction** CEST MRI permits quantitation of macromolecules such as amide proteins that are of interest in cancer metabolism. However, optimal CEST acquisition and analysis methods remain undetermined. In this study, we investigated CEST MRI as an imaging biomarker for early treatment response in 51 TNBC patients receiving NAST and compared the performance with two different CEST saturation power levels and two analysis methods.

**Methods** A total of 51 stage I-III TNBC patients enrolled in the prospective ARTEMIS trial (NCT02276443) had CEST imaging performed on a 3T MRI scanner at baseline before NAST (BL, N = 51), after 2 cycles (C2, N = 37), and 4 cycles (C4, N = 44) of NAST. 33 of the 51 patients had imaging at all 3 time points. 29 of the 33 patients had pathological findings, with N = 16 with pathological complete response (pCR) and N = 13 with non-pCR. Two sets of CEST images using 0.9 and 2.0 µT saturation power levels were acquired and analyzed using the magnetization transfer ratio asymmetry ($MTR_{asym}$) and the Lorentzian line fitting (Mag3.5) methods, for a total of 4 acquisition/analysis combinations. The group averaged CEST signals, $MTR_{asym}$ at 0.9 and 2.0 µT and Mag3.5 at 0.9 and 2.0 µT, at BL, C2 and C4 were determined and evaluated using unpaired (51 patients) and paired (33 patients) Kruskal-Wallis tests. The Mag3.5 at 0.9 µT and the $MTR_{asym}$ at 2.0 µT were further compared between pCR and non-pCR. The group averaged CEST signals at BL, C2, and C4 were evaluated using the Friedman test for the pCR and the non-PCR groups. Separately, the change in the CEST signal from BL to C2 and C4 was determined for each patient and evaluated using the Mann-Whitney test for both groups. $P < 0.05$ was considered statistically significant.

**Results** The $MTR_{asym}$ at BL was higher at 2.0 µT than at 0.9 µT. In contrast, the Mag3.5 at BL was higher at 0.9 µT than at 2.0 µT. The $MTR_{asym}$ at 2.0 µT and the Mag3.5 at 0.9 µT decreased during treatment while the $MTR_{asym}$ at 0.9 µT and the Mag3.5 at 2.0 µT were similar. Both the unpaired and the paired Mag3.5 at 0.9 µT showed a significant decrease at C2 and C4 vs. BL ($p < 0.01$). The unpaired and paired $MTR_{asym}$ at 2.0 µT showed a decrease, although the change was not significant except for the unpaired data at C4. The decrease in the group averaged Mag3.5 at 0.9 µT was significant at C2 vs. BL for the pCR group ($p = 0.04$), while it was not significant for the pCR group at C4 vs. BL and for the non-pCR group at either C2 or C4 vs. BL. The group averaged $MTR_{asym}$ at 2.0 µT changes were not significant for either the pCR or the non-pCR groups. None of the CEST signal changes on a per patient basis at C2-BL, C4-BL and C4-C2 were significantly different between the pCR and the non-pCR groups. Further, none of the group averaged CEST signals at BL, C2 and C4 were significantly different between the pCR and the non-pCR groups.

**Conclusion** Our study demonstrates that the CEST quantitation in TNBC patients undergoing NAST depends on acquisition and analysis. For a maximum change in the CEST effect, Lorentzian line fitting is better paired with acquisition at a low saturation power (0.9 µT) and $MTR_{asym}$ is better paired with acquisition at a high saturation power (2.0 µT). Further, a significant CEST signal decrease was observed in TNBC patients with pCR after NAST when a 0.9 µT saturation power and the Lorentzian line fitting were used. In comparison, the decrease was not significant in non-pCR patients using the same saturation power and analysis method. The results suggest that the CEST signal acquired at 0.9 µT saturation power and analyzed using Lorentzian line fitting may be able to differentiate between pCR and non-pCR among TNBC patients undergoing NAST. Additional studies with a larger patient population are ongoing to further validate our findings and their potential for determining pCR.

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Characteristics of HR+/HER2- patients with recurrent disease from a prospective registry of unresectable locally advanced or metastatic breast cancer: GEICAM/2014-03 (RegistEM)

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**Background:** There is limited prospective data for advanced breast cancer (ABC) patients (pts), unresectable locally or metastatic, treated as per clinical practice. RegistEM, an academic study conducted by a non-profit collaborative group, will provide epidemiological, pathological and clinical data as per routine practice, including treatments for different disease settings, collected from pts' medical records. Understanding the real distribution of BC subtypes is the primary objective. This is a non-interventional cohort study that will enroll approximately 1,867 pts with advanced disease diagnosed from January 2016 to December 2019, either after recurrence or as first diagnosis (*de novo*), in 38 Spanish sites representative of the whole country geography and whose investigators are GEICAM members. Biological samples (primary and/or metastatic tumor tissue, and blood) collection is part of study procedures. **Methods:** In this analysis we describe the characteristics of 229 pts with HR+/HER2- BC documented in a metastatic tumor lesion after disease recurrence and who received adjuvant endocrine therapy (ET). This subpopulation has been identify as an interesting group from a clinical perspective for detailed analysis. Three subgroups of pts have been considered for this analysis based on their disease-free interval (DFI) since the diagnosis of early disease: <36 months (mo), ≥36 mo to <60 mo, and ≥60 mo. **Results:** This subset of pts makes up 13.7% (n=229) of the whole population currently registered (n=1,672). The distribution of pts on <36 mo, ≥36 mo to <60 mo, and ≥60 mo DFI subgroups was 15.3%, 16.6% and 68.1%, respectively, with >50% pts recurring at ≥84 mo and only 1.3% pts at ≤12 mo. Most pts were Caucasian (99.1%) and female (99.6%), and at ABC diagnosis, 75.5% were postmenopausal and their median age was 59 years (33-88); median age was higher in pts with DFI ≥60 mo. Family history of BC and/or ovarian cancer was reported in 31.4% pts, with a slightly higher percentage in pts with DFI <36 mo; an hereditary-risk genetic test was performed in 11.4% pts in total and BRCA2 gene mutation (n=6) was the only one reported. Bone (59%), liver (33.2%), lung (23.1%) and lymph nodes (21.8%) were the most frequent sites of metastases. Visceral disease was present in 63.3% pts and 76% pts had ≤2 locations. Liver involvement was more frequent in pts with DFI <36. The most frequent 1$^{st}$-line therapies were ET/biological therapy (BT) (46.7%) and ET (28.8%). The most common ET/BT regimens were aromatase inhibitor (AI)/cyclin-dependent kinase 4/6 inhibitor (CDKi) (48.6%) and fulvestrant (FUL)/CDKi (28.0%); AIs (67.3%) and FUL (31.0%) were also the most common drugs for ET ( as monotherapy). A 2$^{nd}$-line therapy was reported in 52.4% pts. The median time to progression (TTP) to 1$^{st}$-line therapy was 11.4 mo (1.2-37.0), being similar in pts with DFI <36 mo and ≥36 mo to <60 mo (around 7 mo), and higher in pts with DFI ≥60 mo (13.2 mo). The most frequent 2$^{nd}$-line therapies were ET/BT (33.3%) (FUL/CDKi 42.5%, AI/CDKi 30%), chemotherapy as monotherapy (29.2%) (capecitabine 51.7%, taxanes 20.7%, eribulin 13.8%) and ET (19.2%) (FUL 54.5%, AI 36.4%). Median duration of 2$^{nd}$-line therapy was 5.7 mo (0.03-37.2) and disease progression was reported in 56.7% pts. Most frequent 1$^{st}$-/2$^{nd}$-line therapies between DFI subgroups were similar in type but not in frequency. 3$^{rd}$-line therapy has been reported in 25.8% of 229 pts. **Conclusions**: In pts with HR+/HER2- ABC due to disease recurrence, >50% pts recurred at ≥84 mo. Bone is the most frequent metastatic location in all DFI subgroups. The most common 1$^{st}$- and 2$^{nd}$-line therapies were the ET/BT combination, with AI/CDKi and FUL/CDKi, respectively. The median TTP to 1$^{st}$-line therapy was superior in pts with DFI ≥60 mo.

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# Tucatinib vs placebo in combination with trastuzumab and capecitabine for patients with locally advanced unresectable or HER2-positive metastatic breast cancer (HER2CLIMB): Outcomes by hormone receptor status

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**Background** Tucatinib (TUC) is a highly selective oral tyrosine kinase inhibitor of HER2 with minimal inhibition of EGFR. It was recently approved by the FDA for patients (pts) with HER2+ metastatic breast cancer (MBC), including pts with brain metastases (BM) whose cancers have progressed on at least 1 prior anti-HER2 regimen in the metastatic setting. In the HER2CLIMB (NCT02614794) pivotal trial, pts with HER2+ MBC previously treated with trastuzumab (T), pertuzumab, and trastuzumab emtansine (T-DM1) were randomized to receive TUC or placebo in combination with T and capecitabine (C). The addition of TUC resulted in clinically meaningful and statistically significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in HER2+ MBC pts. Primary methods and outcomes have been reported previously (Murthy, NEJM 2019). Here we present an exploratory analysis describing the outcomes in the HER2CLIMB trial based on hormone receptor (HR) status.

**Methods** Pts were randomized 2:1 to receive TUC or placebo in combination with T and C. All pts had a baseline brain MRI and randomization was stratified by presence of BM, ECOG status, and geographic region. All pts with HER2+ MBC who were positive for either or both estrogen receptor and progesterone receptor (≥ 1%) were assigned to the HR “positive” subgroup. Pts not meeting the above criteria were assigned to the HR “negative” subgroup. For the exploratory HR+/HR- efficacy analysis presented here, PFS per RECIST 1.1 by blinded independent central review was evaluated in the first 480 pts enrolled. OS, PFS in pts with baseline BM, and confirmed ORR in pts with measurable disease were evaluated in the total study population. P values presented for PFS are nominal.

**Results** Overall, 612 pts were enrolled to HER2CLIMB; 370 pts (60%) had HR+ and 242 (40%) had HR- tumors. Baseline demographics and disease characteristics in HR+/HR- subgroups were generally balanced between treatment arms. In the HR+ group, there was a 42% reduction in the risk of progression or death in the TUC arm (hazard ratio: 0.58; 95% CI: 0.42, 0.80; P=0.0008); median (95% CI) PFS was 7.6 mo (7.4, 9.5) in the TUC arm vs 5.6 mo (4.3, 7.4) in the control arm. In the HR- group, there was a 46% reduction in the risk of progression or death in the TUC arm (hazard ratio: 0.54; 95% CI: 0.34, 0.86; P=0.008); median (95% CI) PFS was 8.1 mo (7.0, 11.6) in the TUC arm vs 4.2 mo (3.1, 8.6) in the control arm. In the total population, median OS was 21.7 mo vs 18.2 mo in HR+ in the TUC arm vs control arm, respectively; median OS in HR- was 31.1 mo in the TUC arm vs 14.1 mo in the control arm. In pts with BM in the HR+ group (n=166 [45%]), there was a 52% reduction in the risk of progression or death (hazard ratio: 0.48; 95% CI: 0.31, 0.75; P=0.0008); median (95% CI) PFS was 7.5 mo (5.6, 9.5) in the TUC arm vs 5.1 mo (4.1, 5.7) in the control arm, and median OS was 18.1 mo vs 12.8 mo, respectively. In pts with BM in the HR- group (n=125 [52%]), there was a 50% reduction in the risk of progression or death (hazard ratio: 0.50; 95% CI: 0.27, 0.95; P=0.03); median (95% CI) PFS was 7.8 mo (6.1, 11.6) in the TUC arm vs 5.4 mo (2.9, 8.6) in the control arm, and median OS was 18.5 mo vs 11.5 mo, respectively. In the total population, ORR was numerically higher in the TUC arm vs the control arm regardless of HR status (HR+: 37.4% [95% CI: 30.8, 44.5] vs 27.1% [95% CI: 19.0, 36.6], respectively and HR-: 45.3% [95% CI: 36.7, 54.0] vs 15.6% [95% CI: 7.8, 26.9], respectively).

**Conclusions** Among pts with HER2+ MBC previously treated with T, pertuzumab, and T-DM1, the addition of TUC to T and C showed clinically meaningful improvements of PFS, OS, and ORR independent of HR status. Furthermore, pts with HR+ and HR- MBC with BM derived similar benefit from the addition of TUC to T and C.

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# Trastuzumab deruxtecan (T-DXd; DS-8201) in combination with other anticancer agents in patients with HER2-low metastatic breast cancer: A phase 1b, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast08)

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## Background

In patients (pts) with HER2+ (immunohistochemistry [IHC] 3+ or IHC 2+/in situ hybridization [ISH]+) metastatic breast cancer (mBC), HER2-targeted therapies have greatly improved survival. However, for pts with HER2-low mBC (IHC 1+ or IHC 2+/ISH−), there are no approved HER2-directed therapies. In pts with hormone receptor (HR)+, HER2-low mBC whose disease progresses on standard first-line treatment (endocrine therapy [ET] and CDK4/6 inhibitors), median progression-free survival (PFS) with continued ET alone is ≈ 2 months, and with mTOR or PI3K inhibitors (in *PIK3CA*-mutant tumors) in the second-line setting, PFS ranges from 3.5 to 7.3 months, respectively (André F, et al. ESMO 2018; Dhakal A, at al. ASCO 2018; Rugo R, et al. ASCO 2020). For ET-refractory pts, chemotherapy (CTX) is the standard of care and has a poor benefit-risk ratio. The treatment landscape for pts with HR−, HER2-low mBC is even more limited, consisting largely of CTX (with or without PD-1/PD-L1 inhibitors in the first-line setting). T-DXd is an antibody-drug conjugate composed of a humanized HER2 antibody attached to a membrane-permeable topoisomerase I inhibitor payload via a cleavable tetrapeptide-based linker at a drug to antibody ratio of ≈ 8. In a recent phase 1b study, pts with heavily pretreated (median, 7.5 prior therapies) HER2-low advanced or metastatic breast cancer treated with T-DXd 5.4 or 6.4 mg/kg had a confirmed objective response rate (ORR) of 37.0% (20/54) by independent central review and a median PFS of 11.1 months, and the safety profile was generally manageable (Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896). Here, we describe a phase 1b trial evaluating the safety, tolerability, and pharmacokinetics (PK) of T-DXd in combination with other anticancer agents in pts with HER2-low, HR+ or HR− mBC.

## Study Description

DESTINY-Breast08 is a multicenter, open-label, 2-part study evaluating T-DXd combinations in pts with HER2-low mBC. The 5 treatment modules comprise T-DXd in combination with (1) capecitabine, (2) durvalumab + paclitaxel, (3) capivasertib, (4) anastrozole, and (5) fulvestrant.

*Part 1 (dose finding)*: Each treatment module will enroll 3 to 12 pts per dose level to determine the recommended phase 2 dose (RP2D) in combination; modules 1 through 3 will enroll irrespective of HR status, whereas modules 4 and 5 will be restricted to only HR+ pts. HR+ pts should have received ≥ 1 prior line of ET and ≥ 1 prior line of CTX; HR− pts should have received ≥ 1 prior line of CTX.

*Part 2 (dose expansion)*: Modules 1, 4, and 5 will enroll 20 pts, and modules 2 and 3 will enroll 40 pts using the RP2D determined in part 1 of each module. Patient eligibility per module in part 2 is as follows:

- Module 1 (HR+ or HR−): HR−, only 1 prior line of CTX for mBC; HR+, only 1 prior line of ET but no prior CTX for mBC
- Module 2 (HR−): no prior CTX for mBC
- Module 3 (HR−): only 1 prior line of CTX for mBC
- Modules 4 and 5 (HR+): only 1 prior line of ET but no prior CTX for mBC

The primary endpoint in part 1 is safety and tolerability and determination of RP2Ds. In part 2, the primary endpoint is safety and tolerability, and secondary endpoints include ORR, duration of response, and PFS (all by investigator assessment according to RECIST 1.1) as well as overall survival, PK, and immunogenicity.

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**Publication Number:** PS1-09

Long-term results of prepectoral implant-based reconstruction using braxon®acellular dermal matrix - national audit from United Kingdom

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**Background**Single stage direct-to-implant reconstruction is the most common method of reconstruction in the United Kingdom (UK) after a mastectomy. Prepectoral implant placement with full implant coverage using acellular dermal matrix (ADM) is a relatively new technique with paucity of data on surgical outcomes. We report on long term outcomes of prepectoral breast reconstruction (PBR) using Braxon® ADM from a multicentre audit across the UK**Methods**A retrospective multicentre audit of all direct-to-implant post-mastectomy PBR using Braxon® was conducted. The demographic details, treatment details, 90-day complication rates and implant loss rates for the entire study period were evaluated. Factors affecting major complication rates and implant loss rates were analysed using univariable and multivariable analysis.**Results**Eight hundred and twenty two patients underwent 1020 post-mastectomy PBR across 29 centres in the UK from January 2014 to 2019. Median age of the cohort was 49 years with a median BMI of 25 kg/m$^2$. The median and mean follow-up periods were 14 and 17.54 months respectively. The overall 90-day complication rate was 26.47% with major complications in 13.04% of patients. The 90-day readmission rate was 11.18% and return to theatre rate was 12.25%, with a 90-day implant loss rate of 5.1 percent. The implant loss rate was 6.28% for the entire study period. On multivariable analysis, therapeutic mastectomy (p = 0.008) and a higher breast specimen weight (p = 0.000) were the only factors to significantly impact major complications. Implant loss rates were significantly higher in current smokers (p = 0.000) and patients with previous breast radiation therapy (p = 0.010), axillary nodal clearance (p = 0.007), high breast specimen weight (p = 0.034) and a higher implant volume (p = 0.044) on multivariable analysis.**Conclusion**Implant-based prepectoral breast reconstruction with Braxon® acellular dermal matrix has satisfactory short-term and long-term operative outcomes, comparable to National data from the United Kingdom. Smoking, previous breast radiation therapy, axillary nodal clearance, high breast specimen weight and implant volume could negatively impact complications and implant loss rates. Patient-reported outcomes need to be evaluated.

| Characteristics | Number of patients or procedures |
|---|---|
| Total number of patients | 822 |
| Total number of procedures | 1020 |
| Age (years) | 49 |
| BMI (kg/m$^2$) | 25 |
| Laterality | |
| Unilateral | 624 (75.91) |
| Bilateral | 198 (24.09) |
| Smoker | 49 (4.80) |
| Diabetes | 12 (1.17) |
| Vascular disease | 11 (1.08) |
| Previous breast surgery | 156 (15.30) |
| Previous breast radiotherapy | 34 (3.33) |
| Neoadjuvant chemotherapy | 122 (14.85) |
| Reconstruction type | |
| Immediate | 849 (83.23) |
| Delayed | 25 (2.45) |
| Missing | 146 (14.32) |
| Management of axilla | |
| Sentinel node biopsy | 457 (44.80) |
| Axillary nodal clearance | 112 (10.98) |
| None | 320 (31.37) |
| Missing | 131 (12.85) |
| Type of reconstruction | |
| One-stage | 823 (80.68) |
| Two-stage | 112 (10.98) |
| Missing | 85 (8.34) |
| Hospital stay (days) | 1 (0-10) |
| Breast specimen weight (grams) | 391 (64-3900) |
| Implant size (cc) | 385 (100-700) |
| Histology | |
| Invasive ductal carcinoma | 392 (38.43) |
| Invasive lobular carcinoma | 47 (4.61) |
| Ductal carcinoma in-situ | 167 (16.37) |
| Lobular carcinoma in-situ | 11 (1.08) |
| Not applicable | 276 (27.06) |
| Missing | 127 (12.45) |
| Adjuvant chemotherapy | 167 (20.32) |
| Adjuvant radiation therapy | 166 (16.27) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS6-08

# The PORTRET-tool: A prediction tool for older patients with breast cancer that predicts recurrence, survival and other-cause mortality

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**Introduction** Previous studies have shown that available tools such as ‘Adjuvant Online!” are not able to accurately predict the prognosis of patients aged 65 years or older with breast cancer. Furthermore, all available tools predict prognosis in terms of recurrence-free survival or overall survival, whilst the risk of other-cause mortality is often high in the older patient with breast cancer. This is highly relevant as it may influence treatment decisions. Patient characteristics such as comorbidity and various geriatric variables have shown to be predictive for these outcomes and could enhance the precision of prognostic tools for this target population. The objective of this study was to develop a prediction tool for recurrence, survival and other-cause mortality for older patients with breast cancer who received locoregional treatment, with incorporation of patient-, tumor- and geriatric variables. The tool additionally predicts expected benefits of systemic treatment. **Methods** Data from the large population-based FOCUS cohort was used, consisting of consecutive breast cancer patients in the South-Western part of the Netherlands, diagnosed between 1997 and 2004, aged 65 years and older. It contains detailed information on tumor characteristics, treatment, comorbidity and geriatric parameters. We developed a risk prediction model using a Cox proportional hazards regression model for overall survival and cause-specific Cox proportional hazards models for recurrence and other-cause mortality (defined as mortality without recurrence). The included predictors were derived from the PREDICT tool (consisting of age and various tumor variables), since this tool was previously shown to have the best performance in older adults so far. Predictors were complemented with comorbidity and geriatric variables. Discrimination accuracy was evaluated using time-dependent area under the curve (AUC). The potential annual benefit of chemotherapy was calculated assuming a relative risk of chemotherapy on recurrence of 0.7, derived from data from the most recent updates of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Additional benefit of endocrine treatment will be included in further development of the tool. **Results** A total of 2,744 patients were included for the initial development. For all patients, 5-year follow-up was complete with a high event-rate including 343 recurrences and 831 total deaths of which 586 without recurrence. The strongest predictors for overall survival and non-recurrence mortality were age (HR = 2.14, 95% CI: 1.89 - 2.43 and HR = 2.87, 95% CI: 2.46 - 3.35, respectively) and dementia (HR = 1.52, 95% CI: 1.16 - 1.99 and HR = 1.9, 95% CI: 1.49 - 2.65, respectively), and for recurrence, nodal status (HR = 1.80, 95% CI: 1.45 - 2.24) and tumor grade (HR = 2.96, 95% CI: 1.88 - 4.66)**.** The time-dependent AUC at 5 years for recurrence-specific and other-cause mortality were 0.78 (95% CI: 0.76 - 0.81), and 0.75 (95% CI: 0.72 - 0.78), respectively. The AUC for overall survival was 0.75 (95% CI: 0.72 - 0.78). External validation is currently being performed in a large dataset retrieved from the national cancer registry (N= 13,631). These results will be presented during the symposium. **Conclusion** We have developed a model for predicting 5-year recurrence, other-cause mortality and overall survival, including expected benefits of adjuvant treatment, for older patients with breast cancer, with a good discrimination performance within a large-population based cohort. To our knowledge, this is the first model specifically designed for the older population, including competing risk as a predicted outcome and with incorporation of geriatric variables.

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# Does genomic recurrence score predict for ipsilateral breast tumor recurrence after breast conservation therapy?

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Purpose/ObjectivesGene profiling Recurrence Score (RS) assays are commonly used to identify patients with hormone receptor (HR) positive, HER-2 negative invasive breast cancer (IBC) who might benefit from systemic chemotherapy. More recently, the 21-gene recurrence score assay has been found to correlate with locoregional recurrence (LRR) after mastectomy (SWOG) or lumpectomy (NSABP). In the NSABP analysis, risk of ipsilateral breast tumor recurrence (IBTR) was not correlated with RS and was high in patients younger than 50 years of age irrespective of genomic score. However, tumor bed radiotherapy (RT) boost was not utilized in these protocols. The purpose of this study is to determine if RS predicts for IBTR or LRR in women treated with modern breast conserving therapy (BCT) using RT boost and optimal systemic treatment.
Materials/MethodsWe performed a retrospective review of patients with HR positive, HER-2 negative IBC who underwent gene profile testing and were treated at our institution with BCT and sentinel lymph node biopsy (SLNB) from 2013 to 2017. Both node negative and node positive patients were included. The Oncotype® 21-gene recurrence score assay was used in 84%, Mammaprint® in 12%, and Prosigna® in 4%. 97% received hormonal therapy (HT), 18% chemotherapy (CHT), 58% hypofractionated RT, and 96% a surgical bed RT boost. IBTR and LRR were measured from the end of local treatment to IBTR or LRR, with death or last follow up date as censoring events. The Kaplan-Meier method was used to estimate event-time probabilities for the above endpoints. Predictors of IBTR/LRR were analyzed using log rank tests between groups and with Cox regression for continuous variables. P-values <0.05 were considered significant.
Results 686 evaluable patients were identified with median follow-up of 50 months (Interquartile range [IQR] 36-64 months). Median age was 61 years (IQR 53-68 years). 76% had invasive ductal carcinoma, 64% grade 2 disease, and 18% positive SLNB. RS of any type was low in 60% of patients and intermediate or high in 40%. Four-year IBTR was 0.2% (95% Confidence Interval [CI] 0.0-0.6%) for any low risk RS and 1.6% (95% CI 0.0 - 3.2%) for intermediate or high-risk RS ($p = 0.01$). Tumor grade was also predictive for IBTR ($p < 0.01$), but age < 50 was not ($p = 0.4$). For patients younger than 50, four-year IBTR was 0.9% (95% CI 0.0 - 2.6%) and not affected by RS ($p = 0.231$). On multivariate analysis, grade remained a significant predictor for IBTR ($p = 0.04$), but RS did not ($p = 0.08$). Four-year LRR was 0.5% (95% CI 0.0-1.3%) in patients with a low risk RS and 3.8% (95% CI 1.3-6.3%) in those with intermediate or high risk ($p < 0.01$). Grade ($p < 0.01$) and pathologic tumor size ($p < 0.01$) were also correlated with LRR, although only RS (HR 5.14, 95% CI 1.02-25.9, $p = 0.047$) and pathologic tumor size on (HR 1.05, 95% CI 1.01- 1.09, $p = 0.02$) remained significant on multivariate analysis. Of the 125 patients with positive SLNB, 47% were treated with high tangents and 42% with comprehensive regional nodal irradiation. For node positive patients, LRR was not correlated with low versus intermediate or high RS ($p = 0.07$). However, if intermediate risk Oncotype scores were grouped with low risk Oncotype and Mammaprint scores, then LRR was 0.0% for low and intermediate risk and 9.1% for high risk ($p < 0.01$).
ConclusionsIn this large single institution study, RS did not predict for IBTR in patients with HR positive, HER-2 negative invasive breast cancer in any age group treated with BCT utilizing a surgical bed RT boost and optimal systemic treatment. High RS did predict for high LRR because of higher regional recurrences and can be used as a guide to add comprehensive RT for node positive patients after BCT.

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# Oral paclitaxel and encequidar (oPac+E) versus IV paclitaxel (IVPac) in the treatment of metastatic breast cancer (mBC) patients (study KX-ORAX-001): Progression free survival (PFS) and overall survival (OS) updates

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**Background:** IVPac is widely used to treat patients with breast cancer. oPac+E is oral paclitaxel in combination with Encequidar, an oral, minimally absorbed, specific p-glycoprotein inhibitor that enables the absorption of oral paclitaxel. Results of the phase III trial, KX-ORAX-001, were presented at SABCS, 2019, Abstract # GS6-01. At the time of the database lock for the final analysis of the primary endpoint of confirmed tumor response rate, analyses of PFS and OS were performed. The confirmed tumor response rate was significantly higher in the oPac+E group vs IVPac (35.8% vs 23.4%, p=0.011 ITT, population). The median overall survival was 27.7 months vs 16.7 months, respectively favoring oPac. An update of the duration of response, PFS and OS data comprising an additional 14 months follow-up will be presented. At the time of the update it is projected that approximately 60% of subjects will have had a survival event.
**Methods:** Study KX-ORAX-001 was a phase III, randomized, international study in women with mBC for whom treatment with IVPac was recommended. Eligible patients were randomized 2:1 to receive oPac+E or IVPac. Patients continued treatment until discontinuation due to progressive disease or toxicity. oPac 205 mg/m$^2$ was given once daily for 3 days weekly. E 12.9 mg was given 1 hour before each dose of oPac. IVPac 175 mg/m$^2$ was infused over 3 hours every 3 weeks. The primary endpoint was efficacy defined as tumor response confirmed by BICR at two consecutive evaluations. Key secondary endpoints included PFS, OS. Safety was monitored throughout the study.
**Results:** A total of 402 mBC patients were randomized (oPac+E 265: IVPac 137) and represent the ITT population of which 399 subjects were dosed. Updated data for duration of response, PFS and OS for the ITT and prespecified mITT populations will be presented. (NCT 02594371)

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# Clinical factors and association with treatment modalities in patients with breast cancer and brain metastases who develop leptomeningeal disease

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BACKGROUNDImprovements in systemic therapies have led to significantly improved survival in patients with breast cancer and have created a challenge with regards to management of brain metastases (BM) and leptomeningeal disease (LMD). LMD is a highly aggressive condition, resulting in rapid neurological decline and a short survival of weeks to months. The purpose of this study is to identify clinical factors that can predict for LMD when a patient is diagnosed with BM, and to assess outcomes with various treatment modalities.METHODSA retrospective analysis was conducted using a clinical database at a single institution and included 178 patients with breast cancer and treated BM between 2007-2020. Demographic, clinical, radiographic, and dosimetric data were collected. LMD was diagnosed by cytology or neuroimaging. Chi-square and t-test were used.RESULTSOut of 178 patients with breast cancer and treated BM, 41 (23%) developed LMD. Median age for the study cohort was 51.3 +-13.4 years; those with LMD was 47.9 +-12.3 (p=0.057) years. One of the 178 patients was a male and all 41 with LMD were females. There were 58.5% Caucasian women in the LMD group followed by African-American being 24.4% (p=0.31). Characteristics like number of brain lesions (p=0.57), median size of the largest brain lesion (p=0.70), hemorrhagic/cystic lesions (p=0.68), systemic disease being progressive in 42.6%, stable in 19.3% and 26.1% with no evidence of systemic disease at the time of diagnosis of BM (p=0.34) did not pose a higher risk in developing LMD. For 29% patients the brain lesions were supratentorial, 23.7% were infratentorial and 47.4% patients had both and had a higher risk for LMD (p=0.025). Patients with liver (p=0.45) and bone (p=0.48) lesions did not have higher risk for LMD which was seen in those without lung metastases (p=0.03). In the LMD group, 39% had HR+, 31.7% HER2+, and 41.4% had triple negative breast cancer (TNBC). The higher incidence of HR+ patients could be attributed to the fact that the more aggressive HER2+ and TNBC patients may have not gotten treatment for their BM as they pursued comfort care status. In the LMD group, 13.1% received prior stereotactic radiation, 39.5% whole brain radiation, 10.5% had surgery alone and 36.8% had surgery with pre/post-op radiation. Patients who had any surgery did not have a higher risk for LMD (p=0.26). Surgery did not pose a higher risk for local recurrence, seen in 28% patients (p=0.42) and occurrence of BM at another site, seen in 36.5% patients (p=0.16). CONCLUSIONSAmong breast cancer patients with brain metastases those who develop LMD tend to be younger, with higher risk in Caucasians and African-American women; however, this was not statistically significant. The number, size, hemorrhagic/cystic character of brain lesions did not pose a higher risk whereas occurrence of synchronous lesions in supratentorial and infratentorial locations increased risk of LMD. There was no statistically significant difference in the rates of LMD, local recurrence, CNS recurrence at another site with surgery and/or radiation.

| Ethnicity | Brain metastases (N=178) | LMD group (N=41) (p=0.31) |
|---|---|---|
| Caucasian | 58.4% | 58.5% |
| Hispanic | 12.4% | 4.9% |
| African-American | 19.1% | 24.2% |
| Others | 10.1% | 12.2% |

| Clinical characteristics | Brain metastases | LMD group | P value |
|---|---|---|---|
| Number of brain lesions (Median interquartile range) | 3 (1-8) | 2.5 (1-9) | P=0.57 |
| Median size of the largest brain lesion (cm) | 2.4 1.4 | 2.53 1.69 | p=0.70 |
| Hemorrhagic lesions | 22 | 3 | P=0.68 |
| Cystic lesions | 16 | 3 | |

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**Publication Number:** PS17-09

Development of a potent mutant-ESR1 targeted agent, ERX-245, for treating metastatic therapy-resistant breast cancer

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**Background:** *ESR1* mutations are acquired following ERα targeted therapies and are a major determinant of therapy-resistance. These *ESR1* mutations maintain *ESR1* signaling, albeit in a ligand-independent manner. Effective drugs targeting these mutant (MT) ERα proteins represent a significant unmet clinical need. We had previously shown that ERX-11, an *ESR1*-coregulator binding inhibitor, could block the function of these MT ERα proteins. In this study, we sought to leverage recently published structures of MT ERα to develop more potent analogues of ERX-11. **Methods:** Virtual screening of >250,000 derivatives of ERX-11 was performed with simulated docking on the MT ERα to identify and design analogues of ERX-11. Several hundred analogues were synthesized and tested *in vitro* using multiple BC model cells that express wild type (WT) *ESR1* or mutant (MT) *ESR1 (Y537S or D538G*). Mechanistic studies were performed using RNA-Seq, Western blotting, qRT-PCR and reporter gene assays. The *in vivo* efficacy of the most potent ERX-11 analogue ERX-245 was examined using xenograft, PDX and metastatic models of MT-ER driven BC. **Results:** From our virtual and functional screen, we identified an ERX-11 analogue, ERX-245 as the most potent hit to target MT-ERα. Docking studies modeled a better fit of ERX-245 into the ligand binding domain of both the *Y537S* and *D538G* MT-ERα. ERX-245 potently reduced ($IC_{50}$ ~250 nM) the cell viability of both WT-ERα and MT-ERα driven BC cells but not ERα negative BC cells. ERX-245 significantly reduced the growth (colony formation, clonogenic and mammosphere assays) of MT-ERα BC cells. ERX-245 exhibited synergistic activity in combination with CDK4/6 inhibitors. In distinction to classic SERDs like fulvestrant (which degrade ERα with in 4h), ERX-245 treatment decreased MT-ERα protein levels over 24 hours. PK studies indicated that ERX-245 is more polar and has better solubility and pharmacokinetic properties than ERX-11. ERX-245 reduced tumor growth of subcutaneous xenograft and PDX models driven by MT-ERα as well as the proliferation of xenograft derived MT-ERα explant models. ERX-245 significantly reduced the invasive capability of MT-ERα BC cells i*n vitro* and inhibited both the metastatic capability and growth of metastatic tumors derived from MT-ERα BC cells injected by intracardiac or intratibial routes. **Conclusions**: Taken together, these results indicate that ERX-245 is a potent and pharmacologically translatable analog of ERX-11, with activity against both primary and metastatic tumors driven by MT-ERα.

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# Nci 10013 - A randomized phase 2 study of neoadjuvant carboplatin and paclitaxel, with or without atezolizumab in triple negative breast cancer (TNBC)

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**Background** Inhibition of PD-L1 with atezolizumab combined with chemotherapy has shown acceptable safety and improved survival in patients with metastatic PD-L1 positive triple negative breast cancer (TNBC). Patients with TNBC who do not achieve a pathological complete response (pCR) to neoadjuvant chemotherapy have a high risk of disease recurrence and death. This randomized, open-label, phase 2 trial evaluates neoadjuvant carboplatin and paclitaxel with or without atezolizumab in patients with previously untreated clinical stages II and III TNBC. **Methods** Women aged ≥18 years with clinical stage T2-T4c, any N, M0 primary tumor by AJCC 7th edition staging TNBC; ECOG PS 0-2; and no prior systemic therapy for the indexed breast cancer were eligible. Patients were randomized in a 1:2 ratio to carboplatin AUC5 q 3 weeks x 4 + paclitaxel 80 mg/m2 q week x 12 (Arm A), or carboplatin AUC5 q 3 weeks x 4 + paclitaxel 80 mg/m2 q week x 12 + atezolizumab 1200 mg q3 weeks x 4 (Arm B). Surgery was 3-6 weeks following neoadjuvant chemotherapy. Adjuvant dose-dense doxorubicin and cyclophosphamide was administered q2 weeks with growth factor support to all patients as per routine care. pCR and tumor infiltrating lymphocyte (TIL) percentages are the co-primary endpoints. pCR-evaluable population includes all eligible women who have been randomized and received at least one dose of combination therapy, while the TIL-evaluable population includes all eligible women who have evaluable TIL percentage after one cycle of therapy. A sample size of 67 (22 in Arm A, and 45 in Arm B) provided 80% power at 1-sided alpha = 0.10 to detect a minimum of 15% difference in TIL and 29% improvement (40% vs. 69%) in pCR, respectively. Herein, we report pCR results in the per protocol modified intent-to-treat population (mITT), which includes all eligible patients who were randomized and received at least one dose of combination therapy. **Results** Sixty-seven patients were randomized between 8/2017 and 9/2019. Six patients randomized to Arm A withdrew consent; 2 of these received protocol therapy but are excluded from the mITT analyses as they are not evaluable because definitive pathology reports are not available. Median follow up is 6 months (range 0.3 - 12.6 months). Median age is 52 years (range 25 - 78). Forty-three (64.2%) were Caucasian and thirteen (19.4%) were African American. Twenty-five (37.3%) were pre-menopausal. 67.2% and 32.8% had stages II and III disease respectively. Nine (13.4%) had a germline mutation in either *BRCA1* or *BRCA2*. In the mITT population, 3 of 16 patients achieved pCR in Arm A - 18.8% (95% CI 4.0%- 45.6%), versus 25 of 45 patients in Arm B - 55.6% (95% CI 40.0%-70.4%); p value 0.018. pCR in those with *BRCA* mutations was 50% and 80% in Arm A and Arm B, respectively. Treatment delays were observed in 9 patients (40.9%) in Arm A, and 20 (44.4%) in Arm B; dose reductions occurred in 4 patients (18.1%) in Arm A, and in 6 (13.3%) in Arm B. There were 4 SAEs in Arm A and 10 in Arm B. One patient in Arm B had grade 3 adrenal insufficiency. One patient in Arm B died from recurrent disease during the follow-up period. **Conclusions:** The addition of atezolizumab to neoadjuvant carboplatin and paclitaxel resulted in an increased pCR rate in patients with clinical stages II and III TNBC. However, the pCR in the control Arm A was lower than expected, possibly due to the absence of neoadjuvant anthracyclines. The high pCR rate observed in the experimental arm of this study is similar to that observed in other neoadjuvant trials utilizing anthracyclines, taxanes, and carboplatin in TNBC. Clinical trial information: NCT02883062.

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Phase 2 study of response-guided neoadjuvant sacituzumab govitecan (IMMU-132) in patients with localized triple-negative breast cancer (NeoSTAR)

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**Background:** Optimizing treatments for triple negative breast cancer (TNBC) in the localized breast cancer setting is key to preventing metastatic recurrences and reducing mortality from this devastating disease. Sacituzumab Govitecan (SG), a novel antibody-drug conjugate in which the topoisomerase 1 inhibitor SN-38 (the active metabolite of irinotecan) is coupled to a humanized monoclonal antibody targeting the tumor antigen Trop-2, was granted FDA accelerated approval in April 2020 for treatment of patients with metastatic TNBC. The NeoSTAR clinical trial is evaluating SG in the neoadjuvant setting for patients with localized TNBC. **Trial design:** This is a single arm phase II study of neoadjuvant SG in patients with localized TNBC. SG will be administered via an IV infusion on Days 1, 8 of each 21-day cycle at a starting dose of 10 mg/kg for 4 cycles. After 4 cycles, patients who have biopsy-proven residual disease will have the option to receive additional standard neoadjuvant therapy at the discretion of the treating physician and subsequently proceed to surgery. Those with a complete response on imaging may proceed directly to surgery. A baseline research biopsy prior to initiation of study therapy is required as well as tissue collection following treatment with SG (either at surgery or via biopsy prior to additional neoadjuvant therapy). **Eligibility criteria:** Patients ≥ 18 years of age with previously untreated primary TNBC as determined by the local institution according to ASCO/CAP criteria will be enrolled. Patients must either have a primary tumor >1 cm measured by imaging (cT1c-T4), or be node positive. An ECOG performance score of 0 or 1, and adequate bone marrow, hepatic, and renal function is required. **Specific aims:** The primary objective is to assess the pathological complete response (pCR) rate in breast and lymph nodes (ypT0/isN0) with SG. Secondary objectives include assessment of radiological response rate, evaluation of the safety and tolerability of SG (CTCAE v5.0), disease-free survival (DFS), and quality of life (EORTC QLQ-C30). Exploratory objectives include assessment of potential predictive biomarkers, including Trop-2 expression, DNA damage response markers and immunological markers, as well as changes in cell free DNA with SG. **Statistical methods:** The primary analysis is based on the estimated pCR rate with SG and will be provided as a proportion (with two-sided 95% confidence interval). Accounting for up to a 14% drop out rate, a sample size of 43 patients will provide 80% power to exclude a lower limit of pCR of 20% (alpha 0.05, two-sided test). DFS will be analyzed using Kaplan-Meier methods and descriptive statistics. **Target Accrual:** 50 patients. **Contact:** Dr. Laura Spring (LSpring@mgh.harvard.edu)
**Clinicaltrials.gov #:** NCT04230109

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# High infiltration of adipocytes is associated with inflammation, metastasis as well as favorable tumor immune microenvironment whereas low infiltration is associated with highly proliferative tumor in ER positive breast cancer patients

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**Background:** Cancer associated adipocytes are known to cause inflammation and leads to the cancer progression, and metastasis. In the current study, we defined intra-tumoral adipocytes transcriptionally utilizing a computational algorithm, xCell, which allowed us to quantify infiltrating adipocytes. We hypothesized that high amount of intra-tumoral adipocytes is associated with aggressive cancer characteristics and poor survival outcome.
**Material and Methods:** The clinicopathological data and survival information of 1090 breast cancer patients were obtained from The Cancer Genome Atlas (TCGA), GSE25066 and study by Yau et al. Survival analysis, gene set enrichment analysis (GSEA) were conducted comparing the intra-tumoral adipocyte high and low groups. The association between the amount of intra-tumoral adipocytes and Nottingham pathological grade or AJCC stage were evaluated. CYT score and xCell were utilized to evaluate intratumoral immune cell composition within breast cancer.
**Results:** Our transcriptomically defined intra-tumoral adipocyte appropriately reflected mature adipocytes in a bulk tumor. Surprisingly, intra-tumoral adipocytes high tumors did not demonstrate worse survival, neither OS or DFS, in the whole cohort or any of the subtypes. Less aggressive Stage 1 even trended toward increased intra-tumoral adipocytes although statistically insignificant. Further, less proliferative grade 1 was associated with increased intra-tumoral adipocytes compared with other grades in whole and ER positive/HER2 negative (ER+/HER2-) subtype of TCGA cohort ($p < 0.001$). This result was consistent in GSE25066 cohort ($p < 0.001$). An amount of intra-tumoral adipocytes was weakly inversely correlated with MKI67 expression in three cohorts; TCGA, GSE25066 and the study by Yau et al ($r = -0.235$, $r = -2.09$ and $r = -0.355$, respectively). In agreement with the previous in vitro studies, adipocyte high tumors enriched the gene sets associated with inflammation, such as TNF-α and Inflammatory response. Further, intra-tumoral adipocyte high tumors enriched the gene sets related to metastasis, such as EMT, TGF-β signaling, and Notch signaling. On the other hand, adipocyte high tumors enriched the gene sets related to immune response such as IL2 signaling and IFN-γ especially in ER+/HER2- subtype. The analysis of tumor immune microenvironment revealed that intra-tumoral adipocyte high tumors were associated with favorable tumor immune microenvironment in ER+/HER2- subtype, but not in triple negative (TN). Consistent with the association with pathological grade and MKi67, intra-tumoral adipocyte low tumors enriched the cell cycle and cell proliferation gene sets, such as G2M checkpoint, in both TCGA and GSE25066 cohorts. These results force us to speculate that intra-tumoral adipocytes does cause inflammation and evoke metastatic pathways as previously reported in in vitro studies, but also associate with immune response, whereas adipocyte low tumors are highly proliferative cancers, thus, there are no difference in clinical outcome between them.
**Conclusion:** High infiltration of adipocyte was associated with inflammation, metastatic pathways and favorable tumor immune microenvironment, whereas low infiltration of adipocytes was associated with highly proliferative tumor in ER-positive breast cancer. These cancer biologies may explain the reason why adipocyte infiltration high tumors did not demonstrate worse survival.

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Outcomes after sentinel lymph node biopsy and radiation therapy in women over 70 years old with ER+, HER2-, clinically node negative breast cancer

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Overtreatment of early-stage breast cancer with favorable tumor biology in elderly patients can result in higher rates of complications and morbidities without impacting survival. Guidelines directed towards deimplementation of sentinel lymph node biopsy (SLNB) (Choosing Wisely) and radiation therapy (RT) (National Comprehensive Cancer Network) have been recommended. We sought to describe rates and impact on disease recurrence and survival of SLNB and RT in elderly patients with early breast cancer. Patient data were obtained from the cancer registry and electronic health record from University of Pittsburgh Medical Center, multicenter, single health care system. Consecutive female patients aged ≥ 70 with ER+, HER2- clinically node-negative breast cancer within a health care system from 2010 to 2018 were identified. Rates and patient characteristics associated with receipt of SLNB and RT, as well as local recurrence free survival (LRFS) and disease-free survival (DFS) were compared for patients that were diagnosed between 2010 and 2014 to allow for adequate follow up time. Cox proportional hazards regression was used to estimate hazard ratios (HRs) of mortality. Among 3,361 identified women, 2,195 (65.3%) received SLNB and 1,828 (54.4%) received RT. Rates of SLNB steadily increased (1.0% per year); this trend persisted in 2017 and 2018, even after the Society of Surgical Oncology adopted the Choosing Wisely Guidelines in 2016. During the same time period, rates of RT declined (3.4% per year). To examine outcomes, we limited the analysis to 2109 cases from 2010-2014; median (IQR) follow up time was 4.1 (2.5-5.7) years. Median (IQR) age was 77 (73-82) years. 1373 (65.1%) received SLNB and 1,219 (57.8%) received RT. Patients receiving SLNB were younger (P < 0.001) with smaller (P < 0.0001) and lower stage (P < 0.0001) tumors. They had fewer comorbidities (P < 0.001), longer follow-up times (P < 0.001), were less likely on Medicaid/Medicare (P = 0.0091), and were more often seen at an academic center (P < 0.0001). There was no difference in grade between those that did and did not receive SLNB (P = 0.31) and those that did and did not receive RT (P = 0.13). Multivariate cox proportional hazard analysis showed no effect of SLNB on LRFS (HR = 1.17, 95% CI 0.29-4.75, P = 0.83) or DFS (HR = 0.90, 95% CI 0.44-1.83, P = 0.77). Log rank test showed no difference in 5-year LRFS (P = 0.78) between patients who received (98.5%, 95% CI 97.7%-99.7%) and did not receive (98.1%, 95% CI 96.7%-99.5%) SLNB, but an increase was seen with 5-year DFS (P = 0.023), with 96.2% (95% CI 95.0%-97.4%) of patients disease-free among those who did receive SLNB vs. 93.0% (95% CI 90.6%-95.4%) with no SLNB. Multivariate cox proportional hazard analysis showed that RT was associated with improved LRFS (HR = 0.13, 95% CI 0.03-0.51, P < 0.01) and DFS (HR = 0.32, 95% CI 0.15-0.68, P < 0.01). Log rank test showed a difference in 5-year LRFS (P < 0.0001) for those who received RT (99.4%, 95% CI 98.8%-100%) against those who did not (96.5%, 95% CI 95.0%-98.1%), and a similar difference in 5-year DFS (P < 0.0001) in patients who did (97.0%, 95% CI 95.8%-98.1%) and did not (92.4%, 95% CI 90.2%-94.7%) receive RT. Lower age (OR = 0.89, 95% CI 0.87-0.92) and comorbidities (OR = 0.79, 95% CI 0.66-0.94) were associated with receipt of SLNB, while only age (OR = 0.91, 95% CI 0.88-0.94) was associated with receipt of RT. We conclude that receipt of SLNB has no impact upon DFS or LRFS. This data supports deimplementation of SLNB for this patient population. Receipt of RT is important for controlling locoregional recurrence, supporting use of RT in this patient cohort.

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# Safety and efficacy results from the phase 1/2 study of U3-1402, a human epidermal growth factor receptor 3 (HER3)-directed antibody drug conjugate (ADC), in patients with HER3-expressing metastatic breast cancer (MBC)

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**Introduction:** U3-1402 is a novel, investigational ADC directed against HER3, which is widely expressed in breast cancer. Safety and preliminary antitumor activity of U3-1402 was previously reported in this ongoing, phase 1/2 clinical trial (NCT02980341/JapicCTI-163401). Here we report updated safety data from the dose escalation/dose finding (DE/DF) and phase 2 dose expansion parts, and we present for the first time efficacy data for patients in the expansion part with HR+/HER2− MBC with high or low levels of HER3 expression. **Methods:** In DE/DF, U3-1402 was administered intravenously (IV) Q2W or Q3W at doses ranging from 1.6 to 8.0 mg/kg. Patients had HER3-expressing advanced/unresectable disease refractory/intolerant to standard treatment or for which no standard treatment was available. In the expansion part, U3-1402 was administered IV Q3W to patients with HER3-high (4.8 or 6.4 mg/kg) or HER3-low (6.4 mg/kg) HR+/HER2− MBC or with HER3-high triple-negative breast cancer (TNBC; 6.4 mg/kg). Primary objectives included safety and efficacy of U3-1402; secondary objectives included correlative biomarker and pharmacokinetics analyses. Archival or pretreatment tissue obtained in the 6 months prior to U3-1402 treatment was analyzed by IHC for HER3 expression. **Results:** As of March 2020, all 4 expansion cohorts had completed enrollment. In the DE/DF and expansion parts combined, 172 patients received ≥1 dose of U3-1402 (114 [66%] had HR+/HER2− MBC). Median age was 56 y (range, 30-83 y); 123 (72%) and 49 (28%) patients had an ECOG PS of 0 or 1, respectively. Patients received a median of 6 (range, 1-14) prior systemic therapies. Median treatment duration of U3-1402 was 5 mo (range, 1-30 mo). 101 patients (59%) discontinued because of progressive disease, and 15 (9%) discontinued because of an AE. The most common grade ≥3 treatment-emergent AEs reported were decreased neutrophil count (43 patients [25%]), decreased platelet count (39 patients [23%]), decreased white blood cell count (28 patients [16%]), and anemia (31 patients [18%]). Nine patients (5%) experienced treatment-related interstitial lung disease according to central adjudication, including one grade 5 event. At data cutoff, 85 patients in the HR+/HER2− expansion part were evaluable for efficacy by blinded independent central review. Among 33 patients with HR+/HER2− HER3-high MBC treated with 4.8 mg/kg, 10 (30%) had a response (all partial responses [PRs]), with a clinical benefit rate (CBR; complete response + PR + stable disease for ≥6 mo) of 45% (15/33). Among 31 patients with HER3-high MBC treated with 6.4 mg/kg, 3 (10%) had a response (all PR) with a CBR of 16% (5/31). Among 21 patients with HER3-low MBC treated with 6.4 mg/kg, 6 (29%) had a response (all PRs) with a CBR of 33% (7/21). TNBC data are immature at the time of abstract data cutoff; efficacy by HR status will be provided in the presentation. Membrane HER3 expression levels were dynamic; they varied between archival and pretreatment biopsies and decreased on treatment with U3-1402. Across the doses evaluated, the U3-1402 AUC and $C_{max}$ of the total antibody, intact ADC, and released payload were approximately dose proportional, with minimal accumulation after multiple doses; the released payload $C_{max}$ was highest in cycle 1 and decreased in later cycles. **Conclusions:** In this heavily pretreated MBC population, U3-1402 demonstrated clinically meaningful antitumor activity in HR+/HER2− MBC with high or low levels of HER3 expression. The safety profile of U3-1402 was consistent with that previously reported, with 9% of patients discontinuing because of AEs. Clinical data pertaining to patients with TNBC and correlative analyses (including association of HER3 expression with response) will be presented.

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Alternative splicing events from progesterone exposure differ based on BRCA1 mutation status

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**Background**: Progesterone (P) and progestin are instrumental in the breast cancer risk associated with reproductive hormones. Progesterone receptor (PR) signaling has been shown to be inhibited by the wild-type BRCA1 protein and it is hypothesized that if this inhibition is lost, due to gene mutation, potentially tumorigenic consequences may result. Our efforts are focused on understanding the role PR and P play in *BRCA1* mutation carriers. The purpose of this study was to determine if the presence of a *BRCA1* mutation effects alternative splicing (AS) events.
**Methods**: Mammary organoids from 12 patients, six with a *BRCA1* mutation and six without (WT, control), were cultured *in vitro*. The organoids from each patient were divided into two groups and treated over the course of 28 days to mimic a normal menstrual cycle. One group was treated was estradiol and progesterone (EP) while the other was treated with EP and the PR antagonist telapristone acetate (TPA) to identify PR-mediated effects. After treatment, RNA was extracted from both groups and RNA-sequencing performed. A statistical model, “replicate Multivariate Analysis of Transcript Splicing” (rMATS) was employed to identify AS events. Output from rMATS was then entered into “RNA Map Analysis And Plotting Server” (rMAPS) to identify RNA-binding proteins (RBP) motifs in the region of the splices. Droplet digital PCR (ddPCR) from Bio-Rad was employed, with the use of Evagreen intercalating dye, to validate a subset of the AS events identified by the RNA-Seq data. RNA from eight of the EP treated samples was reverse transcribed and ddPCR performed. The data was analyzed using QuantaSoft Analysis Pro (Bio-Rad). The identified AS events were validated additionally using data generated from solid tissue normals (STN) from premenopausal, *BRCA1*$^{mut}$ and *BRCA1*$^{WT}$ patients, who developed breast cancer, which was available for download from The Cancer Genome Atlas (TCGA).
**Results**: Genes involved in the epithelial-mesenchymal-transition (EMT), progesterone metabolism, and cellular proliferation are significantly differentially spliced in the EP treated *BRCA1*$^{mut}$ tissue (p-value < 0.01 and FDR < 5%) and absent in those with TPA treatment, suggesting the AS is a PR-mediated effect. *CD44*, associated with cellular proliferation and migration, *NCOR2* associated with tamoxifen resistance, and *AKR1C2* associated with progesterone metabolism all showed significant skipped exon (SE) events. Exon 11 in *CD44* and exon 45 in *NCOR2* were skipped in both the *BRCA1* organoids as well as in *BRCA1* STN from TCGA. Skipping of Exon 4 in *AKR1C2* was validated using the ddPCR: the *BRCA1*$^{mut}$ organoids displayed two isoforms, indicative of a skipped exon.
**Conclusions**: PR-mediated alternative splicing events differ in mammary organoids of *BRCA1* carriers compared to non-carriers. We hypothesize that the skipping of Exon 4 of *AKR1C2* in *BRCA1*$^{mut}$ results in a structural alteration that decreases protein activity, leading to increased concentrations of P4 and 5α-pregnane-3,20-dione. This may explain the previously reported high median luteal phase serum P levels (p=0.00034) in BRCA1$^{mut}$/BRCA2$^{mut}$ (PMID: 24140203).

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# Vadis trial: Phase II trial of nelipepimut-s peptide vaccine in women with DCIS of the breast

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**Background:** Peptide cancer vaccines may be most effective when used in earlier stage cancers or pre-cancers where systemic and tumor microenvironmental immune suppression are less profound. Nelipepimut-S (NPS) plus granulocyte-macrophage colony-stimulating factor (GM-CSF) is a vaccine comprised of a human leukocyte antigen (HLA) restricted peptide from the extracellular domain of the HER2 protein (E75) combined with GM-CSF. We have completed a randomized phase II trial of preoperative vaccination with NPS+GM-CSF vs. GM-CSF alone with the primary outcome being NPS-specific cytotoxic T lymphocyte (CTL) responses.
**Methods:** HLA-A2 positive, DCIS patients were enrolled and randomized to either NPS+GM-CSF vs GM-CSF alone. The patients received two vaccinations prior to surgery at 2-week intervals. The number of NPS-specific CTL was measured at specified intervals (pre-vaccination, time of surgery, 1 month (+/- 7 days) post-op, and 3 months (+/- 7 days) post-op) using a flow cytometry-based dextramer assay. Differences in NPS-specific CTL responses between the two groups and between baseline pre-vaccination and 1-month post-op were analyzed using either a two-sample t-test or Wilcoxon rank sum test, when appropriate. The incidence and severity of adverse events, graded according to Common Terminology Criteria for Adverse Events (CTCAE) version (v) 4.03, were recorded and compared between treatment groups.
**Results:** 45 patients were registered; 7 withdrew consent, 1 opted for surgery at an external facility, 20 were ineligible due to negative HLA-A2, and 4 failed screening for other reasons, leaving 13 patients enrolled. The 13 patients were randomized (2:1) into treatment groups, with nine patients receiving NPS+GM-CSF and four patients receiving GM-CSF alone. The two groups were well-matched for age; however, the GM-CSF alone group had higher percentages of African American (50% vs. 22%) and Hispanic (25% vs. 11%) patients as compared to the NPS+GM-CSF group. In general, vaccination was well-tolerated with similar treatment-related toxicity profiles in the NPS+GM-CSF vs GM-GSF groups (Grade 1 - 93.3% vs. 89.3%, Grade 2 - 6.7% vs. 10.7%, respectively). The mean NPS-specific CTL% in the NPS+GM-CSF group at 1-month post-op was double that of the GM-CSF alone group (0.10 +/- 0.12% vs. 0.05 +/- 0.08, p=0.70). In addition, between baseline pre-vaccination and 1-month post-op, the NPS+GM-CSF group experienced an 11-fold increase in percentage of NPS-specific CTL (0.01 +/- 0.02% vs. 0.11 +/- 0.12%) as compared to only a 2.25-fold increase of NPS-specific CTL in the GM-CSF alone group (0.04 +/- 0.07% vs. 0.09 +/- 0.15%).
**Conclusions:** NPS+GM-CSF is safe and well-tolerated when given preoperatively to patients with DCIS. In HLA-A2 positive patients with DCIS, a single inoculation with NPS+GM-CSF can induce in vivo immunity and a continued antigen-specific T-cell response one month post-surgery. This data provides support for further testing of NPS+GM-CSF in the neoadjuvant and adjuvant settings in an attempt to prevent invasive recurrence in DCIS.

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Mouse-intraductal (MIND): The first in vivo model to recapitulate the full spectrum of human DCIS pathology

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**Introduction.** Due to advances in imaging technology and an increase in mammographic screening, there has been a significant increase in the diagnosis rate of ductal carcinoma in situ (DCIS). At the present time, nearly all women undergo surgical removal of DCIS, often followed by adjuvant radiation and in some cases anti-hormonal therapy. Currently, there are no means by which to diagnose DCIS accurately, or to predict which patients benefit from aggressive therapy. Thus, the recommendation for surgery persists, despite studies which support that not all DCIS will subsequently progress to invasive disease. In this context, animal models can be particularly useful in studying DCIS progression. Here, we present the first *in vivo* model of DCIS, referred to as Mouse-INtraDuctal (MIND), in which patient-derived DCIS epithelial cells are injected intraductally and allowed to progress naturally in mice. **Methods.** We performed intraductal injection of DCIS epithelial cells derived from 30 patient samples into 194 total glands. Of the 194, 146 xenografts showed *in vivo* growth, for a 75% take rate). Among the DCIS samples injected into mice, 18 (103 mouse mammary glands) were followed for a median of 9 months . Among those, 50% (9) showed invasive progression while 50% (9) remained non-invasive. DCIS invasive progression was evaluated by performing immunofluorescene staining using anti-smooth muscle actin (SMA) antibody and confirmed by the loss of SMA around the xenografted DCIS like lesions on 3 consequetive sections of FFPE tissues. **Results.** Progressed xenografts exhibited invasive progression, evident by the loss of SMA, as early as 6 months following transplantation. Similar to human DCIS, the cancer cells initially formed *in situ* lesions inside the mouse mammary ducts and mimicked all histologic subtypes including micropapillary, papillary, cribriform, solid and comedo. Among the biomarkers tested, including ER, PR, Ki67, HER2, p53, histology, nuclear and tumor grade, only low ER & PR expression and extent of DCIS growth in xenografts significantly correlated with invasive progression. A high depth targeted sequencing platform (T200) on DNA isolated from LCM captured DCIS of patient and xenograft pairs identified shared (i.e., EGFR) as well as unique (STK11, RUNX1, PIK3CA) mutations in patient/xenograft pairs. Notably, we also observed private mutations that were not shared within the same patient/xenograft pairs. These results indicate the presence of DCIS clonal heterogeneity and that DCIS xenografts may represent one or more clonal subpopulations of patient DCIS. **Conclusion.** The MIND model represents the first realistic *in vivo* model that recapitulates human DCIS progression in a manner that represents the inter- and intra-tumoral heterogeneity of human disease. These innovative mouse models will be invaluable for the discovery of molecular signatures of invasive DCIS by allowing comparison of xenografts with variable propensity for invasive progression. These models will enable the discovery of extrinsic factors that regulate DCIS malignancy as well as testing of pharmaceutical and natural compounds for prevention of DCIS progression to invasive disease.

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An AI-digital breast cancer risk discrimination platform (PreciseDx) using a representative H&E image and selected clinical variables accurately categorized patients with oncotype Dx low risk recurrence scores (RS)

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Background: Clinical practice guidelines emphasize the critical importance of grading and stage in breast cancer treatment. Although histologic grade is subjective, non-quantitative, skill-dependent, and oftentimes inaccurate it remains an independent prognostic feature and therefore plays a direct role in patient management including neoadjuvant therapy vs surgery, and interpretation of genomic studies. We developed an AI-based platform which combines digital H&E features with select clinical variables to assess risk of breast cancer recurrence and evaluated ability to predict Oncotype low risk RS categorization. Methods: Retrospective study to identify a subset of Mt. Sinai, NY invasive ductal breast cancer (IDC) patients from 2010-2016 with H&E stained slides, clinical features and OncotypeDx recurrence scores (RS). Recurrence endpoint(s): local- regional, distant-recurrence free and overall survival. Digital images generated with Philips scanning system; reviewed by two pathologist for tumor content and quality prior to image analysis and feature extraction. Support vector machine learning models were used for initial feature performance and final models generated. Positive predictive value (PPV), sensitivity (S) and likelihood ratios (LR) were used for performance. Results: 391 patients: mean age 57 years, 100% Stage I/II, 59% Grade 2, and 6% LN+ve 0-3; 97% IDC, 100% ER+ve, 94% PR+ve, 0% Her2 amplified; median follow-up 61 months; 323 (83%) low risk (</=25) RS and 68 (17%) high risk RS (>25). There were 23 events (6%) and 13 (56%) were locoregional recurrence. PreciseDx model with age, and PR levels combined with imaging features reflective of mitotic activity and nuclear characteristics (clinical grade not selected) correctly identified LR RS categorization: PPV of 91%, [95CI 0.87-0.94], Se 92% [0.86-0.95] and positive / negative likelihood ratio : 6.8, and 0.5, respectively. Conclusions: Application of an AI-digital breast cancer risk assessment platform using only the H&E image and limited clinical data successfully classified low risk RS patients with high accuracy. Future models will extend outcome to 10 years and evaluate treatment selection and duration

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# Herpet study- PET imaging of HER2 expression in breast cancer using the novel Affibody tracer [18F]GE-226, a first in patient study

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**Background** 20% of breast cancers have over-expression of the human epidermal growth factor receptor-2 (HER2), which is an adverse prognostic factor and used to guide therapy selection. At present HER2 expression can only be determined using biopsy material which is then analysed using immunohistochemistry or fluorescence in situ hybridisation. GE-226 is a radiolabelled Affibody® tracer which binds to the HER2 receptor with high affinity at a different epitope than trastuzumab. Heterogeneous expression does exist but the impact this has on treatment response has not been well assessed. A non-invasive method for determining HER2 expression could have several advantages and help select appropriate therapy for patients.
**Trial Design**Patients with locally advanced or metastatic breast cancer were recruited and scanned for 65 mins after iv injection of 200MBq (mean activity injected for each patient 198 MBq (range 164-219MBq), mean radiochemical purity 94.6%) of tracer, with one dynamic bed position, and then a half-body scan was performed. Blood sampling was used to measure metabolism of the tracer. Safety was recorded. HER2-extracellular domain (ECD) domain was measured in blood. The original accrual target was 16 patients. Tumoural uptake was quantified by semi-quantitative and fully quantitative parameters in HER2 positive and HER2 negative tumours.
**Results**Thirteen patients were recruited. Scans were well tolerated. There were no serious adverse events. GE-226 was metabolised into a single metabolite in the liver. 96.8 % parent remained at 60 minutes post injection. There was a significant difference between HER2 positive and HER2 negative tumoural uptake of tracer as measured by $SUV_{mean}$ and $SUV_{max}$ ($p<0.05$). Comparing HER2 positive to HER2 negative cases, there was also a significant difference between tumour to normal tissue uptake ratios ($p<0.05$). Heterogeneous uptake was observed in the same patient. Tumoural uptake increased over time. Uptake in salivary glands and the thyroid gland was noted. In one patient GE-226 was able to differentiate between lymphadenopathy due to sarcoidosis and cancer and was superior to FDG which had shown widespread uptake in the same patient.
**Conclusions**[18F]GE-226 imaging is well tolerated and shows promise for imaging of HER2 positive breast cancer. Further studies with this agent are now planned.

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Patient-reported outcomes of adolescents and young adults with breast cancer treated with curative intent

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**Purpose**: To evaluate patient-reported outcomes of adolescents and young adults (AYAs) with breast cancer treated with curative intent.
**Methods**: AYA breast cancer patients (defined as diagnosed between 18 to 39 years of age) treated at a large tertiary cancer centre between January 2014 and December 2016 were identified. Patients routinely complete the validated symptom screening tool, the Edmonton Symptom Assessment System-revised (ESAS-r) prior to their clinical encounter. Scores from diagnosis up to 24 months post-diagnosis were obtained from our internal database, with elevated scores defined as $\geq$ 4 for each individual symptom (rated 0-10). Patient, clinical and treatment characteristics were extracted from medical records. Descriptive statistics were used to describe patient, clinical and treatment characteristics, and ESAS-r scores. Time to recurrence was calculated from diagnosis to local or regional recurrence, distant metastasis or death (whichever occurred first). Kaplan-Meier survival analysis and log-rank tests were used to compare time to recurrence between women with vs. without elevated symptom scores. Chi-squared test was used to test the change in number of patients with elevated symptom scores over time. Univariable and multivariable logistic regression models were carried out to assess association between various factors and ESAS-r symptoms of depression, anxiety and well-being within 24 months of diagnosis.
**Results:** Among 258 patients identified, 211 (82%) had accompanying ESAS-r and were eligible for analysis. Median follow-up was 3.9 years. Median age at diagnosis was 35 (20-39), most were clinical stage 2/3 at diagnosis (63%), 20% had triple negative disease, 76% received chemotherapy and 81% received radiotherapy. Overall, symptom burden was the highest (scores $\geq$ 4) for decreased well-being (52%), tiredness (48%) and anxiety (44%). Although symptom burden significantly improved over time, 43%, 38% and 33% of patients, respectively, reported elevated symptoms 24 months post-diagnosis. Multivariable analysis found that elevated anxiety was significantly associated with younger age at diagnosis (p=0.036), receipt of chemotherapy (p=0.01) and presence of long-term toxicity (p=0.0032). Elevated depression, anxiety and well-being were significantly associated with referral to Psychosocial Oncology (p=0.024, p=0.036 and p=0.019, respectively), whereas well-being was also associated with referral to Survivorship Clinic (p=0.043). However, overall rates of referral (24-36%) were much lower than symptom prevalence. There was no association between elevated symptoms and time to recurrence.
**Conclusion:** AYAs diagnosed with breast cancer report high symptom burden that continues to persist up to 24-months post-diagnosis. Patients with elevated psychosocial distress are more likely to be referred to Psychosocial Oncology and Survivorship clinics, indicating that the ESAS-r is a useful screening tool in a real-world setting. However, a gap between symptom burden and intervention exists, providing opportunities for future research.

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High tumor mutational burden (>=10 mut/Mb) is enriched in specific breast cancer pathological subtypes

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**Background**: Pembrolizumab recently received pan-tumor FDA approval for the treatment of patients with unresectable or metastatic solid tumors with tumor mutational burden (TMB) ≥10 mutations per megabase (mut/Mb) and who have no satisfactory alternative treatment options. The KEYNOTE-119 and TAPUR trials have validated TMB as a predictive biomarker using TMB cutoffs of ≥ 10 mut/Mb and 9 mut/Mb, respectively, for benefit from single-agent pembrolizumab in subsets of patients with clinically advanced breast cancer (aBC). Limited data exist on which pathological subtypes of aBC are most likely to be TMB ≥10 mut/Mb (TMB-High). This study analyzed the frequency of TMB-High tumors in aBC subtypes to evaluate variations between subtypes and correlation with additional immunotherapy biomarkers. **Methods**: Utilizing the Foundation Medicine breast cancer database, 5,475 samples with aBC and pathological subtype information were identified. Pathological subtypes included in this study were ER+/HER2-negative invasive ductal carcinoma (IDC), ER-negative/HER2+ IDC (HER2+), triple negative IDC (TNBC), invasive lobular, inflammatory, metaplastic, mucinous and papillary. TMB was determined on 0.8-1.1 Mb of sequenced DNA, and microsatellite instability (MSI) was assessed across 114 loci in 564 cases. PD-L1 was determined in a subset of cases by immunohistochemistry (Ventana SP142). **Results**: TMB-High (≥10 mut/Mb) was common in all breast cancer pathological subtypes except papillary carcinoma (Table 1). TMB-High was most often found in lobular, inflammatory and HER2+ carcinomas (16%, 14% and 12% of cases, respectively). Metaplastic, mucinous and papillary subtypes were least likely to be TMB-High (7%, 7% and 0% of cases, respectively). TMB-High was more common than MSI-High in all subtypes, excluding papillary. Emerging biomarkers that may play a role in mitigating immunotherapy response, such as *MDM2* amplifications and *STK11* alterations, were observed in most subtypes. The frequencies of these alterations, as well as alterations associated with FDA-approved therapies in breast cancer, are provided in Table 1 and will be further discussed. **Conclusions**: TMB-High (≥10 mut/Mb) is common in most pathological subtypes of clinically advanced breast cancer and can identify patients not identified by MSI or PD-L1 testing who may benefit from immunotherapy. Based on the high percentage of advanced breast cancer patients who are TMB-High or have genomic alterations in other biomarkers associated with FDA-approved targeted therapies, comprehensive genomic profiling including TMB and MSI should be considered for all pathological subtypes.

Table 1

| **Pathological subtype** | Invasive ductal carcinoma (IDC) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **ER+, HER2-negative** | **ER-negative, HER2+** | **Triple-negative (TNBC)** | **Invasive Lobular Carcinoma** | **Inflammatory** | **Metaplastic** | **Mucinous** | **Papillary** |
| Cases (n) | 1,237 | 1,953 | 641 | 1,180 | 35 | 389 | 29 | 11 |
| Age | 55 (23-89) | 55 (20-89) | 53 (20-85) | 62 (24-89) | 54 (28-87) | 59 (28-89) | 55 (30-80) | 61 (38-78) |
| **Tumor mutational burden (TMB)** | | | | | | | | |
| TMB ≥ 10 mut/Mb | 8% | 12% | 9% | 16% | 14% | 7% | 7% | 0% |
| TMB ≥ 20 mut/Mb | 2% | 2% | 3% | 7% | 6% | 2% | 3% | 0% |
| **Additional immunotherapy biomarkers** | | | | | | | | |
| MSI-High | 0.2% | 0.1% | 0.4% | 0% | 0% | 0% | 0% | 0% |
| PD-L1+ (≥1% Ventana SP142) | N/A | N/A | 47% | N/A | N/A | 26% | 0% | N/A |
| *MDM2* amplification | 6% | 5% | 3% | 2% | 0% | 2% | 3% | 18% |
| *STK11* alteration | 1% | 1% | 2% | 1% | 3% | 3% | 3% | 0% |
| **Additional biomarkers associated with FDA-approved therapies** | | | | | | | | |
| *BRCA1/2* alteration | 3%/6% | 2%/3% | 7%/3% | 1%/4% | 6%/6% | 4%/3% | 3%/0% | 0%/9% |
| *ERBB2* amplification | 0% | 100% | 0% | 3% | 26% | 3% | 34% | 9% |
| *NTRK 1/2/3* rearrangement | 0%/0%/0% | 0%/0%/0% | 0%/0%/0% | 1%/0%/0% | 0%/0%/0% | 0%/0%/1% | 0%/0%/0% | 0%/0%/0% |
| *PIK3CA* alteration | *38%* | *38%* | *19%* | *56%* | *34%* | *38%* | *21%* | *36%* |

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# Novel chimeric small molecule AC682 potently degrades estrogen receptor with oral anti-tumor efficacy superior to fulvestrant

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Modulation of estrogen activity and/or synthesis has been the mainstay therapeutic strategy for estrogen receptor (ER)-positive breast cancer. Fulvestrant, which provides superior clinical benefit over aromatase inhibitors and selective ER modulators, achieves its potent ER signaling inhibition through unique ER degradation activity beyond direct antagonism. Despite this superiority, the efficacy of fulvestrant appears limited by poor drug exposure through intramuscular injection. Up to 50% of ER baseline levels remained after 6 months of fulvestrant treatment. Therefore, an oral ER degrader with optimal pharmacokinetic profile may lead to better convenience and efficacy than fulvestrant. Here we report preclinical characterization of our novel oral ER degrader development candidate, AC682, a chimeric small molecule containing both ligands of ER and E3 ligase discovered with our ACCU-Degron technology. Through engaging E3 ligase and ER simultaneously, AC682 induced potent ER degradation with a sub-nanomolar half-maximal degradation concentration ($DC_{50}$) in multiple ER-positive breast cancer cell lines tested, including a tamoxifen-resistant long-term estrogen deprived (LTED) cell line and cell lines expressing clinically-relevant ESR1 variants (Y537S and D538G). Proteasome-dependent ER degradation by AC682 peaked after a few hours of treatment, resulting in diminished expression of ER-regulated genes and subsequent cell growth inhibition. In the *in vivo* setting, oral dosing of AC682 achieved substantial drug exposure and oral bioavailability, with well tolerance in multiple animal species. In estradiol-dependent MCF7 xenograft tumors, oral daily dosing of AC682 led to dose-dependent tumor growth inhibition/regression and concomitant tumor ER protein reduction more than 90% at study termination. In particular, 3 mg/kg oral daily dosing achieved tumor stasis. When administrated in combination with CDK4/6 inhibitor Palbociclib, AC682 showed clear synergy in both the estradiol-dependent MCF7 model and a tamoxifen-resistant MCF7 model. In a patient-derived xenograft model, which bears ESR1 Y537S mutation and is hormone-independent, AC682 significantly inhibited tumor growth whereas fulvestrant only showed weak efficacy. In conclusion, oral chimeric ER degrader AC682 demonstrated robust ER degradation and anti-tumor efficacy in preclinical models, supporting its continued investigation in the clinic.

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# Targeting depressive symptoms in younger breast cancer survivors: A randomized controlled trial of mindfulness meditation and survivorship education

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**Purpose** Breast cancer before age 50 comprises 25% of incident breast cancer cases in women. Younger breast cancer survivors (YBCS) are at increased risk for the negative effects of cancer diagnosis and treatment, including elevated levels of depression and related symptoms (i.e., anxiety, stress, fatigue, sleep disturbance, vasomotor symptoms), leading to significantly diminished quality of life. **Patients and Methods** This Phase III, randomized, multi-institution trial was designed to examine the efficacy of two brief interventions- mindfulness meditation and survivorship education - for YBCS (ClinicalTrials.gov NCT03025139). We recruited women diagnosed at age 50 or younger with early-stage breast cancer who had completed cancer treatment between 6 months and 5 years earlier and endorsed at least mild depressive symptoms. Participants were randomly assigned to Mindful Awareness Practices (MAPs), Survivorship Education (SE), or wait-list control (WL). Both intervention programs were tailored for YBCS and included 6 weeks of structured content delivered in a group format. Assessments were conducted at baseline, post-intervention, and at 3- and 6-month post-intervention follow-ups. The primary outcome was depressive symptoms (Center for Epidemiologic Studies Depression scale; CESD) at post-intervention; secondary outcomes included anxiety (Generalized Anxiety Disorder-7), fatigue severity (Fatigue Symptom Inventory), sleep disturbance (Insomnia Severity Index), and hot flashes (BCPT symptom checklist). **Results** We enrolled and randomized 247 women (85 MAPS, 81 SE, 81 WL). On average, participants were 45.4 years old at study entry and had been diagnosed 2.6 years earlier. Linear mixed models were conducted to compare each intervention group to WL on primary and secondary outcomes, controlling for baseline differences across groups in study site, race, and marital status. MAPs led to significant reductions in depressive symptoms at post-intervention and at 3- and 6-month follow-up relative to WL ($P$s < .01); see Table 1. SE also led to significant reductions in the CESD at post-intervention and 3-month follow-up ($P$s < .01). Both MAPs and SE produced reductions in anxiety at post-intervention relative to WL ($P$s < .05), though effects did not persist over follow-up. MAPs also had beneficial effects on other secondary outcomes, yielding significant decreases in fatigue severity, sleep disturbance, and hot flashes that persisted over the 6-month follow-up ($P$s < .05). In contrast, there was minimal evidence that SE impacted these outcomes. **Conclusion** Two brief behavioral intervention programs specially designed for YBCS were effective in reducing depressive symptoms and, in the case of mindfulness, improving related symptoms (fatigue, sleep disturbance) that pose serious threats to younger women's health and well-being after cancer. These interventions are standardized, manualized, and have the potential for wide dissemination over virtual platforms. **Table 1** Adjusted means and standard error (SE) for CESD depressive symptoms by group and time, controlling for study site, race, marital status. A CESD score of 16 or greater indicates moderately severe depressive symptoms. P-values are for differences between intervention and waitlist control groups in change over time between Baseline and Post-Intervention (1-2), Baseline to 3-month Follow-up (1-3), and Baseline to 6-month Follow-up (P 1-4).

| | **Baseline** | **Post-intv** | ***P* (1-2)** | **3 mo FU** | ***P* (1-3)** | **6 mo FU** | ***P* (1-4)** |
|---|---|---|---|---|---|---|---|
| **Group** | CESD | CESD | | CESD | P | CESD | |
| Mindful Awareness Practices (MAPs) | 18.4 (1.0) | 13.6 (1.1) | .001 | 13.4 (1.1) | <.001 | 12.9 (1.1) | .013 |
| Survivorship Education (SE) | 17.4 (1.1) | 13.3 (1.1) | .007 | 13.6 (1.2) | .003 | 12.7 (1.2) | .063 |
| Waitlist (WL) | 16.5 (1.1) | 16.3 (1.1) | | 17.3 (1.2) | | 14.6 (1.1) | |

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Impact of neratinib on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: Findings from the phase 3 NALA trial

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**Background:** The development of central nervous system (CNS) metastases presents a considerable challenge in metastatic breast cancer (MBC) due to the limited availability of evidence-based treatments. Up to 50% of patients with HER2-positive (HER2+) MBC develop CNS metastases during the course of their disease. Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, has demonstrated activity against CNS metastases in HER2+ MBC in two phase 2 studies (NEfERT-T, TBCRC 022) and one phase 3 study (NALA); significant benefits for predefined CNS endpoints were reported in NEfERT-T and confirmed in NALA. Here we present an exploratory analysis of patients from NALA with CNS involvement at enrollment.
**Methods:** NALA was an international, randomized, open-label, active-controlled, phase 3 study in patients with HER2+ MBC who had received ≥2 lines of HER2-directed therapy in the metastatic setting (ClinicalTrials.gov: NCT01808573). Patients with asymptomatic metastatic brain disease managed with stable doses of corticosteroids for ≥14 days prior to randomization were eligible, whereas patients with symptomatic or unstable brain metastases were excluded. Patients were randomized (1:1 ratio) to neratinib (N; 240 mg qd po) + capecitabine (C; 750 mg/m$^2$ bid po) or lapatinib (L; 1250 mg qd po) + C (1000 mg/m$^2$ bid po). Co-primary endpoints were centrally assessed progression-free survival (PFS) and overall survival (OS). Intervention for symptomatic metastatic CNS disease was a secondary endpoint. CNS disease at baseline was defined as patients with treated or untreated disease in the 'brain' assessed by investigator at enrollment. CNS imaging was not mandatory at screening.
**Results:** Of the 621 patients enrolled in NALA, 101 (16%) had documented baseline CNS disease and 520 (74%) had no CNS disease at baseline. Patients with CNS disease had a lower performance status and were more likely to have hormone receptor-negative disease than those with no CNS disease; no major imbalances of baseline characteristics were noted between treatment arms. Overall, 78 (77%) patients had previously received CNS radiation [whole brain, n=59 (58%); stereotactic, n=17 (17%); unknown, n=2 (2%)], and 5 (5%) patients had undergone CNS surgery. Median treatment duration was 5.7 (IQR 2.8-8.5) months for N, and 3.5 (IQR 2.1-6.9) months for L. PFS, OS, and cumulative incidence of interventions for symptomatic CNS disease are summarized in the table. No new safety signals were detected.
**Table.** Efficacy outcomes in patients with and without CNS disease at baseline

| | **Intention-to-treat (n=621)** | | **CNS metastases at baseline - Yes (n=101)** | | **CNS metastases at baseline - No (n=520)** | |
|---|---|---|---|---|---|---|
| | **N+C (n=307)** | **L+C (n=314)** | **N+C (n=51)** | **L+C (n=50)** | **N+C (n=256)** | **L+C (n=264)** |
| **PFS[a]** | | | | | | |
| Hazard ratio (95% CI) | 0.76 (0.63-0.93) | | 0.66 (0.41-1.05) | | 0.76 (0.62-0.94) | |
| P-value | 0.0059 | | 0.0741 | | 0.0099 | |
| Restricted mean PFS[b], months | 8.8 | 6.6 | 7.8 | 5.5 | 9.0 | 6.9 |
| Difference, months | 2.2 | | 2.3 | | 2.1 | |
| **OS** | | | | | | |
| Hazard ratio (95% CI) | 0.88 (0.72-1.07) | | 0.90 (0.59-1.38) | | 0.85 (0.68-1.06) | |
| P-value | 0.2086 | | 0.6352 | | 0.1517 | |
| Restricted mean OS[b], months | 24.0 | 22.2 | 16.4 | 15.4 | 25.6 | 23.6 |
| Difference, months | 1.7 | | 1.0 | | 2.0 | |
| **Incidence of CNS intervention** | | | | | | |
| Overall cumulative incidence[c], % | 22.76 | 29.19 | 40.13 | 47.79 | 19.16 | 24.65 |
| P-value | 0.043 | | 0.430 | | 0.067 | |

[a]Centrally confirmed; [b]Restriction prespecified as 24 months for PFS, and 48 months for OS; [c] % requiring intervention for CNS disease (competing risk model)

**Conclusions:** Regardless of the status of CNS metastases at baseline, patients appeared to have better outcomes in the N+C arm compared with the L+C arm.

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# Telemedicine usability for cancer care during the COVID-19 pandemic

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**Background** Healthcare delivery via telemedicine has increased substantially amid COVID-19. The George Washington Cancer Center (GWCC) now provides cancer care services via tele-visits for patients at high risk of morbidity and mortality secondary to COVID-19. This study was performed to assess usability of virtual cancer care delivery for patients and providers across specialties.
**Methods** Participants included patients and providers surveyed to assess baseline usability after initiating tele-visits. Surveys included demographics, Telehealth Usability Questionnaire (TUQ), and questions on perceived safety and preferences around telemedicine. Subjects also provided open-ended feedback for quality improvement.
**Results** For patients (n=133), 93% of surveys sent were completed and analyzed. Most patients were between ages 60-69 (26%), 70-79 (24%), 50-59 (22%). Breast cancer (41%) was the most commonly reported cancer type. Mean patient TUQ scores based on a 5-point scale (1-strongly disagree, 5 - strongly agree) were: 4.4 for Interface Quality (IfQ), 4.3 for Ease of Use (EU), 4.2 for Usefulness (U) and Satisfaction (S), 4.1 for Interaction Quality (ItQ), 3.4 for Reliability (R). No association was found between mean TUQ scores and age groups (p=0.33), sex (p=0.79), timing of diagnosis in relation to telemedicine visit (p=0.67), stage of diagnosis (p=0.98), or treatment type (p=0.65). However, patients with more telemedicine visits did score significantly higher in Reliability (P=0.018) and Satisfaction (P=0.039), compared to those with fewer telemedicine visits.
Compared to in-person visits, 77% of patients agreed/strongly agreed that telemedicine made them feel safer, 75% agreed/strongly agreed that it reduced stress, and 72% expressed interest in using it with other medical specialties.
For providers (n=109), 84% of surveys sent were completed and analyzed. Most providers were between ages 30-39 (33%) or 40-49 (21%), and 41% had 50 or more experiences with telemedicine. The predominant specialty participating was Internal Medicine (27%). Mean provider TUQ scores were 4.3 for U, 4.1 for S, 3.8 for EU, 3.7 for ItQ, 3.6 for IfQ, and 2.7 for R. No association was found between mean TUQ scores and experience with telemedicine (p=0.31), age groups (p=0.06), or specialty (p=0.53). However, providers with more experiences with telemedicine scored significantly higher in Satisfaction (p=0.01) and Usefulness (p=0.02).
The majority of providers (97%) agreed/strongly agreed that telemedicine improves access to care, yet 59% expressed concern about missing something they may have caught in person. Furthermore, older providers generally had lower reliability scores compared to younger providers (p=0.03), and also showed generally greater concern about losing personal interface with patients with the use of telemedicine than younger providers (p= 0.006).
**Conclusion**
The utility of telemedicine in cancer care during the COVID-19 pandemic was perceived favorably by both patients and providers. All patient groups scored highly on perceived safety, reduced stress and improved access, independently of subject characteristics. Older providers were more wary of the reliability of telemedicine and its effects on patient-provider relationships. These findings provide a useful benchmark for advancement of virtual care delivery in cancer care, beyond the COVID-19 pandemic.

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# Tumour infiltrating lymphocytes of prognostic value in different molecular breast cancer subgroups and as a suggestive predictive factor for adjuvant tamoxifen benefit in premenopausal patients after 30 years follow-up

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**BACKGROUND** The molecular breast cancer subgroups comprise diverse immune biology; for human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC) and triple-negative breast cancer (TNBC) abundance of tumour infiltrating lymphocytes (TILs) have been shown to indicate good prognosis and could predict pathological complete response after neoadjuvant chemotherapy. In contrast, the clinical relevance of TILs in estrogen receptor-positive/HER2-negative (ER+/HER2-) tumours is not settled. We primary aimed to analyse the prognostic effect of TILs on BC-free interval (BCFi) in premenopausal patients, stratified by molecular subgroups. The secondary aim was to investigate the predictive value of TILs on tamoxifen benefit.
**METHODS** Archival tissue from primary tumours was collected from patients included in the SBII:2pre trial. In this study, 564 premenopausal women were randomised between two years of adjuvant tamoxifen or no systemic treatment regardless of hormone-receptor status. TILs were scored on whole tissue sections and the tumours were divided into ER+/HER2- (n = 255), HER2+ (n = 65) and TNBC (n = 95) molecular subgroups by immunohistochemistry and *in situ* hybridisation (ISH). The prognostic value of TILs was evaluated in patients allocated to no systemic therapy, whose tumours were successfully scored for TILs and had IHC/ISH data for generating molecular subgroups (n = 221). All patients with ER+ tumours and successfully annotated TILs were considered for prediction of tamoxifen benefit (n = 321). The median follow-up was 28 years and the prognostic and predictive analyses were performed by cumulative incidence curves and Cox regression analyses.
**RESULTS** TILs were successfully scored in 477 tumours with available ER status and the proportion of low (<10%), intermediate (10-49%) and high (≥50%) TILs were 52% (n = 248), 33% (n = 157) and 15% (n = 72), respectively. High infiltration of TILs was a favourable prognostic factor (univariable analysis: hazard ratio$_{BCFi}$ ($HR_{BCFi}$) 0.40; 95% confidence interval (CI) 0.22-0.71; $P$ = 0.002) (Table 1). The results were essentially the same in the ER+/HER2- molecular subgroup ($HR_{BCFi}$ 0.40; 95% CI 0.14-1.09; $P$ = 0.07). Adjuvant tamoxifen improved prognosis in patients with ER+ tumours and TILs levels <50%, (univariable analysis $HR_{BCFi}$ 0.63; 95% CI 0.47-0.84; $P$ = 0.002), which was not observed in patients displaying high immune infiltration (≥50%) ($HR_{BCFi}$ 0.84; 95% CI (0.24-2.86); $P$ = 0.77). However, evidence for differential effect of tamoxifen in categories of TILs, i.e. interaction, was weak.
**CONCLUSIONS** We demonstrate a long-term favorable prognostic value of levels of TILs in a cohort of premenopausal BC patients. This effect seems to be extended to the ER+/HER2- subgroup. A beneficial effect of tamoxifen in ER+ patients was observed in patients with tumours of low TILs infiltration as compared to patients with tumours of high immune infiltration, but we could not confirm a treatment predictive effect.

Table 1. Uni- and multivariable Cox regression analyses of BCFi and OS (control arm)

| | **Univariable*** | | **Multivariable** | |
|---|---|---|---|---|
| **Endpoint** | **BCFi** | **OS** | **BCFi** | **OS** |
| | **HR (95% CI); *P* value** | | | |
| **TILs, category***** | | | | |
| **All molecular subgroups** | (n = 221) | | (n = 213) | |
| Low (Ref.) | 1.00 | 1.00 | 1.00 | 1.00 |
| Intermediate | 1.10 (0.78-1.54); 0.61 | 1.26 (0.88-1.80); 0.21 | 0.61 (0.40-0.93); 0.02 | 0.65 (0.41-1.02); 0.06 |
| High | 0.40 (0.22-0.71); 0.002 | 0.52 (0.29-0.95); 0.03 | 0.22 (0.11-0.43); <0.001 | 0.23 (0.11-0.48); <0.001 |
| **ER+/HER2-** | (n = 136) | | (n = 135) | |
| Low (Ref.) | 1.00 | 1.00 | 1.00 | 1.00 |
| Intermediate | 1.02 (0.63-1.64); 0.94 | 1.02 (0.61-1.71); 0.95 | 0.69 (0.42-1.15); 0.16 | 0.65 (0.37-1.15); 0.14 |
| High | 0.40 (0.14-1.09); 0.07 | 0.55 (0.20-1.52); 0.25 | 0.20 (0.06-0.60); 0.004 | 0.30 (0.10-0.96); 0.04 |
| **HER2+** | (n = 38) | | (n = 35) | |
| Low (Ref.) | 1.00 | 1.00 | 1.00 | 1.00 |
| Intermediate | 1.47 (0.62-3.49); 0.39 | 1.07 (0.45-2.56); 0.88 | 0.47 (0.14-1.60); 0.23 | 0.38 (0.11-1.31); 0.13 |
| High | 0.28 (0.08-0.97); 0.05 | 0.27 (0.08-0.96); 0.04 | 0.06 (0.01-0.56); 0.01 | 0.05 (0.01-0.39); 0.005 |
| **TNBC** | (n = 47) | | (n = 43) | |
| Low (Ref.) | 1.00 | 1.00 | 1.00 | 1.00 |
| Intermediate | 0.76 (0.31-1.87); 0.55 | 1.24 (0.49-3.14); 0.65 | 0.59 (0.21-1.67); 0.32 | 1.02 (0.34-3.11); 0.97 |
| High | 0.27 (0.08-0.88); 0.03 | 0.44 (0.14-1.36); 0.16 | 0.38 (0.11-1.39); 0.15 | 0.59 (0.16-2.26); 0.44 |

*Stratified by Region
**The following variables were included in multivariable analysis: age (≥40 vs.<40 years), nodal status (0 vs.1-3 vs. ≥4), tumour size (>20 mm vs. ≤20), NHG (1 vs. 2 vs. 3), ER (positive vs. negative), PR (positive vs. negative), HER2 (positive vs. negative), LVI (present vs. absent) and TILs (high vs. intermediate vs. low). Stratified by Region.
*** TILs were categorised as low: <10%, intermediate: 10-49% and high: ≥50%
*Abbreviations*: *BCFi* breast cancer free-interval, *OS* overall survival, *TILs* tumour infiltrating lymphocytes, *HER2* human epidermal growth factor receptor 2, *TNBC* triple-negative breast cancer, *NHG* nottingham histological grade, *ER* estrogen receptor, *PR* progesterone receptor, *HR* hazard ratio, *CI* confidence interval

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# Androgen and ESR1 mutant receptors mechanistically collaborate for overexpression of genes associated with poor outcomes in ER-positive metastatic breast cancer

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**Background:** Recurrences are delayed for years with endocrine therapy (ET), but resistance ultimately evolves with the development of ER+ metastatic breast cancer (MBC). ESR1 mutations are acquired in MBC undergoing ET in about 20-40% of patients. We have previously demonstrated that AR overexpression confers resistance to both tamoxifen and aromatase inhibitor treatments. We discovered that AR protein is up-regulated in tumors expressing ESR1 mutations, and herein explore the functional consequences of AR-ESR1 mutant co-expression on metastatic progression of breast cancer. **Objective:** We hypothesize that ET resistance mechanisms driven by AR overexpression and acquisition of ESR1 mutations co-evolve under the selective pressure of therapy to drive distant metastasis. We investigated whether AR engages in novel genomic binding interactions with mutant ER to promote tumor progression. **Methods:** Expression profiling of CRISPR-Cas9 engineered cell lines was integrated with chromatin immunoprecipitation-sequencing (ChIP-Seq) to define the genomic distribution of ER and AR binding sites. Genomic distribution of AR-ER co-occupied binding sites from MBC patient tumors, and a gene expression signature associated with patient outcomes was generated using using Cox Regression analysis to calculate Hazard Ratios for recurrence free survival from gene expression in the KMPlotter Breast Cancer Dataset and signature validation by Kaplan Meier analysis in the ER+ METABRIC patient cohort. **Results**: AR protein was post-transcriptionally elevated in ESR1 mutant cells, including distant metastatic tumors from ESR1 mutant xengraft models. Transcriptome data showed significant elevation of Cancer Hallmark pathways, including epithelial-mesenchymal transition (EMT) and estrogen response, but down-regulation of androgen response genes. However, both ER and AR functions were constitutively activated, independent of their respective ligands in ESR1 mutant-expressing models. AR was disproportionally re-distributed to selected enhancer genomic regions, but also heterochromatin in ESR1 mutant compared to cells with WT ER in the presence of estrogen. In addition, AR-ER co-occupied sites were increased in enhancer regions in ESR1 mutant cells, and these sites best discriminated distal ER enhancer regions in non-responder patients and MBC. . The expression of genes co-bound by AR and ER were significantly associated with shorter recurrence-free and overall survival in ER+ breast cancer. Treatment with AR agonists blocked distant metastasis of ESR1 mutant PDX models *in vivo*, in part due to reduction in ER protein and ER binding to select genomic sites. **Conclusions**: Our results demonstrate that unliganded AR collaborates with ESR1 mutations to regulate genes associated with the metastasis of ER+ breast cancer. We hypothesize that in an ESR1 mutant genomic background, AR acquires ER co-activator functions that are blocked with AR agonists, suggesting a unique hormonal therapeutic vulnerability in tumors with ESR1 mutations.

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# Sox4 and smarca4 upregulate glycolysis-driven tumor proliferation through hexokinase 2 in tnbc

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**Background** Triple-negative breast cancer (TNBC) accounts for nearly 1-in-4 breast cancer related deaths in the United States each year despite representing 10-12% of newly diagnosed cases. This aggressive disease, which is largely synonymous with the basal-like molecular subtype, predominantly affects younger women and women of African American decent. Despite a number of recent advances, overall survival has not drastically improved, highlighting the need to better understand mechanisms regulating tumor growth and progression as a means to identify novel therapeutic opportunities in these patients.
**Methods** In order to identify the functional impact of overexpression of the oncogenic transcription factor SOX4 and its co-factor SMARCA4 in TNBC, RNAseq and ChIPseq analyses were used to identify SMARCA4-dependent and -independent SOX4 gene expression programs. Analyses of more than 3,000 tumor samples from the METABRIC and TCGA cohorts was used to investigate the functional implications and clinical association of these gene expression programs in human tumors. Mass spectrometry (MS)-based metabolomic profiling in conjunction with genetic and pharmacological-based *in vitro* studies were used to demonstrate the impact of these programs on tumor cell metabolism, cell viability and proliferation.
**Results** We, and others, have previously demonstrated that the oncogenic transcription factor SOX4 is overexpressed in basal-like tumors. In order to identify mechanisms by which this protein mediates breast cancer tumorigenesis, we first identified SOX4 co-factors. Immunoprecipitation follow by MS was used to identify the SWI/SNF ATPase SMARCA4 as a prominent SOX4 cofactor that is concurrently overexpressed in basal-like tumors. Mechanistic studies showed that this complex is required to maintain an active open chromatin conformation at regulatory regions upstream of SOX4-regulated genes. ChIPseq and RNAseq-based analyses were next used to investigate the role of this complex in TNBC signaling and tumorigenesis. Our analyses identified SMARCA4-dependent and -independent SOX4 gene expression programs and demonstrated that SMARCA4-dependent SOX4 signaling is associated with poor clinical outcome. Further *in silico* analyses of human tumors indicate that each program mediates distinct down-stream signaling; SMARCA4-dependent signaling is associated with altered tumor metabolism and increased proliferative signaling. Consistent with this premise, *in vitro* studies showed that SOX4 and SMARCA4 are essential for breast tumor cell proliferation, survival and colony formation. Metabolomic profiling of breast cancer cell lines demonstrated that SOX4 overexpression resulted in increased glycolysis. The effect of SOX4 and SMARCA4 on cell metabolism was validated by demonstrating that this complex can mediate intracellular glucose consumption. Finally, we determined that SOX4 and SMARCA4 cooperatively regulate mRNA expression of hexokinase 2 (HK2), which catalyzes for the first step in glucose metabolism, and demonstrated that HK2 activity is essential for SOX4/SMARCA4-regulation of glycolysis. Importantly, *in vitro* genetic and pharmacological studies identified a link between HK2 activity, glycolysis and SOX4/SMARCA4-mediated cell proliferation and viability in TNBC.
**Conclusions** Our studies have identified SOX4 and its transcriptional cofactor SMARCA4 as being uniformly overexpressed in basal-like or TNBC tumors. These analyses demonstrate that SOX4 and SMARCA4 cooperatively promote tumorigenesis in TNBC cells, in part, by modulating glycolysis and cell proliferation through transcriptional regulation of HK2. Given the drug-ability of the glycolysis pathway, these results have potential clinical implications for treatment of TNBC patients.

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Validation of a predictive model for potential response to neoadjuvant endocrine therapy (NET) in postmenopausal women with clinical stage II or III estrogen receptor positive (ER+) and HER2 negative (HER2-) breast cancer (BC): An ALTERNATE trial analysis (Alliance A011106)

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**Background:** NET is offered to postmenopausal patients (pts) with clinical stage 2/3 ER+/HER2- BC to promote breast-conserving surgery. Also limited surgical accessibility during the COVID19 pandemic has increased NET utility. Inability to identify ET-resistant disease at diagnosis risks disease progression (PD) and delays more effective treatments. Dowsett *et al.* recently demonstrated that baseline levels of ER, progesterone receptor (PR), Ki67 (>15% vs ≤15%), and Ki67 (>10% vs ≤10%) 2-4 weeks (wks) after starting NET may improve appropriate patient (pt) selection for NET (PMC7280290). The ER, PR and Ki67-based prediction model divides pts with primary ER+/HER2- BC into 3 groups for appropriateness for NET: (Group 1) NET is likely to be *inappropriate* (Allred ER <6 or ER 6 and PgR <6), (Group 2) NET *may be appropriate* and a biopsy for on-treatment Ki67 analysis may be considered after 2-4 wks of NET (2A: ER 7 or 8 and PgR <6 and 2B: ER 6 or 7 and PgR ≥6) given that on-treatment Ki67 >10% has been associated with worse outcome (PMC5455353), or (Group 3) NET is *appropriate* (ER 8 and PgR ≥6). The ALTERNATE trial (NCT01953588) randomized postmenopausal women with clinical stage II or III, ER+ (Allred score 6-8)/HER2- BC to receive anastrozole (ANA), fulvestrant (FUL), or ANA + FUL for 6 months, unless Ki67 was >10% on wk 4 or 12 biopsy, in which case pts were triaged to receive neoadjuvant chemotherapy (NCT) or surgery. As previously reported, the ET-sensitive disease (mPEPI 0 plus pCR) rates were similar across the treatment arms and overall 22% (286 of 1,299) pts had Ki67 >10% at wk 4 or 12. The ALTERNATE trial therefore provides a large independent data set to evaluate the NET appropriateness model.

**Results:** Among 1,299 eligible pts randomized to receive 6 months of NET, 214 were excluded due to absent HR Allred score (n=41) or absence of pre-treatment and wk 4 Ki67 determinations (n=173). The proportions of the remaining 1,085 pts in Group 1, 2 and 3 were 1% (n=10), 43% (n= 468), and 56% (n=607), respectively. On-study Ki67 >10% prompting conversion from NET to NCT/Surgery occurred in: Group 1 90% (9 of 10), Group 2 30% (141 of 468), and Group 3 17% (104 of 607) (Table 1). Among the 1,075 pts in Groups 2 and 3, 260 (24%) pts had Ki67 ≤15% at baseline (BL), among whom only 14 (5.4%) had Ki67 >10% at wk 4, compared to 231 of the 815 (28.3%) who had BL Ki67 >15% and subsequent Ki67 >10% at wk 4. 2% of pts who remained on NET due to on-treatment Ki67 <10% had PD. Response and PEPI-0 rates by group will be reported. **Table 1 Baseline levels of ER, PR, and Ki67 in Relation to Wk 4 Ki67 (N=1,085)**

| | | **Baseline** | | | **Week 4** | | |
|---|---|---|---|---|---|---|---|
| **Group** | **N** | **ERAllred Score** | **PRAllred Score** | **Ki67** | **Ki67 ≤10%N (%)** | **Ki67 >10%N (%)** | |
| 1 | N=2 | 6 | <6 | ≤15% | 0 (0%) | 2 (100%) | 9 (90) |
| | N=8 | 6 | <6 | >15% | 1 (12.5%) | 7 (87.5%) | |
| 2A | **N=64** | **7 or 8** | **<6** | **≤15%** | **61 (95.3%)** | **3 (4.7%)** | 90 (30.1) |
| | N=235 | 7 or 8 | <6 | >15% | 148 (63%) | 87 (37%) | |
| 2B | **N=46** | **6 or 7** | **≥6** | **≤15%** | **42 (91.3%)** | **4 (8.7%)** | 51 (30.2) |
| | N=123 | 6 or 7 | ≥6 | >15% | 76 (61.8%) | 47 (38.2%) | |
| 3 | **N=150** | **8** | **≥6** | **≤15%** | **143 (95.3%)** | **7 (4.7%)** | 104 (17.1) |
| | N=457 | 8 | ≥6 | >15% | 360 (78.8%) | 97 (21.2%) | |

**Conclusion:** ALTERNATE trial data support a model whereby levels of ER, PR and Ki67 at diagnosis can be used for the identification of postmenopausal pts with primary ER+/HER2- BC who are appropriate for NET. When baseline ER Allred scores are >6 and Ki67 ≤15%, there is a low likelihood of ET-resistant disease. When BL Ki67 is >15%, ET sensitivity is variable, and on-treatment biopsy for Ki67 may assist in triaging regarding NET appropriateness,
particularly given the extremely low local PD rates seen in ALTERNATE when on-treatment Ki67 was <10%. **Support:** U10CA180821, U10CA180882, U24CA196171, UG1CA189856, U10CA180868 (NRG); NCI BIQSFP, BCRF, Genentech, AstraZeneca. https://acknowledgments.alliancefound.org; Clinical Trials.gov Identifier: NCT01953588

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# Dietary supplement use in a healthy eating and exercise lifestyle intervention in breast cancer survivors: The lifestyle exercise and nutrition (LEAN) study

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**Background:** Dietary supplements (DS), defined as herbal preparations, vitamins and minerals (DSHEA Act 1994), are used by 70% of cancer survivors. The World Cancer Research Fund/American Institute for Cancer Research 2018 Cancer Prevention Recommendations specify not to use DS to protect against cancer. There is some evidence that DS are linked to harmful outcomes, including increased mortality and breast cancer recurrence. DS have potential pharmacokinetic interactions via cytochrome P450 enzyme and pharmacodynamic interactions via estrogenic or hepatotoxic activity, which may increase or reduce clinical efficacy or potentiate adverse effects of Tamoxifen and Aromatase Inhibitors (AIs). This analysis examines baseline usage of DS and potential interactions with Tamoxifen and AIs among breast cancer survivors enrolled in the Lifestyle, Exercise, and Nutrition (LEAN) study, a randomized healthy eating and exercise lifestyle intervention. **Methods:** We examined the use of DS in 151 breast cancer survivors enrolled in the LEAN Study. Women with a body mass index (BMI) ≥ 25 kg/m $^2$ were randomly assigned to a 6-month healthy eating and exercise lifestyle intervention (n=93) or to usual care (n=58). At baseline and 6 months, we asked participants to self-report regular DS use, defined as at least 3 times a week for at least one month. The intervention group received evaluation and counseling of DS use by a Registered Dietitian (RD) with a Certified Specialty in Oncology Nutrition (CSO). Potential interactions of moderate and major ratings between DS with Tamoxifen and AIs (Letrozole, Exemestane and Anastrozole) were identified through the Natural Medicines Database by both a pharmacist specializing in oncology and a RD, CSO. **Results:** Out of 151 women, at baseline 120 (80%) reported using DS. Fifty-four different formulations were enumerated. The majority of women (72, 60%) were taking ≥ 3 formulations. One quarter of women (29, 24%) were taking ≥ 5 formulations (range = 1 - 20). Of the 54 formulations, 33% had potential interactions with Tamoxifen and/or AIs according to the Natural Medicines Database. Total interactions by medication were: 18 Tamoxifen, 14 Letrozole, 14 Exemestane, 9 Anastrozole. The majority of these interactions (87%) were associated with herbal preparations. **Conclusions:** Our findings are indicative of the high prevalence of DS use among breast cancer survivors and the potential risk of interactions with prescribed hormonal therapy. More research is needed to test if counseling from a RD, CSO can reduce DS use and ultimately lead to better outcomes due to fewer interactions with breast cancer treatments.

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# Impact of *UGT1A1* status on the safety profile of sacituzumab govitecan in the phase 3 ASCENT study in patients with metastatic triple-negative breast cancer

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**Background:** Trophoblast cell-surface antigen-2 (Trop-2) is highly expressed in many epithelial tumors, including triple-negative breast cancer (TNBC). Sacituzumab govitecan (SG) is an antibody-drug conjugate composed of an anti-Trop-2 antibody coupled to SN-38, the active metabolite of irinotecan, via a unique hydrolyzable linker that allows SN-38 release intracellularly and in the tumor microenvironment (bystander effect). SG received accelerated approval in April 2020 for the treatment of patients with metastatic TNBC (mTNBC) who received at least 2 prior therapies for metastatic disease. The most common adverse events (AEs) observed with SG are neutropenia and gastrointestinal toxicity, also seen with irinotecan. To provide further information on SG, additional safety analyses from ASCENT, a randomized, phase 3 confirmatory study of SG versus standard-of-care chemotherapy in patients with mTNBC, will be reported. **Methods:** In the global, multicenter, open-label, phase 3 ASCENT study (NCT02574455), 529 patients with mTNBC refractory to or relapsing after at least 2 prior chemotherapies were randomized 1:1 to receive SG (10 mg/kg intravenously on days 1 and 8 every 21 days) or single-agent treatment of physician's choice (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival measured by central independent review per RECIST v1.1. Secondary endpoints included objective response rate, duration of response, overall survival, and safety. An exploratory analysis of incidence of grade 3-5 AEs by *UGT1A1* genotype was also performed. Post-hoc analysis of the time to onset and duration of key AEs will be performed, and descriptive analyses on alopecia, nausea and vomiting will also be provided. **Results:** Exploratory safety analyses by *UGT1A1* allele status will be shown as well as time to onset and duration of neutropenia and diarrhea. Further descriptive analyses on alopecia, nausea, and vomiting will be provided along with AE management strategies. **Conclusions:** These analyses will provide further insights into the safety profile of SG and appropriate AE management strategies for patients with previously treated mTNBC to allow optimal therapeutic exposure.

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*HER2 L755S* mutation is acquired upon resistance to lapatinib and neratinib and confers cross-resistance to tucatinib and trastuzumab in HER2-positive breast cancer cell models

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**Background**: The role of HER2 mutations in anti-HER2 resistance is gaining more importance in HER2-positive (+) breast cancer (BC). The common *HER2 L755S* mutation is further enriched in metastatic lesions compared to primary tumors. Despite their mounting significance, effective therapies for HER2-amplified/mutant tumors are lacking. We recently reported that acquired resistance to lapatinib (Lap)-containing regimens is mediated by *HER2 L755S*, which could be overcome by the irreversible pan-HER tyrosine kinase inhibitor (TKI) neratinib (Nrb). However, less is known about the role of L755S in resistance to new generation TKIs, and the clinically implementable therapeutic strategies to overcome it. **Materials and Methods**: Our recently developed HER2+ BT474 cell models with acquired resistance to Lap (LapR) or Nrb (NrbR), developed through long-term exposure to increasing doses of the respective drug, and their naïve parental (P) counterparts were used. The resistant derivatives and their cognate P cells were subjected to proteomic (Reverse phase protein array (RPPA) and western blot) and transcriptomic (RNA-seq) characterization. For drug efficacy studies, change in cell growth was assessed using the *in situ* imaging-based high-throughput IncuCyte system. **Results**: Proteomic profiling of the resistant models and their P equivalents revealed partial restoration of HER2 phosphorylation and downstream signaling in the LapR and NrbR derivatives. Consistent with activated mTOR signaling observed in the resistant cells, we detected reduced levels of phospho (p)-RAPTOR S792, which is otherwise essential to inhibit the mTOR complex 1 (mTORC1). In addition, p-P38MAPK T180/Y182 levels were reduced. RNA-seq analysis revealed the presence of *HER2 L755S* mutation in the LapR and NrbR derivatives, but not in P cells, suggesting that the HER signaling reactivation could be attributed to acquisition of *HER2 L755S*. Interestingly, the NrbR cells co-harbor other pathogenic mutations in key BC related genes, the therapeutic and functional significance of which is being investigated. Importantly, the NrbR derivatives were cross-resistant to Lap and the monoclonal antibody trastuzumab (T). Next, we determined the efficacy of Nrb and the HER2-selective TKI tucatinib (Tuca), both recently approved for metastatic HER2+ BC, either alone or in combination with T. Nrb effectively inhibited the growth of LapR cells, although a higher dose (IC50: ~50nM) was required to inhibit the growth compared to that needed for naïve P cells (~IC50: ~2nM). When combined with T, Nrb was effective in inhibiting the LapR cell growth, though the inhibitory effect may very well be driven entirely by Nrb. On the other hand, the resistant derivatives were cross-resistant to Tuca, both as a single-agent and in combination with T. We then evaluated the efficacy of the antibody drug conjugate TDM1 and the irreversible pan-HER TKI poziotinib. In contrast to the high sensitivity of P cells to both these agents, a spectrum of effect was observed in the NrbR derivatives, with responses ranging from partial growth inhibition by poziotinib to complete response with TDM1, suggesting their therapeutic potential against tumors harboring HER2 mutations. **Conclusions**: Our findings suggest that *HER2* mutations, particularly *HER2 L755S*, that emerge under the pressure of potent HER2-targeted therapy may confer cross-resistance to other single agent or combination HER2-targeted therapy. This holds important therapeutic implications in light of current treatment landscape. An in-depth molecular characterization of our resistant models to determine the differential gene expression and mutational profile is ongoing to gain additional mechanistic insights and to guide discovery of other actionable targets.

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**Publication Number:** PS9-09

# Web-based intervention to improve knowledge, intent to screen and uptake of breast cancer screening among long-term, high-risk Hodgkin lymphoma survivors who received chest radiation

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**Background** Many cancer survivors experience late effects from their cancer treatment including second cancers. Breast cancer risk in Hodgkin lymphoma (HL) survivors is estimated at 35% by age 50 years[1] with a 40-fold increase when treated with chest radiation prior to age 20 years[2]. For patients who received chest radiation between ages 10 and 30 years, NCCN recommends annual screening mammogram and breast MRI 10 years after chest wall radiation or after age 30 and 25 years respectively[3]. We designed a web-based intervention to improve knowledge, intent to screen and uptake of breast cancer screening among long-term, high-risk HL survivors.**Methods** We invited 263 long-term HL survivors treated with chest radiation, of which 60 women were enrolled. Participants were randomized 1:1 to web-based intervention or control groups. The web-based intervention consisted of daily, interactive, highly tailored learning modules over the course of one week. Both groups received handouts on potential complications from cancer treatment and screening recommendations. All participants were invited to a baseline survey, first follow-up survey 1-2 weeks post intervention, and a final survey 3 months post intervention. In total, 53 participants completed the baseline survey, and to-date 41 the first follow-up survey. The last 3-month follow-up surveys are due in fall 2020. We compared frequencies of who correctly answered questions regarding potential complications from prior treatment and breast cancer screening recommendations at baseline vs. first follow-up in the intervention and control groups using Chi-squared and Fisher's exact tests. P value < 0.05 was considered significant.**Results** At baseline, participants were on average 49 years old, and 22.4 years out from their HL diagnosis. Baseline self-reported adherence to annual mammography and breast MRI screening was low: 55% of all participants reported receiving annual mammograms, and only 6% reported annual MRIs. At baseline, 79% of participants reported awareness of complications from previous treatments however, only 27% correctly identified national guidelines on breast cancer screening for HL survivors who received chest radiation. At one week after the intervention, individuals assigned to the intervention (compared with controls) more often 1) reported knowing how to reduce the risk from prior treatments (89.5% vs. 50%, p = 0.009), 2) correctly identified national guidelines on screening (63.2% vs. 27.3%, p=0.007) at first follow-up. Our preliminary data did not show an increase in intent to screen or uptake of screening shortly after intervention.

| | **Intervention N=30 (%)** | **Control N=30 (%)** | **p-value** |
|---|---|---|---|
| Identified national guidelines on breast cancer screening for HL survivors who received chest radiation | 12 (63.2) | 6 (27.3) | 0.007 |
| Reported knowing what to do to reduce risk of complications from prior cancer treatment | 17 (89.5) | 11(50.0) | 0.009 |

**Conclusions** Adherence to breast cancer screening recommendations is low among long-term, high-risk HL survivors. Preliminary analysis of an RCT comparing a web-based intervention to paper handouts identified improved knowledge regarding current national guidelines on breast cancer screening and how to reduce the risk of complications from prior HL treatments. Further research should address barriers to screening and interventions to address them. **References**1.Moskowitz CS et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol* 32, 2217-2223, 20142.van Leeuwen FE et al. Second cancer risk following Hodgkin's disease: a 20-year follow-up study. *J Clin Oncol* 12, 312-325, 19943.NCCN Guidelines Breast Cancer Screening & Diagnosis 2019

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# Medicaid expansion associated with earlier stage and improved reconstruction rates in low income breast cancer patients

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**Introduction:** Substantial delays in time to initiation of treatment (TTT) following diagnosis of breast cancer (BC) can inflict a toll on quality of life and can decrease cancer-specific survival. Among low-income, non-elderly Ohio women having newly-diagnosed breast cancer with local or regional spread, we examined TTT and other measures where income-related disparities have been documented, comparing 2011-2013 (pre-Medicaid-expansion) vs. 2014-2016 (post-expansion). Our primary hypothesis was that TTT would decrease following 2014 Medicaid expansion.**Methods:** Using data from the Northeast Ohio Cancer Assessment and Surveillance Engine (NEO-CASE), a multilevel data infrastructure linking Ohio cancer registry data with community data, we identified 30-64 year-old women with new diagnosis of invasive, non-metastatic BC who were uninsured or on Medicaid when diagnosed. TTT was defined as days from diagnosis to first BC treatment with any modality. We excluded women with TTT=0 (likely coding error). The main exposure was pre- or post-Medicaid expansion period defined as 2011-2013 or 2014-2016, respectively. We examined additional key demographic and treatment variables before and after expansion and in multivariate analysis of TTT. We used a previously-described probability-weighting approach based on neighborhood median income to approximate excluding women with incomes above 138% of Federal Poverty Level. As a control analysis, we compared pre- and post-expansion TTT among privately insured women, probability weighted to select for higher income individuals.**Results:** Our study population included 1177 and 1143 women diagnosed with BC pre- and post-expansion, respectively. Demographic characteristics were similar, though mean age increased by 1.2 years (p<0.01) post-expansion. Mean TTT increased by 2 days post-expansion, from 41.1 to 43.1 (p=0.18). The control analysis showed a similar small post-expansion increase. Though no significant change in TTT was observed, the percent uninsured in the low-income group fell by more than half (from 32.9% to 14.1%; p<0.01), and the percent of women diagnosed with regional stage disease decreased from 38.1% to 30.9% (p<0.01). The percent of women undergoing reconstructive surgery increased from 12.1% to 16.7% (p<0.01) from the pre- to the post-Medicaid expansion period, a change not observed in the privately-insured control group. Cox proportional hazards regression models controlling for the effect on TTT of covariates shown in the table revealed an adjusted hazard rate (AHR) of 0.950 (95% CI 0.855 to 1.056) associated with Medicaid expansion. Stage-stratified Cox models showed a similar lack of effect among women with local and regional disease. **Discussion:** TTT increased by 2 days post-expansion; however, this increase was neither statistically significant nor clinically meaningful. Despite the lack of improvements in TTT, we note the dramatic drop in the percent uninsured among BC patients post-expansion, as well as a marked decrease in the percent of women diagnosed with regional-stage disease, and an increase in BC patients undergoing reconstruction. Taken together, these trends show an overall positive impact of Medicaid expansion on BC process of care and outcome measures.

| | Pre-expansion | Post-expansion | p |
|---|---|---|---|
| N | 1177 | 1143 | |
| Mean TTT in days (SD) | 41.1 (37.1) | 43.1 (33.7) | 0.18 |
| Mean age at diagnosis (SD) | 51.6 (8.39) | 52.8 (8.14) | <0.01 |
| Non-Hispanic African American (%) | 269 (22.9) | 225 (19.7) | 0.07 |
| Married/Partnered (%) | 408 (34.7) | 417 (36.5) | 0.38 |
| Uninsured (%) | 387 (32.9) | 161 (14.1) | <0.01 |
| Non-metropolitan census tract (%) | 285 (24.2) | 232 (20.3) | 0.03 |
| Area Deprivation Index 9 or 10: most deprived (%) | 274 (23.3) | 238 (20.8) | 0.17 |
| Regional disease (%) | 448 (38.1) | 353 (30.9) | <0.01 |
| Reconstructive surgery (%) | 143 (12.1) | 191 (16.7) | <0.01 |
| Breast conserving surgery (%) | 509 (43.2) | 590 (51.6) | <0.01 |

**Publication Number:** PS15-09

Adverse events in breast cancer patients treated with concurrent or sequential radiation therapy and CDK 4/6 inhibitors in metastatic setting

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Background. Radiation therapy (RT) is important modality in MBC patients, however, there is paucity of data on safety and feasibility in combining radiation and a cyclin-dependent kinase 4 and 6 inhibitors (CDK 4/6i). No sufficient data were gathered in clinical trials and a few small retrospective series were published; it is important to extend these data. Theoretically, concerns pertain both the augmentation of effect (toxicity) or decrease of treatment effectiveness. Methods. 116 patients with MBC were treated in our center with CDK 4/6i (ribociclib n=59, palbociclib n=57) between 2018-2020. 26 patients were also treated with RT and were included into further analysis. 10 patients were treated with concurrent RT and 16 patients with sequential RT. Median age of patients was 55 years (range 23-78). 11 patients (42%) were diagnosed with de novo MBC, whereas 15 patients (57%) with recurrent breast cancer. 16 patients received prior chemotherapy, 6 of them less than 1 year before CDK 4/6i treatment. 73% of patients received CDK 4/6i in first line setting. Bones were the main metastatic site in the majority of patients, whereas visceral metastasis were diagnosed in 9 patients (35%). Overall 32 RT treatments in 26 patients were performed. Various RT regimens were used, including 8 Gy in 1 fraction (n=10), 20 Gy in 5 fractions (n=9), 30 Gy in 10 fractions (n=3). SBRT was performed in 5 patients and chest wall irradiation in 3 patients. The majority of patients received palliative radiotherapy to the bones, including 6 patients (23%) with RT to the pelvic area. Results. Nineteen patients (73%) experienced G2 and G3 neutropenia, with no G4 case. Neutropenia G≥2 occurred during first cycle of CDK 4/6i treatment in 50% of patients (n=8) after sequential RT and signicantly more often in patients after concurrent RT (all treated, n=10; p= 0.0095). No neutropenia was observed in 7 patients after sequential RT (27%). 4 patients (15%) had CDK 4/6i dose reduction, including 1 patient treated with concurrent RT and 3 patients treated with sequential RT. In all 4 patients the cause of dose reduction was prolonged G3 neutropenia. Patients were treated as follows: 60yo patient received RT 8 Gy in 1 fraction for bone metastases in lumbar and thoracic spine and ribs; 31yo patient received RT 20 Gy in 5 fractions for central nervous system, then 20 Gy in 5 fractions for bone metastases in thoracic, lumbar and sacral spine (all of these treatments were performed during 4 weeks before CDK 4/6i first dose). The following two patients received additionally doxorubicin-based chemotherapy shortly before CDK 4/6i treatment. At median follow up of 17 months (range 9-20 months) none of these patients discontinued treatment because of toxicity: one patient continue ribociclib at first dose reduction level, two patients continue ribociclib at second dose reduction level and one patient continued ribociclib treatment for 11 consecutive months and then CDK 4/6i treatment was ended because of disease progression. There was no difference in neutropenia rate in patients treated previously with chemotherapy (n=16) and chemo-naïve patients (n=10; p=0.6680). No cases of acute radiation-induced enterocolitis or enhanced dermatologic toxicity were found. No other serious adverse events were observed. Conclusions. We found that concurrent RT leads to more frequent neutropenia than sequential RT, although it did not change treatment course in the majority of patients and appeared well-tolerated. Potential risk factors for radiation-induced CDK4/6i dose reduction might be extensive radiation fields and previous chemotherapy in metastatic setting. Until now, combined RT is not a part of adjuvant CDK 4/6i clinical trials protocols. Excellent tolerance of this combination supports future consideration of this scenario in clinical trial setting.

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The use of magnetic resonance imaging (MRI) in predicting pathological complete response(pCR) in the breast and axilla after the addition of immunotherapy to neoadjuvant systemic therapy (NST)

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**Introduction:** Immunotherapy use is increasing as an adjunct to current NST for breast cancer treatment with the goals of increasing pCR and down staging tumors. In this study, we assessed the effectiveness of MRI in the evaluation of tumor response after neoadjuvant immunotherapy in combination with NST. **Methods:** We retrospectively reviewed the clinicopathological data of 105 women undergoing Immunotherapy in conjunction with NST at a single institution. All patients had been enrolled in IRB approved protocols and had undergone definitive surgery. Patients were excluded for: failure to complete at least two thirds of treatment, no pre or post treatment MRI, or surgery in an outside institution. We analyzed 73 patients from 5 distinct treatment protocols including: (1) 24 Triple negative breast cancer (TNBC) patients (pts) treated with Intratumoral Talimogene laherparepvec (TVEC) in combination with weekly paclitaxel followed by dose dense Adriamycin and Cytoxan (ddAC); (2) 19 HER2/Neu positive (HER2+) pts treated with subcutaneous interferon gamma (IFN-γ) in combination with weekly paclitaxel with trastuzumab and pertuzumab (HP); (3), 7 HER2+ pts treated with 3 weeks of HER2 pulsed dendritic cell vaccines (DC1) followed by Taxotere, Carboplatin, and HP; (4), 14 pts on the ISPY2 trial: 8 TNBC and 4 Hormone receptor positive, HER2/Neu negative (HR+) pts randomized to treatment with pembrolizumab with weekly paclitaxel followed by ddAC (2 also received additional SD101), and 2 TNBC pts treated with Durvalumab, Olaparib and Paclitaxel, followed by ddAC and (5) 9 HR+ pts on neoadjuvant Durvalumab and an Aromatase Inhibitor for 6 cycles. **Results:** A total of 73 patients were included in the study. Median age was 51 years (range 27-76); 46.6% of patients had TNBC, 35.6% had HER2+ and the remaining 17.8% were HR+ HER2- . The median clinical tumor size was 3.4cm (range 1.3-10.6) pre therapy and 1cm (range 0-10.1) post therapy. The pCR was 38.2%, 57.7%, and 0% respectively for TNBC, HER2+, HR+ tumors. Complete radiological response (rCR) of both the axilla and breast was 41.2%, 61.5% and 7.7%, for TNBC, HER2+ and HR+ tumors. The sensitivity of MRI to detect in breast pCR was 65.6% with a specificity of 81%, NPV and PPV of 75% and 73.3% respectively. MRI identified 37 pts with suspicious axillary nodes on pretreatment MRI; of these 30 had fine needle aspiration (FNA) confirmed metastatic disease. Post treatment, 70.3% (26/37) had normalized axillary nodes. Of those with normalized nodes, 26.9% (7/26) had residual cancer on final pathology. Of the patients with confirmed FNA lymph node metastasis, axillary pCR of 63.3% was achieved. The sensitivity and specificity of MRI to detect pCR within the axilla was 87% and 50% and NPV and PPV 70% and 74.1%, respectively. 3 patients had axillary disease on final pathology but no suspicious imaging and a benign FNA. **Conclusion:** The addition of immunotherapy to current NST strategies can improve pCR and decrease residual cancer burden. The PPV and NPV of MRI to predict pCR in patients undergoing immunotherapy in combination with NST remains within the ranges described in patients undergoing NST alone. MRI remains a useful tool to guide surgical management but is not accurate enough to replace pathological evaluation.

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# Pathologic features of the inter-regimen biopsy predict response to neoadjuvant therapy in the I-SPY 2 TRIAL

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**Background**: I-SPY 2 is a neoadjuvant platform trial open to patients with locally advanced, molecular high-risk breast cancer. In a concerted pursuit of mid-therapy response biomarkers, we evaluated inter-regimen biopsies, to identify patients who may be candidates for treatment de-escalation. In a pilot study, we observed that absence of carcinoma in an inter-regimen biopsy may predict pathologic complete response (pCR). In this expanded study of 100 participants, we sought to confirm that finding and assess pathologic features of the inter-regimen biopsy as predictors of tumor response to neoadjuvant therapy.
**Methods**: Digital H&E images of 100 inter-regimen (12 week) image-guided breast biopsies +/- ancillary immunohistochemistry (p63 and/or cytokeratin) were reviewed by 9 I-SPY affiliated pathologists to record 1) tumor bed and 2) presence/absence of residual invasive carcinoma (IC) (with tumor cellularity scored as 0-100%). The data set included 393 cores (mean 3.9 (2-4) cores/biopsy). Fisher's exact t-test was used for association of presence/absence of IC with pCR, and tumoral hormone receptor (HR) and HER2 status. Association between biopsy tumor cellularity and residual cancer burden (RCB) indices used Pearson's correlation.
**Results**: In the biopsy set, 84 (84%) had ≥80% inter-observer diagnostic agreement on both 1) presence of tumor bed and 2) presence/absence of IC (53 IC+ /31 IC-). IC+/IC- biopsies had equal numbers of evaluable tissue cores. The primary tumors were 63% HR+/37% HR-. The presence of IC in the biopsy correlated with tumoral HR/HER2 status (p=0.0014: 74%: HR+HER2-; 62%: TN; 60%: HR+HER2+; 10%: HR-HER2+). Of 31 patients with IC- biopsies, 25 (80%) went on to pCR, whereas only 7/53 (13%) of patients with IC+ biopsies had pCR, conferring an odds ratio for pCR of 26, Fisher p=7.5E-10. Overall, IC- biopsies had a positive predictive value (PPV) for pCR of 81%, with a PPV for HR- tumors of 94% vs. 67% for HR+ tumors (Table 1). In the 6 IC- biopsies from patients with non-pCR ("false-negatives"), most were HR+ (5/6, Table 1), and tumor bed size in the resection specimen was smaller than for IC+ biopsies with non-pCR: 276 $mm^2$ (0.4-1000 $mm^2$) vs. 1166 $mm^2$ (1-11960 $mm^2$). In contrast, the 46/53 IC+ biopsies in patients with non-pCR had a PPV for predicting non-pCR of 86%, (PPV for HR+ tumors: 94% vs. PPV for HR- tumors: 66%. Tumor cellularity in the biopsy (mean 37%, [2.5-93%]) did not correlate with RCB index (p=0.57) or RCB breast-only index (p = 0.17) at resection.
Table 1: PPV for pCR/non-PCR by Inter-regimen Biopsy Status

| Inter-regimen biopsy with or without Invasive carcinoma (IC+/-) | pCR | non-pCR | PPV (Sensitivity) for pCR(IC-Biopsies) | PPV (Sensitivity) for non-pCR(IC+ biopsies) |
|---|---|---|---|---|
| IC- biopsies | | | | |
| All | 25 | 6 | 81% (78%) | - |
| HR+ | 10 | 5 | 67% (83%) | - |
| HR- | 15 | 1 | 94% (75%) | - |
| IC+ biopsies | | | | |
| All | 7 | 46 | - | 86% (88%) |
| HR+ | 2 | 36 | - | 94% (88%) |
| HR- | 5 | 10 | - | 66% (91%) |

**Conclusion:** In this 100 biopsy set from the I-SPY2 trial, the absence of residual carcinoma in inter-regimen biopsies was highly predictive of pCR, particularly for HR- tumors. The "false-negative" biopsies (IC-/non-pCR) were predominantly HR+ tumors with small residual tumor beds at resection. Conversely, the presence of carcinoma in inter-regimen biopsies was highly predictive of non-pCR, particularly for HR+ tumors. These data demonstrate the utility, and the limitations, of the inter-regimen biopsy as one tool to identify patients who may benefit from therapeutic de-escalation.

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# Achievability of 2030 sustainable development goals in breast cancer control

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**Background**
The United Nations Sustainable Development Goals (SDGs) target a one-third reduction in non-communicable disease (NCD) mortality between the years 2015 and 2030. Cancer accounts for 22% of NCD deaths, and breast cancer is the leading global cause of female cancer mortality, despite its high survivability. Therefore, reducing female breast cancer mortality is critical to any nation's achievement of this goal. However, sex-based disparities in healthcare are evident in lower-resource settings, and lack of infrastructure for breast cancer control leads to greater underdiagnosis in low- and lower middle-income countries (LICs & LMICs). Mortality may be a biased indicator due to the impact of differing incidence rates. Therefore, the mortality-to-incidence ratio (MIR) was examined as a practical indicator of breast cancer control. We projected mortality and MIR for women with breast cancer in 195 countries to quantify progress in breast cancer control and assess the feasibility of achieving the 2030 NCD mortality target of the SDGs.

**Methods**
We used data on incidence and mortality rates for female breast cancer reported by The Global Burden of Disease Study 2017 for the years between 2000-2017. For each country, we projected mortality rate and MIR for female breast cancer by national income level from 2018-2030 using generalized linear mixed-effects models. We stratified our results by country's Gross National Income per Capita (GNI/capita) and income group as defined by the World Bank.

**Findings**
Between 2017 and 2030, global breast cancer mortality is projected to increase by 12.4% from 19.02 (95% confidence interval [CI]: 17.36-20.64) to 21.38 ( 95% prediction interval [PI]: 19.03-23.93), while MIR is projected to decrease by 10.3% from 0.404 (95% CI: 0.385-0.425) to 0.362 (95% PI: 0.342-0.383). In 2017, MIR was 2.22 times higher in low-income countries (LICs) and 1.71 times higher in lower-middle income countries (LMICs) than in high income countries (HICs). Although MIR is projected to decrease between 2017 and 2030 across all income groups (15.9% in HICs, 10.61% in UMICs, 3.66% in LMICs, 10.2% in LICs), 2030 MIR is projected to be 2.37 times higher in LICs and 1.96 times higher in LMICs when compared to HICs.

**Interpretation**
Use of mortality to measure progress towards SDGs can be misleading in the context of breast cancer control. Simultaneously increasing mortality and incidence may still imply improvement, if mortality is increasing at a slower rate than incidence. Therefore, MIR is a better indicator of progress in breast cancer control. The decreasing global breast cancer MIR from 2015 to 2030, despite increasing mortality, indicates that global progress is being made in breast cancer. Despite globally decreasing MIR, the disparity between HICs and LICs may increase between now and 2030 in the absence of significant resource-stratified policy reform.

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**Publication Number:** PS2-09

# Next generation sequencing (NGS) in older adults with breast cancer using tissue-based and circulating tumor DNA (ctDNA) assays

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**Background:** With advances in next generation sequencing (NGS) and now approved targeted therapy in breast cancer, genomic testing to identify potentially actionable mutations has become a common practice in patients (pts) with advanced breast cancer using both ctDNA and traditional tissue-based assays. Less is known regarding physician practice patterns in obtaining NGS testing and the practical implications of testing in older adults with breast cancer.**Methods:** Pts with advanced breast cancer underwent molecular profiling using a plasma-based ctDNA NGS assay (Guardant360® or Tempus®) between 5/2015 and 5/2020 at Siteman Cancer Center. Pts with advanced breast cancer who underwent genomic profiling using a tissue-based NGS assay (Tempus®) between 12/2017 and 5/2020 at this institution were also included. Clinicopathological histories were obtained from the medical record. Correlations were examined using a Fisher's exact test.**Results:** During 5/15-5/20, 244 pts underwent ctDNA testing and 147 pts had a tissue-based NGS assay performed. There was no significant difference between the number of pts ≥ 65 years-old who underwent ctDNA testing (n=78, 32.0%) and tissue testing (n=37, 25.2%). There was no statistically significant difference between date of metastatic diagnosis and date of NGS testing between the older and younger cohorts. In pts who underwent tissue-based NGS testing, there was no significant difference between site of tissue tested (distant recurrence vs local) in the older and younger cohorts. The most common clinical managements following both ctDNA and tissue-based testing are presented in Table 1. Out of the 391 pts who underwent testing, 27 pts had both ctDNA and tissue-based NGS performed. Pts ≥ 65 were less likely to have both assays performed (n=3, 11.1%; p<0.05). In pts undergoing both assays, there were high concordance rates of *ESR1* (81.5%) and *PIK3CA* (81.5%) mutations. Mean time between tissue and plasma collection for NGS testing in pts undergoing both assays was 356.4 days.

Table 1

| clinical management following NGS testing | ≥65 years-old | <65 years-old | p value |
|---|---|---|---|
| no actionable mutations | 41 (35.7%) | 123 (44.6%) | p=0.1 |
| testing results saved for potential future use | 27 (23.5%) | 45 (16.3%) | p=0.1 |
| change in management | 15 (13.0%) | 41 (14.9%) | p=0.6 |

**Conclusion:** Older adults, who are typically less likely to be included in clinical trials, may still benefit from NGS to reveal potentially targetable mutations. It is reassuring in our cohort that older adults had ctDNA and tissue-based NGS performed at similar rates as part of standard of care treatment. The clinical management following NGS testing was also not significantly different in the older adult cohort. Older adults were less likely to have both tissue and ctDNA testing performed however, given the high concordance rates between tests, this may be less clinically relevant.

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# Chemotherapy-induced nausea and vomiting (CINV) risk after prior breakthrough CINV: Unmasking the false average

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**Background**: Although many studies have demonstrated consistent levels of effectiveness of CINV prophylaxis for the entire study population across multiple chemotherapy cycles, rarely have studies reported how each patient's risk of subsequent CINV differs based on prior cycle breakthrough CINV with the same prophylaxis. We lack data on whether prophylaxis continues to fail in the same group of patients each cycle, or whether failure is random with each subsequent cycle. We sought to evaluate individual patients' risk of repeat CINV in each subsequent chemotherapy cycle. **Methods**: In a prospective, 4-cycle CINV prophylaxis trial of oral or intravenous combination netupitant/palonosetron (NEPA) + dexamethasone (day 1) for patients with breast cancer receiving anthracycline + cyclophosphamide (AC), we defined CINV as vomiting or use of rescue medication during days 1-5 after chemotherapy. Patients without CINV were classified as complete response (CR); the rest as treatment failure (TF). We analyzed patients' sequences of CR and TF, and compared CR or TF for cycles 2-4 based on cycle 1 outcomes, using chi-square statistics. To provide context, we performed a post-hoc similar analysis of results reported by Herrstedt et al [2005] from a clinical trial of ondansetron + aprepitant (APR) for patients with breast cancer receiving 4 cycles of AC. **Results**: The 402 female patients in the NEPA trial received a total of 1,299 cycles. In cycle 1, 99 (24.6%) patients experienced TF (TF1); over all 4 cycles, TF occurred 253 times (19.5%). Patients with CR in cycle 1 (CR1) had a ≥92% rate of CR in cycle 2; their rates of repeat CR were similar in each subsequent cycle. Patients with TF1 had nearly equal risk of CR or TF in cycle 2 (45:55); thereafter 85% of this TF1 subgroup repeated their cycle 2 outcome (CR or TF) in cycles 3 and 4. Over all cycles of NEPA, patients with CR1 subsequently had CR in >90% of cycles 2-4; those with TF1 subsequently had TF in 49.8% of cycles 2-4 (p<0.0001) (see Table). We separately examined Herrstedt's evaluation of 433 patients across 1537 cycles with APR. In cycle 1, TF was seen 213 times (49.2%), with TF reported in 46.7% of cycles 1-4. We found that patients with CR1 had an 80.5% rate of CR in cycle 2 and repeat CR rates were higher in subsequent cycles. Patients with TF1 had TF in cycle 2 (TF2) at a rate of 78.4%, with 76.6% TF3 and 72.7% TF4. For APR, CR1 resulted in subsequent CR in 78.6% of cycles 2-4 while patients with TF1 again had TF in 74.8% of cycles 2-4 (p<0.0001). Patients with TF1 were more likely to later drop from the study (see Table). Notably, among those with CR1 after APR, the few patients who later had TF in any cycle, had a subsequent repeat failure rate similar to those with TF1. **Conclusions**: When patients receiving guideline-recommended triple antiemetic prophylaxis successfully avoided CINV in their first cycle of HEC, they had 80-95% likelihood of repeating that success in later cycles. After NEPA, those whose prophylaxis failed in cycle 1 did not face a similar high risk of repeat failure in cycle 2. The pattern of repeat failure after aprepitant was different, with a high repeat failure risk starting in cycle 2. These findings strongly suggest that consistent population average CR rates reported across cycles may mask a higher repeat failure rate for individual patients that experience cycle 1 CINV, particularly for aprepitant. Further study of this phenomenon is needed for other HEC regimens, and to confirm the lack of high repeat failure seen in cycle 2 for NEPA.

Repeat CINV in Later Cycles, Based on Cycle 1 Results

| | **NEPA** | | | **Aprepitant + Ondansetron** | | |
|---|---|---|---|---|---|---|
| **Initial Cycle Result** (n/total initial cycles) | **CR1 (303/402)** | **TF1 (99/402)** | **CR1 vs TF1 (P value)** | **CR1 (220/433)** | **TF1 (213/433)** | **CR1 vs TF1 (P value)** |
| **Subsequent CR cycles** (n, % of total subseq. cycles) | 636 (93.0%) | 107 (50.2%) | <0.0001 | 464 (78.6%) | 124 (25.2%) | <0.0001 |
| **Subsequent TF cycles** (n, % of total subseq. cycles) | 48 (7.0%) | 106 (49.8%) | | 126 (21.4%) | 370 (74.8%) | |
| **Total subsequent cycles** (n, % of total subseq. cycles) | 684 (100%) | 213 (100%) | | 590 (100%) | 494 (100%) | |
| **Dropped vs ITT*** (n, % ITT cycles) | 225 (24.8%) | 84 (28.3%) | 0.2263 | 70 (10.6%) | 145 (22.7%) | <0.0001 |

***** The NEPA trial was closed when the last patient completed the first cycle, resulting in an artificially high proportion of patients that did not complete 4 cycles.

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Development and validation of a tool integrating the 21-gene recurrence score and clinicopathlogic features to individualize prognosis for distant recurrence and prediction of absolute chemotherapy benefit in early breast cancer

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**Background:** The 21-gene recurrence score (RS) provides prognostic information for distant recurrence (DR) and predictive information for chemotherapy (CT) benefit in early breast cancer, whereas clinicopathologic features provide only prognostic information. We used patient-specific meta-analysis (PSMA) methods (Crager et al, J Appl Stat 2014 [PMID: 26664111]; Tang et al. J Clin Oncol 2011 [PMID: 22010013]) to develop an online tool that assesses individualized estimates of DR risk and absolute CT benefit. We also externally validated this new tool for estimating DR risk in an independent cohort.**Methods:** The PSMA included 10,004 women with hormone-receptor positive, HER2-negative, node-negative breast cancer from the NSABP B-14 (n=577) trial receiving endocrine therapy (ET) alone and TAILORx trial receiving ET alone (n=4854) or CT plus ET (n=4573). The baseline risk used TAILORx event rates with ET alone. A patient-specific estimator of absolute CT benefit was computed by combining PSMA of the individualized relative CT effect from the TAILORx and NSABP B-20 (n=550 HER2-negative) trials and risk estimates with ET alone. External validation of DR risk estimation was performed in an independent cohort of 1098 women enrolled in the Clalit Health Service registry who had a 21-gene RS performed, of whom 222 (20%) received CT in addition to ET as per the recommendation of their treating physician guided by the RS. **Results:** The new tool is more informative for DR risk than RS or clinicopathologic factors alone ($p<0.001$, likelihood ratio test). The risk estimate was significantly associated with DR risk in the independent Clalit cohort ($p<0.001$), and closely approximated the observed 10-year DR risk (Lin concordance 0.962). Since the RS strongly influenced CT use, propensity score matching could not appropriately be used for evaluation of CT benefit in Clalit. Using this tool for a 55-year-old woman with a low clinical risk 1.5 cm intermediate grade tumor, the absolute CT benefit estimate ranges from 0% to 15% as RS ranges from 11 to 50; this compares to a range of 2% to 8% if the relative CT benefit were held constant. Over the same RS range for a 55-year-old woman with high clinical risk 2.5 cm poor grade tumor, the tool's absolute CT benefit estimate ranges from 1% to 33% compared to 4% to 17% if the relative CT benefit were held constant. This indicates that incremental CT benefit observed with higher RS is driven not only by a higher underlying recurrence risk, but also by prediction of relative CT benefit.**Conclusions:** We describe a validated clinical tool integrating clinicopathologic and genomic features to guide adjuvant chemotherapy of hormone-receptor positive, HER2-negative, axillary node-negative breast cancer with greater precision than using clinicopathologic or genomic data alone. The individualized CT effect prediction provided by the RS, based on contemporary treatments, contributes substantially to the estimate of absolute CT benefit. Support: This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: U10CA180794, U10CA180820, U10CA180822, U10CA180868, and UG1CA189859. The content is solely the responsibility of the authors. Mention of commercial products does not imply endorsement by the U.S. government. Additional support was provided by the Breast Cancer Research Foundation, the Komen Foundation, and the Breast Cancer Research Stamp (BCRS) issued by the United States Postal Service.

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Development of a breast cancer risk assessment model for *ATM* mutation carriers incorporating tyrer-cuzick and a polygenic risk score (PRS)

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**Background:** Germline pathogenic variants (PVs) in the moderate penetrance *ATM* gene confer a roughly 2-fold increased risk for breast cancer. Currently, any woman with an *ATM* PV meets the >20% lifetime risk threshold for consideration of relatively aggressive screening recommendations, which include initiating screening at younger ages and consideration of breast MRI. We and others have previously shown that breast cancer risks for women with inherited PVs in many hereditary breast cancer genes can be adjusted using PRS data, breast cancer family history, and other clinical information. Herein we show the development of a comprehensive breast cancer risk model for *ATM* PV carriers incorporating a previously described 86-variant PRS along with family history/clinical information captured by Tyrer-Cuzick V7.02. **Methods:** This IRB-approved study included de-identified clinical records from 353,809 women of European ancestry who were tested clinically for hereditary cancer risk with a multi-gene panel. Model development analyzed *ATM* PV carriers ($N$=2,666) and women negative for breast cancer gene PVs ($N$=351,143) who were tested between September 2013 and November 2019 (July 2019 for non-carriers). Women with the unusually high risk *ATM* c.7271 allele were excluded from analysis. Risk estimates incorporating *ATM*, PRS, and Tyrer-Cuzick were calculated using a fixed-stratified method that accounted for correlations between risk factors in a manner equivalent to multivariable co-estimation. Risk stratification was assessed in an independent cohort of *ATM* carriers ($N$=272) who were tested after November 2019 and were not included in model development. **Results:** We detected significant positive correlation of *ATM* status with breast cancer family history ($p=1.6\times10^{-7}$). Within *ATM* PV carriers, we observed positive yet non-significant (at alpha <0.05) correlation between PRS and breast cancer family history ($p$=0.10); joint effects were co-estimated using the fixed-stratified method. After adjusting for multiple testing, we found no evidence of interaction of *ATM* status with clinical factors, or PRS with clinical factors within *ATM* carriers. In an independent cohort, 30.1% of *ATM* carriers were categorized as having low breast cancer risk (<20%), 58.5% as moderate risk (20-50%), and 11.4% as high risk (>50%). **Conclusions:** In *ATM* PV carriers, our comprehensive model allowed for differentiation of *ATM* PV carriers into low, moderate, and high breast cancer risk categories. Precision breast cancer risk estimation may inform individualized clinical screening and prevention strategies.

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# The impact of non-classic LCIS on the natural history of DCIS

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Background: Classic lobular carcinoma in situ (C-LCIS) and non-classic LCIS (NC-LCIS) are histologically and biologically distinct types of lobular neoplasia. Little is known about the impact of NC-LCIS on risk of recurrence when found in association with concomitant malignancy. We sought to assess oncologic outcomes in patients with DCIS and concomitant NC-LCIS as compared to DCIS with concomitant C-LCIS treated with breast conservation.
Methods: Upon IRB approval, an institutional database was accessed to identify patients with a diagnosis of C-LCIS + DCIS or NC-LCIS+DCIS in the same core biopsy and/or excisional biopsy specimen. All pathology slides relevant to the diagnosis were confirmed by internal review. Patients with prior or concurrent ipsilateral invasive breast cancer and/or prior ipsilateral DCIS were excluded. Use of adjuvant therapies and the incidence of ipsilateral and contralateral DCIS and invasive breast cancer were compared in the 2 groups. Statistical analysis was performed using the chi-square test.
Results: Among patients diagnosed with DCIS between 1996 and 2015 and treated with breast conserving surgery, 69 also had C-LCIS and 13 also had NC-LCIS (the diagnosis of NC-LCIS was not encountered until 2000). Median patient age was 55 years (range 40-88), 42 (51%) had a family history of breast cancer and 5 (6%) had a prior diagnosis of atypical proliferative breast lesions; these factors did not differ between patients with C-LCIS+DCIS and NC-LCIS+DCIS. Patients with NC-LCIS+DCIS were more likely to present with mammographic distortion (25% vs 6%, p=0.03), to have been diagnosed by core biopsy, and less likely to have ER positive (67% vs 91%, p=0.03) or PR positive (50% vs78%, p=0.014) DCIS. In 78% of the patient cohort, final excision margins were negative, and these proportions were not different between the 2 groups The median number of surgeries performed to obtain clear surgical margins which was 2 (range 1-4) for the entire cohort and for C-LCIS+DCIS and NC-LCIS+DCIS, individually. 78.% of C-LCIS+DCIS patients and 54% of NC-LCIS+DCIS patients received adjuvant radiation (p=0.064), and 45% of C-LCIS+DCIS patients took adjuvant hormonal therapy, while none of the NC-LCIS+DCIS patients did (p=0.002). At median follow-up of 78 (1-260) months for C-LCIS+DCIS and 60 (1-197) months for NC-LCIS+DCIS, there were no differences observed in the incidence of ipsilateral and contralateral breast cancer (10.1% vs 7.7% , p=0.19, and 10.1% vs 0%, respectively, p=0.78). One of 13 patients (7.7%) with NC-LCIS+DCIS, who developed an ipsilateral invasive carcinoma, was subsequently diagnosed with bone metastasis.
Conclusions: Patients with NC-LCIS+DCIS were more likely to have ER and/or PR negative DCIS and only 54% of this cohort received radiation, yet local-regional recurrence rates were low and not different
between NC-LCIS +DCIS and C-LCIS+DCIS patients. Despite the more aggressive histologic features of NC-LCIS, these data do not suggest that NC-LCIS associated with DCIS portends a different prognosis that C-LCIS associated with DCIS. Larger studies are needed to confirm these findings.

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Partitioning of cancer therapeutics in nuclear condensates

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The molecules of the cell are compartmentalized into membrane- and non-membrane-bound organelles. Many non-membrane-bound organelles are phase-separated biomolecular condensates with distinct physicochemical properties that can absorb and concentrate specific proteins and nucleic acids involved in discrete biochemical processes. We reasoned that selective condensate partitioning might also occur with small molecule drugs whose targets occur within condensates, and that the therapeutic index and efficacy of such compounds might therefore relate to their ability to partition into condensates. To test this idea, we focused our study on nuclear condensates reported in cell lines, demonstrated they occur in normal human and malignant breast cancer, and developed assays to test clinically active antineoplastic small molecule drugs relative to these condensates.To study the behavior of drugs within condensates, these were modeled in vitro with purified proteins and visualized by fluorescent confocal microscopy. We found that cisplatin, tamoxifen, JQ1, THZ1, and mitoxantrone are concentrated in specific protein condensates in vitro, and that this occurs through physicochemical properties independent of the drug target. For each drug, the small molecule partitioned into the same condensate in vitro in which its established target resides in vivo. A screen of a chemically diverse fluorescent probes and mutant-protein condensates demonstrated that pi-system interactions between aromatic moieties in the protein and small molecule govern concentration in condensates. These results show that clinically important drugs partition into specific protein condensates in vitro by virtue of defined chemical properties, thereby altering their local concentration.Alkylating agents are a class of commonly used antineoplastic compounds, of which cisplatin is a prominent example. In vitro droplet assays revealed that cisplatin is selectively concentrated in transcriptional condensates, and that this ability is required for efficient platination of target DNA. In cell studies revealed that cisplatin preferentially targets DNA contained within MED1 condensates, and disrupts the genetic regulatory elements that compose phase-separated transcriptional condensates. Live cell imaging demonstrated that transcriptional condensates are dissolved by cisplatin, whereas other condensates remain intact. Thus, we conclude that cisplatin preferentially modifies transcriptional condensate-associated DNA in cells, and that this causes selective condensate disruption. The mechanisms that produce drug resistance can provide clues to drug activity in the clinical setting. Investigating the behavior of tamoxifen within ER transcriptional condensates demonstrated that it disrupts these condensates in vitro and on oncogenes in cells; hormonal therapy resistant ESR1 mutations render these condensates resistant. MED1 overexpression, a poorly understood mechanism of tamoxifen resistance, increased the size of ER-MED1 condensates, thereby rending tamoxifen more dilute and ineffective when concentrated therein. This suggest that altering the size and nature of transcription condensates in breast cancer can mediate drug resistance in the clinical setting.Our results show that antineoplastic drugs partition selectively into condensates, that this can occur through physicochemical properties independent of their molecular targets, and that resistance to drugs may occur through condensate altering mechanisms. These results have implications for development of efficacious cancer therapeutics; effective target engagement will depend on factors such as drug partitioning in condensates. Assays of the type described here may thus help optimize condensate partitioning, target engagement, and the therapeutic index of drugs for cancer treatment.

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Pre-operative pembrolizumab (Pembro) with radiation therapy (RT) in patients with operable triple-negative breast cancer (TNBC)

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**Background:** Pembrolizumab (pembro)-mediated checkpoint blockade has shown only modest efficacy in triple negative breast cancer (TNBC). Pathologic complete response (pCR) rates in TNBC are 34-55% with neoadjuvant chemotherapy and 26% with neoadjuvant stereotactic radiation therapy (RT) alone. However, because RT induces immune-mediated cell death that can generate a rich supply of tumor antigens and trigger anti-tumor immunity, the addition of pembro to RT can generate robust anti-tumor immune responses as demonstrated in metastatic TNBC. If administered in the pre-operative setting, immune therapy plus RT could induce long-term tumor-specific memory, and ultimately, improve cure rates. This study aimed to establish the safety of pre-operative pembro plus RT in 20 TNBC patients for whom lumpectomy and adjuvant RT were planned and to explore predictive biomarkers (NCT03366844).
**Methods:** Women planning breast conserving surgery for operable, stage II/III, TNBC were enrolled in this single-institution pilot study. Study treatment consisted of pre-operative pembro (200mg IV) followed 3 weeks later by pembro (200mg IV) plus RT (24 Gy/3 fractions) to the primary breast tumor followed 3-5 weeks later by standard-of-care (SOC) neoadjuvant chemotherapy. Adjuvant RT was administered per SOC after surgery, but without a boost dose. Research blood and tumor biopsies were obtained at baseline, at week 4 prior to pembro/RT, and at week 6-8 prior to chemotherapy initiation. Co-primary endpoints were: safety/tolerability (defined by the number of patients who do not necessitate a delay in SOC chemotherapy or surgery) and change in tumor infiltrating lymphocyte (TIL) score. Secondary endpoints include safety/toxicity up to 19 weeks after study enrollment and pathologic complete response (pCR) rate.
**Results:** 20 patients were enrolled and completed all treatment (pembro, RT, chemotherapy and surgery) as of July 2020. The median age is 55y (range 33-70y). The stage distribution is IIA (11), IIB (6), IIIA (2) and IIIC (1) with biopsy proven nodal involvement in 55%. All patients received a taxane containing regimen, 12/20 (60%) received carboplatin and 15/20 (75%) received an anthracycline. Three patients did not complete the planned course of chemotherapy, two of whom had residual disease. None of the patients experienced significant delay (>2 weeks) in receiving SOC treatment. There were no observed grade 3 or 4 toxicities observed during the pembro +/- RT treatment. Grade 4 colitis in 2/20 was reported during SOC chemotherapy and was attributed to pembro. The most frequent grade 1/2 toxicities were nausea (4/20), arthralgia (15/20), fatigue (16/20), maculopapular rash (1/20), diarrhea (1/20) and mucositis (1/20). At the time of surgery, 12/20 (60%) were ypT0N0 and 13/20 (65%) were ypT0/Tis. 15/20 (75%) achieved an RCB 0/1, 4/20 (20%) were RCB 2 and 1/20 (5%) was RCB 3. Of the 11 patients
with node-positive disease at diagnosis, 9/11 (82%) became ypN0, 1/11 (9%) became ypN1mic and 1/11 (9%) became ypN1a. No patients progressed during treatment. Change in TILs after pembro or pembro-RT did not correlate with treatment response, however baseline TIL count ≥10% in the initial biopsy was associated with pCR ($p = 0.005$). Further profiling of the immune cells in the biopsies revealed that RCB 0/1 patients were strongly associated with increased numbers of CD8+ T cells and lower numbers of CD11b+ myeloid cells following the combination of pembro and RT.
**Conclusions:** Neoadjuvant pembro plus RT prior to SOC chemotherapy is safe/feasible and may increase pCR rates and clearance of nodal metastases beyond chemotherapy alone. A phase 2 study of checkpoint blockade + RT expansion of this trial (n=50) is currently accruing.

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Real-world analysis of concomitant medication use with potential drug-drug interactions (DDI) in patients with metastatic breast cancer (MBC) treated with cylin dependent kinase (CDK) 4/6 inhibitors

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**Background**: In combination with endocrine therapy, the CDK4/6 inhibitors (CDK4/6i) ribociclib, palbociclib, and abemaciclib have improved progression free survival and in some cases overall survival in women with hormone receptor positive (HR+)/HER2 negative MBC. Use of concomitant medications and the potential for drug-drug interactions (DDI) is an important issue in clinical oncology, particularly among patients with MBC treated for long durations of time with CDK4/6i, and could lead to sub-optimal medication adherence or subsequent dose reductions/discontinuations. **Objective**: To describe concomitant medication use that could lead to DDI with CDK4/6i as well as CDK4/6i dosing, adherence, and discontinuation patterns in real-world clinical practice. **Methods**: Adult women with HR+/HER2- MBC initiating treatment with ribociclib, palbociclib, or abemaciclib as the first CDK4/6i (index therapy) were retrospectively identified from the Optum Clinformatics Data Mart (1/1/2017 - 9/30/2019), a large US healthcare claims database. Eligibility included 3 months of baseline (pre-index date) and at least 3 months of follow-up (post-index date) data. Concomitant medications (identified from the literature) evaluated at baseline included CYP3A inhibitors and inducers, P-glycoprotein (P-gp) inhibitors and inducers, and medications associated with risk of torsades de pointes (TdP). Treatment persistence was analyzed using Kaplan-Meier (KM) as time from index date to discontinuation, defined as an interruption of at least 90 consecutive days of the index treatment or end of patient enrollment or switch to another medication. Adherence was measured by proportion of days covered (PDC), using the recommended administration schedule of 21 days of treatment followed by 7 days off. **Results**: A total of 2,994 women were included: 184 initiated ribociclib as first CDK4/6i; 2,550 palbociclib; and 260 abemaciclib. Median duration of follow-up was 13.7 [Interquartile range (IQR)] 11.8); 13.1 (IQR 13.5); and 9.3 (IQR 9.2) months. The majority in each cohort were postmenopausal (ribociclib: 89.1%; palbociclib: 92.8%; abemaciclib: 90%) and received the index CDK4/6i as > 2nd line of therapy (ribociclib: 81.5%; palbociclib: 87.6%; abemaciclib: 88.9%). Mean age (66.4; 66.8; and 65.3 yrs) and National Cancer Institute comorbidity index [mean/SD: 1.2 (1.6); 1.2 (1.7); 1.1 (1.6)] were similar for the ribociclib, palbociclib, and abemaciclib cohorts, respectively. Patients with ≥ one concomitant medication (60.3%; 64.2%; 65.8%) and those with > one medication associated with TdP (57.1%; 59.4%; 61.9%) were similar for the 3 cohorts. The CDK4/6i discontinuation rates, starting dose, dose reduction, and adherence results are listed below (Table). **Conclusions**: Use of concomitant medications that could lead to a DDI with a CDK4/6i, especially those with risk of TdP, CDK4/6i treatment discontinuation, and adherence was similar between ribociclib, palbociclib, and abemaciclib in this real-world retrospective descriptive study. More patients in the ribociclib cohort maintained starting dose and less decreased to <50% of the starting dose compared to palbociclib and abemaciclib, although the cohort is small. Results are limited by the relatively smaller number in the ribociclib and abemaciclib cohorts.

Descriptive analysis on characteristics in follow up period by index drug group

| | Ribociclib (N = 184) | Palbociclib (N = 2550) | Abemaciclib (N = 260) |
|---|---|---|---|
| Discontinuation of Index Treatment, n (%) | 96 (52.2) | 1266 (49.7) | 123 (47.3) |
| Starting dose, mean (SD) | 532.6 (141.1) | 118.5 (13.4) | 287.7 (56.6) |
| Patients with first time dose change | | | |
| No change during the entire follow up period, n (%) | 148 (80.4) | 1740 (68.2) | 176 (67.7) |
| Decrease > 50%, n (%) | 7 (3.8) | 0 (0) | 5 (1.9) |
| Decrease ≤ 50%, n (%) | 20 (10.9) | 773 (30.3) | 68 (26.2) |
| Adherence (PDC), mean (SD) | 0.85 (0.2) | 0.87 (0.2) | 0.87 (0.2) |

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**Publication Number:** PD2-11

# Breast cancer index is a molecular signature of endocrine responsiveness that determines extended endocrine benefit independent of prognostic risk

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**Background:** For patients with early stage, hormone receptor positive (HR+) breast cancer, extension of endocrine therapy beyond 5 years reduces the ongoing risk of late distant recurrence and new primary breast cancer but is associated with potentially serious toxicities and side effects that can impair quality of life. While risk stratification by clinicopathological factors and prognostic biomarkers is recommended to guide patient selection, predictive biomarkers that are directly informative of therapeutic response are critical for clinical utility. Breast Cancer Index (BCI) is a gene expression-based signature that reports: 1) BCI Prognostic (BCI Score), which combines the Molecular Grade Index (MGI) with the HOXB13/IL17BR (H/I) ratio to provide individualized risk of late (post-5y) distant recurrence, and 2) BCI Predictive (BCI H/I), which predicts benefit from extended endocrine therapy. In this study, BCI and endocrine benefit from 5 vs 2.5y of extended letrozole were examined by comparing the deterministic effects of prognostic risk vs endocrine response in patients treated in the IDEAL trial.**Methods**: 908 patients with available tumor tissue were included in this pre-specified and blinded analysis, with recurrence-free interval (RFI) as the primary endpoint. Kaplan-Meier and Cox proportional hazards regression were performed using pre-defined assay cut-points. Clinically high prognostic risk was defined as pN+ and ≥pT2; low prognostic risk was defined as pN0 or pN1 and pT1 or G1. Genomic risk was defined by BCI prognostic categories (High vs Low risk). **Results:** Patients classified with endocrine responsive disease by BCI (H/I)-High status showed a statistically significant benefit from 5 vs 2.5y of letrozole irrespective of clinical risk, whereas those classified as BCI (H/I)-Low did not show benefit in either clinical risk category. Both clinically High and Low risk patients derived a similar magnitude of benefit when stratified as BCI (H/I)-High (12.5% and 15.1%, respectively).

| Prognostic Risk | BCI Predictive | N | HR (95% CI) | P value |
|---|---|---|---|---|
| **Clinical Risk** | | | | |
| High Risk: N+/ T2+ (N=353) | High BCI(H/I) | 162 | 0.32 (0.10-0.98) | 0.035 |
| | Low BCI(H/I) | 191 | 1.13 (0.55-2.31) | 0.742 |
| Low Risk: N0 or N1 & T1 or grade 1 (N=404) | High BCI(H/I) | 191 | 0.15 (0.03-0.66) | 0.004 |
| | Low BCI(H/I) | 213 | 0.75 (0.33-1.70) | 0.484 |
| **Genomic Risk** | | | | |
| High BCI Score(N=621) | High BCI(H/I) | 341 | 0.42 (0.20-0.89) | 0.020 |
| | Low BCI(H/I) | 280 | 1.05 (0.58-1.88) | 0.880 |
| Low BCI Score(N=227) | High BCI(H/I) | 60 | 0.35 (0.04-3.38) | 0.344 |
| | Low BCI(H/I) | 167 | 0.64 (0.22-1.92) | 0.425 |

Evaluation of BCI (H/I) predictive performance in the context of BCI prognostic risk categories showed similar results. In particular, patients with High Risk/High Likelihood to benefit showed significantly improved outcomes with extended therapy (HR 0.42 [0.20-0.89]; absolute benefit 10.7%; P=0.020), whereas those with High Risk but Low Likelihood to benefit did not show response to extended endocrine therapy (HR 1.05 [0.58-1.88]; absolute benefit -0.7%; P=0.880), despite considerable risk of late distant recurrence (~20%). **Conclusion**: Results from this study highlight distinct tumor biology underlying recurrence risk vs endocrine responsiveness in HR+ early stage breast cancer. BCI (H/I) as a molecular signature to identify patients with endocrine responsive disease is a key determinant of benefit and improved outcome with extended endocrine therapy. Prediction of endocrine benefit with BCI (H/I) is a more actionable approach vs risk assessment to individualize discontinuation of or continued treatment with prolonged durations of endocrine therapy.

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*Esr1* mutation as a potential predictor of abemaciclib benefit following prior cdk4/6 inhibitor (cdk4/6i) progression in hormone receptor-positive (hr+) metastatic breast cancer (mbc): A translational investigation

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**Background**: CDK4/6 inhibitors have emerged as the standard of care for HR+ MBC. However, there is limited insight into the potential benefit of abemaciclib following prior progression on palbociclib or ribociclib. Based on a multi-center cohort of patients with HR+ MBC who had received abemaciclib after prior palbociclib progression (Wander SA et al ASCO 2019), we have previously reported that abemaciclib after prior CDK4/6i progression was well tolerated and that a subset of patients derived durable clinical benefit. Identifying molecular predictors of sensitivity to abemaciclib after prior CDK4/6i progression constitutes an important area of research. Given the high frequency of *ESR1* mutations in HR+ MBC with antiestrogen resistance, we evaluated the translational impact of *ESR1* mutations in mediating response to abemaciclib in this setting.
**Methods**: To evaluate abemaciclib sensitivity in ESR1 mutant cell lines, T47D HR+ breast cancer cells were modified to over-express multiple mutant ESR1 isoforms via lentiviral infection and antibiotic selection. These isoforms included *ESR1 Y537S, Y537N,* and *D538G*. In an additional T47D cell line, RB1 expression was knocked down via CRISPR. The resulting derivative cell lines were grown in the absence of estrogen (via charcoal-stripped serum, CSS) or in escalating doses of abemaciclib. Cell viability was measured via cell-titer-glo assay. For clinical validation, we identified patients with MBC who had ESR1 mutations detected by targeted sequencing of cell-free DNA (cfDNA), via CLIA certified Guardant assay, and had abemaciclib exposure following prior progression on palbociclib or ribociclib in the existing multi-center cohort from six US institutions.
**Results**: All *ESR1* mutant derivative cells demonstrated enhanced growth in estrogen deprivation compared to GFP controls, as expected, and were similarly sensitive to escalating doses of abemaciclib monotherapy *in vitro,* suggesting that *ESR1* mutations do not confer resistance to abemaciclib. Interestingly, two patients with *ESR1* mutations (in the absence of concurrent driver alterations in *RB1*, *FGFR*, *CCNE2*, and *ERBB2*) demonstrated progression on palbociclib and sensitivity to abemaciclib. In one patient, cfDNA obtained prior to palbociclib and fulvestrant exposure failed to reveal any ESR1 alteration. Following progression on palbociclib, and prior to sequential exposure to abemaciclib, an *ESR1 Y537N* alteration was identified. The patient went on to receive 16 months of abemaciclib monotherapy. In a second patient, an *ESR1 D538G* alteration was identified following progression on palbociclib and fulvestrant. The patient had several intervening regimens, and subsequently went on to receive abemaciclib and fulvestrant for 16 months. RB1-null T47D cells were resistant to abemaciclib monotherapy *in vitro*, as expected and, in the clinical dataset, the presence of alterations in previously identified genomic mediators of CDK4/6i resistance, such as *RB1*, were associated with progression on both palbociclib and abemaciclib.
**Conclusions**: HR+ breast cancer cells expressing mutant ESR1 isoforms were resistant to estrogen deprivation but retained sensitivity to abemaciclib *in vitro.* Furthermore, patients harboring *ESR1* mutations via targeted sequencing of cfDNA, in the absence of other known mediators of CDK4/6i resistance, were shown to derive clinical benefit from abemaciclib following prior progression on palbociclib. These results suggest that patients with HR+ MBC, *ESR1* mutation, and clinical resistance to anti-estrogen treatment and palbociclib may be candidates for abemaciclib treatment. Further research is warranted to confirm these novel translational observations.

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Mutational burden of the normal breast during age and pregnancy

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**Background:** The potential for accumulation of somatic mutations in the healthy breast throughout life and pregnancy is poorly understood. In particular, the unique mutational landscape of both epithelial and stromal components of the mammary gland has not been investigated in depth. As cancer risk correlates with both age, age of first-time pregnancy and other factors including pregnancy itself, we wished to study mutational rate over time, using these landmarks. **Methods:** Here, using whole genome sequencing, we determined how the rate of mutations in both cancer drivers and passenger mutations are affected by both age and pregnancy. We aimed to describe for the first time how the mammary epithelium and stroma differ in their mutational burden. **Results:** Our analysis of epithelial and stromal laser-capture micro-dissected DNA from 25 normal breast samples of nulliparous and age-matched early- and late-parous women collected from Komen Tissue Bank, University of Indiana, shows that the mammary gland is characterised by known COSMIC signatures SBS1 and SBS5, both of which correlate with age ($p<0.05$). Using a non-negative matrix factorization approach, we identified a novel signature HB1 for a subset of samples which could not be fitted into the known signature database. Differences between the two cellular compartments were observed mostly in the enrichment pathway of mutated genes, notably a significant enrichment in mutations in the PI3K-Akt signalling pathway in the epithelium. We found that parous stroma is associated with a significant enrichment in mutations in the 3'UTR of genes, suggesting that regulation of the environment in the post-partum breast could preferably occur via these pathways. Alike other normal tissue, the mutational burden of the mammary gland significantly increases with age ($P<0.05$) and we observed parity-associated patterns of mutational burden, particularly evident in the epithelial compartment. The nulliparous epithelium is characterised by a significant increase of mutations ($p<0.05$), but mutated clones are maintained at a consistently small size. Conversely, the number of somatic mutations in the parous epithelium is not significantly affected by age, but age is positively correlated with bigger clone sizes ($P<0.05$) in this group. This trend suggests that possible cancer-associated mutations may have a lower probability of occurring but higher chance of expanding within the parous breast with age, compared to the nulliparous breast. To confirm this, we detected mutations in known driver genes in all the healthy samples, with some occurrence of known individual pathogenic variants.**Conclusions:** We show the mutational landscape of the healthy breast and highlight differences in the epithelial and stromal cellular compartments. We show how mutated cells, including mutations in driver genes for breast cancer, and genetic alterations change in the contest of pregnancy and age, provide a possible explanation for pregnancy-associated breast cancer risk.

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Serial MRI and pathology combined to select candidates for therapy de-escalation in the I-SPY 2 TRIAL

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**Background**: The I-SPY 2 TRIAL, open to patients with locally advanced, molecular high-risk breast cancer, aims to bring each patient to pathologic complete response (pCR) with a minimum of toxicity. Here we test the hypothesis that imaging (MR volume predictors) combined with core biopsy may be used to accurately select candidates who show early response and provide an option of treatment de-escalation at mid-therapy (12 weeks).
**Methods**: Of 100 I-SPY 2 patients with pathologist-assessed core biopsies at the inter-regimen time point (~12 weeks through treatment) and pCR data, 87 also had serial MR images and were considered in this study. Eleven I-SPY 2 TRIAL pathologists independently provided a digital assessment of the presence or absence of residual invasive cancer from H&E stained, and any requested ancillary IHC, images from imaging-guided core biopsies. Pathology predicts pCR if there is a consensus of no invasive residual disease. We generated predictions for all (55) unique pairs over the 11 pathologists, where pCR is predicted if both pathologists find no invasive cells. MRI pCR prediction models were previously developed on an independent dataset of ~990 I-SPY 2 patients, and applied to this cohort. Volume-based prediction models were previously optimized within each subtype and predicted probability thresholds were selected over a range of positive predictive value (PPV). In this study, MR predicts pCR (positive test) if the predicted probability is above a threshold that yields a given PPV value. For each pathologist pair, we combined pathology-based and MR-based predictors into a predictive-RCB (pre-RCB); and pre-RCB predicts a patient as pCR (RCB0) if both MR and pathology predicts pCR. Predictive performance is assessed by calculating the mean and range of PPV and sensitivity.**Results**: 39% (34/87) of the patients in this study achieved pCR. Over all pairs of pathologists, on average 80% of pathology-only predicted pCRs were true pCRs (mean PPV = 80% [range: 69-92%]), and 74% of patients who achieved pCR were predicted pCR by pathology alone (mean sensitivity = 74% [65-82%]). We assessed combinations with MR probability thresholds at PPV levels 50%-70%; and observed the best balance of PPV and sensitivity for the pre-RCB when MR thresholds were set at 50% PPV level. At this threshold setting, the pre-RCB achieved a PPV = 92% [83-100%], meaning on average 92% of predicted pCRs were true pCRs, and this improvement in positive predictive performance over pathology alone is achieved with a lower but still-reasonable 53% sensitivity [33-62%].
**Conclusion:** Pre-RCB, which predicts a patient as pCR if both MR and inter-regimen pathology predicts pCR, provides clinically actionable accuracy for treatment de-escalation for early responders (PPV>90%). Adding a final MR review at the time of early surgery may further improve performance. Resulting from data presented in this abstract, the pre-RCB algorithm, including the final MR review, has been operationalized and will be used prospectively to identify patients who are highly likely to have already achieved pCR by the inter-regimen timepoint.

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Solti-1804 HER2-PREDICT: A biomarker research study of DS8201-A-U301 -U302 and -U303 trials

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**Background:** Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 15-20% of breast cancers (BC). At the same time, HER2-low tumors (immunohistochemistry 1+ or 2+ with no gene amplification) comprise ~50% of all BC. DS-8201a is an anti-HER2 antibody drug conjugate that has shown very promising response rates both in HER2+ and HER2low BC. However, not all patients respond or benefit to the same extend. Thus, there is a need to identify predictive biomarkers. Here, we hypothesize that by performing several molecular studies in both tissue and plasma samples of those patients participating in the pivotal DESTINY-Breast trials, we will shed more light about the molecular features of HER2+ BC and better characterized the patient population according to their benefit from this promising new anti-HER2 agent. **Methods:** HER2-PREDICT is a multi-center, observational study within the biomarker program of SOLTI group, which will include patients who will participate, are participating or previously participated in the Daiichi Sankyo INC sponsored phase III trials: DS8201-A-U301 (NCT03523585), -U302 (NCT03529110) and -U303 (NCT03734029). Patients with HER2-positive or HER2-low unresectable and/or metastatic breast cancer may be included in SOLTI-1804 HER2-PREDICT study if randomized to the DS-8201a arm. All patients need to consent for obtaining a fresh tumor biopsy or donating an archival metastatic biopsy. Primary tumors are allowed under SOLTI acceptance. Additionally, patients included before initiating DS-8201a therapy will provide blood samples for biomarker analyses on Cycle 1 Day 1 (C1D1), C2D1 and end of treatment. The primary objectives are (1) to identify an optimal *ERBB2* mRNA cut-off point predictive of Ds-8201a response and (2) to evaluate the correlation of baseline *ERBB2* mRNA levels (as a continuous variable) with overall response rate (ORR) in the Ds-8201a-treated cohorts. Secondary objectives includes: to evaluate the association of *ERBB2* mRNA levels, PAM50 intrinsic subtypes and immune-related genes with ORR, progression-free survival and overall survival; to design a new gene expression signature predictive of Ds-8201a benefit; to correlate early changes in ctDNA with Ds-8201a benefit and to identify acquired somatic mutations of resistance to DS8201a upon progression in plasma samples. Collection of tumor biopsies is an essential part of this study. Pathological analysis includes hematoxylin and eosin (H&E) staining, identification of areas with greater amount of tumor cells and determination of their tumor cell percentage. RNA will be isolated and analyzed at the nCounter (Nanostring Technologies). Molecular intrinsic subtypes will be identified by a research-based version of PAM50. Furthermore, we aim to evaluate 771 additional genes (+5 housekeeping genes) that encompass important genomic signatures and individual genes of importance for breast cancer by means of the nCounter®Breast Cancer 360 Panel. Somatic mutations in *PIK3CA*, *TP53*, and additional genes (e.g., *GATA3* and *ERBB2*) will be identified using next-generation sequencing (NGS). Also, a comprehensive NGS gene panel will be performed under the Ion Torrent or Illumina platforms to DNA extracted from FFPE tumor blocks and to circulating tumor DNA (ctDNA) in plasma samples. **Current status:** Since December 13th, 2019, a total of 10 patients have been included, 5 of them with blood samples. As of today, 13 out of 15 Spanish sites are recruiting patients. Clinical trial identification: NCT04257162

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# Investigating the clinical utility of tumor mutational burden in predicting rapid progression and death in patients with metastatic breast cancer

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**Background** Up to 30% of breast cancer patients will eventually relapse with metastatic disease. With an increasing array of therapeutic options, there is an ongoing need for predictive biomarkers to help guide treatment strategies including sequencing of therapies in the metastatic setting. We sought to evaluate the prognostic and predictive potential of a panel-specific tumor mutational burden (TMB) in metastatic breast cancer patients.
**Methods** METAMORPH is a prospective, longitudinal cohort study. Eligible patients (pts) had newly diagnosed or progressive metastatic breast cancer and enrolled prior to starting a new line of therapy (physician's choice) at the University of Pennsylvania. Pts underwent tissue biopsy of a suspected metastatic site. Tumor samples were analyzed for mutations and copy number alterations (CNA's) using our institution's CLIA-certified Center for Personalized Diagnostics (CPD) targeted gene panel, which evolved over the course of the study from 20 genes to 152 genes. TMB-high (TMB-H) was defined as ≥3 mutations and/or copy-number gains (CNG) among 18 genes shared across all panel versions. Pts were followed for time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The frequency of rapid progressors and rapid death (defined as having progressed or died within 3 months of enrollment, respectively) was assessed.
**Results** Three hundred pts enrolled from 2013-2020, of whom 200 pts had CPD reports generated. Of these, 12 pts were excluded due to either no treatment change on enrollment (n=11) or different primary cancer on biopsy (n=1). Thus 188 pts were included in this analysis. The median age was 55 years (range 28-79). 77% of pts identified as white, 18% as Black or African American, and 3.2% as Asian. Pts had a median of 1 line (range 0-12) of prior systemic therapy in the metastatic setting. 46.8% had no prior therapies for MBC, while 31% had ≥3 prior lines of therapy. 74.4% were HR+, 22.8% TNBC, and 2.7% HR-/HER2+. 6.9% of the cohort were classified as TMB-H. The average mutation/CNG rate was 2.2/sample, and 22.5% had no mutations or CNA's. The most common mutations were TP53 (35%) and PIK3CA (26%).
While TMB-H patients showed a statistically non-significant trend towards shorter median TTP and PFS compared with TMB-L, they comprised a significantly greater proportion of rapid progressors (54.5% vs 24.1%, p=0.027), with an odds ratio for rapid progression of 3.8 (95% CI 1.08-13.2). In a multivariate logistic regression analysis, TMB-H remained independently associated with rapid progression when adjusted for receptor subtype and next line of therapy. Receptor subtype analysis revealed that ER- (including ER-/PR+) patients with TMB-H had a shorter median TTP compared to ER- TMB-L (147 vs 68 days, p=0.03). TMB-H was also associated with significantly shorter OS compared with TMB-L (587 vs 648 days, p=0.02; HR 2.2 [95% CI 1.11-4.41]). 44.4% of TMB-H pts died within 3 months of enrollment, as compared to 11.0% of TMB-L pts (p=0.005), with an odds ratio for rapid death, adjusted for number of previous lines of therapy and receptor subtype, of 6.7 (95% CI 1.5-31.0).
**Conclusion** MBC pts who are TMB-H represent a population who are highly resistant to standard therapies, progress rapidly, and have significantly shorter overall survival with more rapid time to death. Our data support further studies investigating the utility of TMB as a predictive biomarker in directing patients away from standard treatment options and towards novel approaches e.g. immunotherapy.

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# Impact of BRCA mutation status on immune infiltration, chemosensitivity, and prognosis of breast cancer patients treated with neoadjuvant chemotherapy

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Context: The majority of BRCA mutation carriers diagnosed with breast cancer (BC) are treated with chemotherapy. The effectiveness of standard neoadjuvant chemotherapy (NAC) in BRCA associated BC compared to noncarriers has been poorly explored. Objectives: To assess whether the BRCA mutation status modifies the immune infiltration, chemosensitivity, and prognosis of breast cancer. Methods: We retrospectively identified in our institutional database all consecutive patients with BRCA germline mutation status available treated with NAC between 2002 and 2012. Microbiopsy specimens and paired surgical samples were evaluated for pre-NAC and post-NAC immune infiltration (stromal TILs, str TILs; intratumoral TILs, IT TILs). Response to chemotherapy was assessed by pathological complete response (pCR) rates. Association of clinical and pathological factors with pCR, overall survival (OS), and relapse free survival (RFS) was assessed by univariate and multivariate analyses. Results: Overall, 267 patients were included in this study (46 BRCA carriers and 221 BRCA noncarriers). The median age at BC diagnosis was 40 years old, and most of the patients (n=227, 85%) were premenopausal. Patients repartition by subtype was as follows: luminal (n=90, 33.7%), TNBC (n=110, 41.2%), HER2-positive (n=67, 25.1%). BRCA mutation carriers were likely to have familial history of BC (73.9% vs. 52.3%, p = 0.012), and be diagnosed with TNBC (58.7% vs 37.6%; p = 0.006), than noncarriers. No pattern was significantly different between BRCA mutation subgroups regarding age, body mass index, histology, tumor size, grade or Ki67. TIL levels were available in 192 patients. Neither pre-NAC stromal TIL levels nor IT TILs were significantly different by BRCA status in the whole population, nor in each BC subtype. PCR rates were significantly higher in BRCA mutation carriers (p= 0.035), and this association remained statistically significant only in the luminal BC subtype (p=0.006) after stratification by BC subtype (Pinteraction= 0.056). After multivariate analysis, only BC subtype and pre-NAC str TILs were independent predictors of pCR. Post-NAC stromal and intra-tumoral TIL levels were significantly higher luminal subtype (p=0.009 and p=0.019, respectively). After a median follow-up of 90 months, RFS and OS were not different between BRCA carriers and noncarriers, neither in the whole population nor after stratification by BC subtype. Discussion: In our study, BRCA status was associated with an enhanced response to standard NAC, particularly in luminal BC patients, in addition to higher post-NAC TIL levels. Whether patients with luminal BC and BRCA mutation derive benefit from second line immunotherapy after NAC completion remains to determine.

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# Patient reported outcomes and health care utilization of UPMC breast cancer survivorship clinic patients

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**Background**. The number and longevity of cancer survivors is growing due to aging of the population, improving cancer treatments, and earlier detection. The Institute of Medicine has recommended creation of guideline-concordant models of cancer survivorship care and clinics for this growing population with unique needs. There is currently little data on how cancer survivors seen at a survivorship clinic fare compared to those seen in routine oncology clinics in terms of quality of life and health care utilization. At the University of Pittsburgh Medical Center (UPMC), we performed a descriptive analysis of healthcare utilization and patient reported outcomes (PROs) of cancer survivors seen at survivorship clinic compared to at oncology clinics.
**Methods**. The population consisted of breast cancer patients who received care at UPMC survivorship or oncology clinics (control) between January 2012 and December 2018. PROs were collected at each clinic visit and included the SF-12, the Edmonton Symptom Assessment Scale (ESAS), Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) scales. Cancer diagnoses and staging were obtained from the UPMC Network Cancer Registry. Patient demographics, mortality, ED visits and inpatient stays were extracted from the electronic medical record. ED utilization and inpatient admissions were examined one-year prior to survivorship care compared to 90-days after the start of survivorship care. Categorical and continuous data were examined by Wilcoxon rank sum tests and likelihood-ratio chi-squared tests, respectively. A p-value <0.05 was considered statistically significant.
**Results**. Data from 680 cancer survivors were included, of which 285 patients received their follow-up care in survivorship clinic and 395 patients received their follow up care in oncology clinics. Baseline demographics were comparable between the two groups, except survivorship clinic patients (SCPs) had higher 1-year mortality (3.5% vs. 0.5%, p=0.003) and cancer stage (62% vs. 48% ≥ stage II, p=0.044). SCPs had significantly more ED visits at baseline and their number of ED visits remained higher than control once enrolled in survivorship clinic, although this trended down after 90 days in survivorship clinic (table 1). Inpatient visits were significantly increased for SCPs as compared to controls at 90 days after enrollment in survivorship clinic (6.4% with ≥ 1 inpatient admission vs. 1.8%, p=0.003). SCPs had consistently worse PROs compared to controls. Prior to enrolling in survivorship clinic, SCPs had higher rates of moderate to severe depression (22.4% with PHQ-9 score of 10-24 vs. 7.8%, p=0.002) and anxiety (20.6% with GAD-7 scores of 10 - 21 vs. 9.2 %, p<0.001) and this remained elevated at all time points compared to controls, although these rates appeared to decrease over time. SCPs also rate their overall health lower than controls on the SF-12 and they have higher symptom severity across most ESAS symptoms.
**Conclusions**. Cancer survivors who are referred to and receive care in survivorship clinic have poorer quality of life and higher health care utilization at baseline and over time when compared to patients who receive care in oncology clinics. This observation suggests that survivorship clinics may be seeing cancer survivors with higher symptom burden and health care needs. This warrants future efforts to better understand, support, and prevent morbidity of survivorship clinic patients.

Table 1. ED and Hospital Utilization Among Survivorship Clinic Patients and Controls.

| | **Pre-Survivorship Clinic** | | | **After Enrollment in Survivorship Clinic** | | |
|---|---|---|---|---|---|---|
| | **1 Year** | | | **90 Days** | | |
| **# ED Visits** | **Control (%)** | **Survivorship (%)** | **P** | **Control (%)** | **Survivorship (%)** | **P** |
| 0 | 345 (87.3) | 199 (69.8) | <0.001 | 382 (96.7) | 250 (87.7) | <0.001 |
| 1+ | 50 (12.7) | 86 (30.2) | | 13 (3.3) | 35 (12.3) | |
| **# Inpatient Admissions** | | | | | | |
| 0 | 319 (80.8) | 225 (79.0) | 0.341 | 388 (98.2) | 267 (93.7) | 0.003 |
| 1+ | 76 (19.3) | 60 (21.0) | | 7 (1.8) | 18 (6.4) | |

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Natural transition targeted surgery

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Background: Breast conserving surgery is the standard in T1-T3 primary breast cancer. The cosmetic result is very much depending on the surgeon´s experience, the tumor-size/breast ratio and the technique applied. To improve cosmetic outcome and reduce repeated surgery, we have proposed a nomogram earlier (1) which has been cited by the American Society of Breast Surgeons Consensus Conference (2). In this nomogram, we proposed 5 simple oncoplastic techniques to handle the vast majority of breast cancer cases with a good cosmetic result. However, these techniques used direct access to the mammary gland, leaving scars in the visible skin of the breast. To avoid this, we chose a more natural access to the mammary gland at the natural transitions. Methods: We conducted a prospective open-arm study including all primary invasive and non-invasive breast cancer cases of tumor stages AJCC 0-III A (Version 8.0). Access to the tumor was chosen according to the proximity of the tumor to one of the following natural transitions (Areola, Lateral Insertion of the breast, inframmary fold): Non-palpable tumors and those undergoing neoadjuvant chemotherapy had to be marked by a wireand clippes before. Intraoperative ultrasound was applied before skin incision and after removal of the tumour (ultrasound of the specimen to confirm clear margins). Resection was performed as a segmentectomy and SLN biopsy and axillary clearance was done according to current guidelines.Results: 84 patients with breast conserving NTT-surgery have been enrolled so far. 76 patients had primary surgery with stage distribution as follows: Tis (1), T1a (3), T1b (8), T1c (30), T2 (30), T3 (4) and T4b(1). 8 patients had neoadjuvant chemotherapy with stage distribution as follows: ypT0 (3), ypT1a(2), ypT1c(1) and ypT2 (2). Histopathology was predominantly invasive-ductal breast cancer (70), followed by invasive-lobular (6), ductulo-lobular (5), invasive-ductal and DCIS (1),invasive-ductal and mucinous (1) and mucinous only (1). After first surgery 77 patients had a tumor resection according to the nomogramm of NTT-surgery with free margins and 7 with involved margins, thus 91,6 % tumors were resected with free margins at first surgery. The remaining 8,4 % were margin-free after second surgery. Conclusion: Scars were not visible on the surface of the breast outside of natural transitions and rate of free margins was high at 91,6 % without impairment due to the remote access to the mammary gland. We report a high patient satisfaction. Patient-reported outcome in detail has been evaluated by validated questionnaires and will be presented onsite.
References:1. Rezai M., Knispel S., Kellersmann S., Lax H., Kimmig R., Kern P: Systematization of Oncoplastic Surgery: Selection of Surgical Techniques and Patient-Reported Outcome in a Cohort of 1,035 Patients, Ann Surg Oncol (2015) 22:3730-37372. Landercasper J. et al.: Toolbox to Reduce Lumpectomy Reoperations and Improve Cosmetic Outcome in Breast Cancer Patients: The America Society of Breast Surgeons Consensus Conference, Ann Surg Oncol 22, 3174-3183 (2015)

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Evaluation of SGN-LIV1a followed by AC in high-risk HER2 negative stage II/III breast cancer: Results from the I-SPY 2 TRIAL

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**Background:** I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within molecular subtypes defined by receptor status and MammaPrint (MP) risk to evaluate novel agents as neoadjuvant therapy for women with high-risk stage II/III breast cancer. The primary endpoint is pathologic complete response (pCR, ypT0/Tis ypN0). SGN-LIV1A is an investigational antibody drug conjugate consisting of an antibody to LIV1A, a zinc transporter highly prevalent in breast cancer, and a highly potent microtubule inhibitor, monomethyl auristatin E. Retrospective IHC analysis of LIV1A expression levels amongst tumor samples from 100 previous ISPY-2 patients showed 88% of breast tumor samples with moderate to high expression of LIV1A (Yau, C. et al SABCS 2018).**Methods:** Women with tumors ≥ 2.5cm were eligible for screening. Only HER2 negative (HER2-) patients were eligible for this treatment, hormone-receptor positive (HR+) patients had to have MP high molecular profile. Treatment included SGN-LIV1A 2.5 mg/kg (max dose 250 mg) every 3 weeks x 4, followed by doxorubicin/cyclophosphamide (AC) every 2-3 weeks x 4. The control arm was weekly paclitaxel x 12 followed by AC every 2-3 weeks x 4. All patients undergo serial MR imaging where response at 3 & 12 weeks combined with accumulating pCR data are used to estimate, and continuously update, predicted pCR rate for the trial arm. Analysis set was modified intention to treat with patients who switched to non-protocol therapy counted as non-pCR and not as their pCR status at time of surgery. The goal is to identify/graduate regimens with ≥85% Bayesian predictive probability of success (i.e. demonstrating superiority to control) in a future 300-patient phase 3 neoadjuvant trial with a pCR endpoint within signatures defined by HR & HER2 status & MP result. This investigational arm was eligible for graduation in 3 of 10 pre-defined signatures: HER2-, HR+HER2- and HR-HER2-. Regimens may also leave the trial for futility (< 10% probability of success), maximum sample size accrual (10% ≤ probability of success <85%), maximum time in trial (2 years) or for safety as recommended by the independent DSMB. **Results:** Sixty patients were randomized and evaluable to SGN-LIV1A. The study arm was stopped due to reaching the predetermined time limit for patient accrual of 2 yrs. Final estimated pCR rates are below. The estimated pCR rates were similar between the SGN-LIV1A and control arms for any tumor subtype. Preliminary safety events for SGN-LIV1A include increased rates of transaminitis and hyperglycemia and reduced rates of peripheral neuropathy compared to control. One patient was removed from the analysis as she was determined to have angiosarcoma of the breast. Notably, this patient had a dramatic early response and subsequent pCR to SGN-LIV1A treatment. **Conclusion:** The value of I-SPY 2 is to give insight about the performance of an investigational agent's likelihood of achieving pCR. SGN-LIV1A delivered every 3 weeks was comparable to paclitaxel for the primary endpoint of pCR in I-SPY2 and may have a similar side effect profile, however, with less peripheral neuropathy. Clinical trials evaluating weekly dosing of SGN-LIV1A are ongoing. A trial of SGN-LIV1A in the treatment of angiosarcoma is under consideration at this time.

Final Estimated pCR Rates and Predictive Probabilities

| | Estimated pCR rate(95% prob interval) | | | |
|---|---|---|---|---|
| Signature | SGN-LIV1A | Control | Probability SGNLIV1A Superior to Control | Predictive Probability of Success in Phase 3 |
| HER2- | 0.16 (0.08-0.24) N= 60 | 0.20 (0.16-0.25) N= 327 | 0.18 | 0.02 |
| HR-/HER2- | 0.25 (0.12-0.37) N=36 | 0.28 (0.21-0.35) N=146 | 0.31 | 0.06 |
| HR+/HER2- | 0.09 (0-0.18) N=24 | 0.14 (0.09-0.19) N=181 | 0.15 | 0.03 |

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# Circulating tumor DNA (ctDNA) as a diagnostic tool to identify putative germline *BRCA* mutations

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**Background:** As the role of precision medicine in metastatic breast cancer (MBC) expands, there is an increasing emphasis on diagnostic tools to characterize both somatic and germline alterations that drive carcinogenesis. Circulating tumor DNA (ctDNA) has provided an important means for *real-time*, non-invasive detection and monitoring of tumor somatic alterations without standard paired white blood cell testing. However, its application for the detection of germline mutations remains relatively understudied. Here, we characterize the role of *BRCA1&2* ctDNA mutant allele frequency (MAF) to identify underlying putative germline *BRCA1&2* mutations.

**Methods:** Patient data were retrospectively obtained under an IRB-approved protocol to review ctDNA data at Northwestern University between 2015 and 2020. All ctDNA samples were analyzed using the Guardant360 next-generation sequencing (NGS) assay (Guardant Health). Patients with ctDNA alterations in the *BRCA* genes were identified at all mutant allele frequencies (MAF). Clinical data were collected including breast cancer subtype, prior lines of therapy, tissue-based NGS and germline testing information. Separate CLIA-approved testing performed per standard of care was used as the gold standard for germline testing. Statistical analysis was used to test the association of MAF cut-offs with the presence or absence of a germline alteration. Receiver operating characteristic (ROC) analysis was performed.

**Results:** We identified 127 patients with breast cancer who underwent ctDNA collection. There were 69 HR+ HER2-, 24 HER2+, and 34 triple negative breast cancer (TN) patients. Of these, 8 patients had known *BRCA1* germline mutations, as confirmed with separate germline testing, and 9 patients had known *BRCA2* germline mutations. *BRCA1* germline mutations were significantly association with age < 40 (p=0.016) and triple negative subtype (p=0.042). Mean ctDNA *BRCA1* MAF was 2.27% (Standard Deviation {SD} 10.19%) and mean *BRCA2* MAF was 2.04% (SD 9.51%). *BRCA1/2* MAF was analyzed with respect to germline mutations through ROC analysis. For *BRCA1* ctDNA MAF cut-off 32.4% was associated with confirmed putative germline mutation. This cutoff demonstrated sensitivity of 1 and specificity of 0.99. Area under the curve (AUC) was 1.00 at this cut-off. For *BRCA2*, ctDNA MAF cutoff of 28.5% was associated with confirmed putative germline mutations. This cutoff demonstrated sensitivity of 0.86, specificity of 0.99 and AUC of 0.93.

**Discussion:** ctDNA alterations of *BRCA1* with MAF>32.4% and *BRCA2* with MAF>28.5% in clinical ctDNA testing were useful criterion to identify germline *BRCA* mutations. The data suggest the potential to utilize ctDNA as a diagnostic tool to predict germline mutations based on MAF thresholds. Future prospective studies are needed to determine how ctDNA testing may be incorporated into existing clinical algorithms to refer patients for germline testing.

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**Publication Number:** PD6-10

# $^{18}$F-fluoroestradiol (fes) and $^{18}$f-fluorodeoxyglucose (fdg) pet imaging in metastatic lobular breast cancer

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Background: The histology and pattern of spread in lobular breast cancer has presented challenges in estimating extent of disease by traditional imaging methods. $^{18}$F-FES is an estrogen analogue PET imaging tracer which measures tumor ER expression at multiple tumor sites simultaneously. It is FDA approved in the US and will be available in 2021, pressing clinicians to define the role of FES in patients with breast cancer before use in practice. We compared quantitative FES-PET and clinical FDG-PET SUV uptake between patients with metastatic lobular carcinoma.
Methods: Metastatic lesions in patients with primary ER+ lobular breast cancer were retrospectively evaluated with FES- and FDG-PET. SUV uptake was calculated in 38 patients enrolled in various studies at our institution. Up to ten matched lesions in each patient were assessed for a total of 192 lesions. Pairwise t-tests were performed to measure the difference between paired FES and FDG lesions.
Results: Among metastatic breast cancer patients with lobular histology, 87% of patients had a positive FES scan. The majority of positive scans demonstrated uptake in all sites, with only a small percentage (6%) lacking FES uptake in at least one lesion. Uptake was noted in various metastatic tumor sites including bone (78%), soft tissue/lymph node (17%), breast (8%) and lung (1%). Mean (range) SUVmax in FES and FDG respectively was 3.38 (0.88, 9.08) and 4.14 (1.25, 9.49). Paired lesion analysis showed concordance between the two imaging modalities in lesions with low SUV uptake. FES and FDG uptake, however, could be discordant in both directions (FES > FDG, and FDG > FES) when there is higher level of uptake in at least one of the tracers. This was specifically seen in the 150 bone lesions, possibly indicating differences in lesion phenotype or response to therapy.
Conclusions: FES and FDG scans demonstrate similar average SUV uptake in metastatic lobular breast cancer, suggesting that both scans have utility in detecting lobular histology. Our data suggests that at higher SUV values, FES may provide additional information to FDG. Discordance between FES and FDG SUV uptake in the same lesions, especially in bone, has important implications for staging and assessing response to therapy. Large prospective trials are needed to define the clinical utility of FES-PET in metastatic lobular breast cancer.
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# Inhibition of estrogen biosynthesis by hops, licorice species, and their bioactive compounds

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**Introduction:** Breast cancer risk continues to rise following menopause, despite the cessation of ovarian estrogen synthesis. Pathways involving increased aromatase activity and inflammation in the breast microenvironment are implicated. Their concerted disruption could be protective against breast cancer. Popular botanicals for menopausal health, such as hops (*Humulus lupulus*), three licorice species (*Glycyrrhiza glabra*, *Glycyrrhiza inflata*, *Glycyrrhiza uralensis*) extracts, and their bioactive compounds have shown estrogenic and chemopreventive properties *in vitro* and *in vivo*. Their effects on aromatase expression and activity, and on inflammatory responses in the breast are not well characterized.**Methods:** Inhibition of aromatase activity by hops extract, its compounds (8-prenylnaringenin, 6-prenylnaringenin, and xanthohumol); three licorice extracts, and their bioactive compounds, (liquiritigenin, isoliquiritigenin, 8-prenylapigenin, and licochalcone A) were evaluated fluorometrically, using aromatase supersomes. Computational docking was performed to assess the binding of the bioactive compounds to the binding pocket of aromatase crystal structure compared to the known aromatase inhibitors, letrozole (non-steroidal) and exemestane (steroidal). Using qPCR, the effect of treatments on aromatase mRNA expression in breast microstructures of menopausal women was evaluated. The effects of hops and licorice on transactivation of NF-kB in MCF-7 breast cancer cells were studied, using a luciferase assay.**Results:** Among the extracts, one of the licorice species, *Glycyrrhiza inflata* showed the highest aromatase inhibitory potency ($IC_{50} \approx 1$ µg/mL). Among the compounds, the phytoestrogens 8-prenylnaringenin ($IC_{50} = 50$ nM or 17 ng/mL) from hops, liquiritigenin (400 nM or 0.1 µg/mL), and 8-prenylapigenin ($IC_{50} \approx 590$ nM or 0.2 µg/mL) from licorice exhibited the highest potency. Computational docking suggested that these phytoestrogens bind to the aromatase binding pocket like the aromatase inhibitor, letrozole. This effect was not observed with non-estrogenic bioactive compounds including 6-prenylnaringenin and xanthohumol from hops as well as isoliquiritigenin and licochalcone A from licorice. Hops and 8-prenylnaringenin reduced aromatase expression in breast microstructures by 60% ($P < 0.05$). Moreover, hops and licorice extracts suppressed NF-kB-luciferase activity by 70% in MCF-7 cells ($P< 0.01$). **Conclusions:** Hops, licorice species, and their phytoestrogens inhibit aromatase activity and expression. The extracts suppress NF-kB transactivation in MCF-7 cells, suggesting inhibition of inflammatory response. Further studies will better elucidate the potential of these popular botanicals and their bioactive compounds for preventing breast cancer in menopausal women.

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# Monitoring neoadjuvant chemotherapy using diffuse optical tomography breast imaging system

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**Background:** Optical based imaging modalities have shown promise for monitoring tumor response to neoadjuvant chemotherapy (NAC) in patients with breast cancer. In this study, we evaluate whether changes in deoxy-hemoglobin concentration values acquired by a Diffuse Optical Tomography Breast Imaging System (DOTBIS) over different time points are associated with tumor response.
**Methods:** This is a retrospective evaluation of 55 stage II-III BC patients in the neoadjuvant setting who received weekly paclitaxel x 12, followed by dose-dense adriamycin/cyclophosphamide every 2 weeks x 4. The patients were enrolled in this cohort study between 2011 and 2019, and DOTBIS images were acquired from the patient whole breast volume at 6 different time points: at baseline (TP0); two weeks after the first taxane infusion (TP1); after four infusions of taxane (TP2); at the end of the taxane regimen and before starting AC cycle (TP3); after two AC infusions (TP4); and at the end of NAC and before surgery (TP5). ctHHb tumor concentration was measured using low-intensity near-infrared light and normalized by the non-tumor region ctHHb mean value ($ctHHb_N$). In order to evaluate whether pCR status, menopausal status, and molecular subtype classification influence the change of $ctHHb_N$ over time, we designed a multilevel mixed-effect statistical model. pCR was defined as no invasive tumor cells from the breast and axillary tissue at surgery (ypT0 ypN0).
**Results:** 20 patients had pCR and 35 were classified as non-pCR. The estimate average $ctHHb_N$ for pCR tumors at baseline was 4.02. There was a significant reduction in $ctHHb_N$ levels for pCR group at TP1 (-1.31, p = .0001) and TP2 (-1.36, p = .0416). Changes in $ctHHb_N$ levels compared to baseline (TP0) values were statistically significant different between pCR and non-pCR at all time points except at the end of the taxane cycle (TP3), Table 1. No significant changes over time were identified between molecular subtypes groups, or between pre- and post-menopausal status.
Table 1 - Changes in $ctHHb_N$ levels compared to baseline (TP0) values between pCR and non-pCR at all imaging time points. Bold values indicate statistical significance at p <.05 level.

| Time Point | Mean Difference ± Std. Error | p-value |
|---|---|---|
| TP1 | 1.92 ± 0.40 | **0.0000** |
| TP2 | 2.04 ± 0.82 | **0.0145** |
| TP3 | 0.83 ± 1.03 | 0.4198 |
| TP4 | 2.71 ± 0.87 | **0.0021** |
| TP5 | 2.63 ± 0.90 | **0.0037** |

**Conclusions:** Our study adds to the body of evidence reported for diffuse optical imaging methods applied to breast cancer treatment response. These results show that DOTBIS measured features, such as $ctHHb_N$, change in accordance with pCR status after 2 weeks under NAC, and there are differences in time evolution between the pCR groups. Reduction in $ctHHb_N$ levels represents the chemotherapeutic- induced changes in the tumor microvasculature: lower $ctHHb_N$ values associate with the reduction in tumor cell proliferation, and consequently in oxygen consumption. Future studies are warranted to evaluate whether early response prediction might determine if earlier treatment changes alter patient outcome.

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# How low is low risk: MINDACT updated outcome and treatment benefit in patients considered clinical low risk and stratified by genomic signature, age and nodal status

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**Background** With 8.7 years follow-up, the prospective phase III randomized MINDACT trial (EORTC 10041/BIG3-04) continues to meet its primary objective, i.e. 95.1% (95%CI 93.1-96.6), 5-year distant metastasis-free survival (DMFS) in clinical high (C-High)/genomic low (G-Low) risk patients who did not receive adjuvant chemotherapy (ACT) (Cardoso et al., ASCO 2020). In addition, about half of the MINDACT patients had a low clinical risk (C-Low) defined by pre-specified clinical-pathological characteristics. Here, we evaluated the outcome of this C-Low population stratified by the 70-gene signature (MammaPrint®) (G-Low or G-High) for outcome considering age, and present data on the total G-low population (C-Low and C-High combined). **Methods** Of 6693 patients enrolled in the MINDACT trial between 2007 and 2011, 3337 were C-Low, characterized as mainly T1, grade 1 or 2, and node negative. We evaluated the pre-specified DMFS, distant metastasis free interval (DMFI), and overall survival (OS) rates at 5 and 8 years in the C-Low population: i) in patients with genomic low risk (C-Low/G-Low, n=2744) who were recommended to receive endocrine therapy only (for 99% HR+), and ii) in C-Low/G-High who received ACT or not following randomization (ITT, n=690, 81% HR+). Exploratory analyses by age, ≤50 and >50, were conducted for ACT vs no ACT received in C-Low/G-High. In parallel we estimated survival rates for all G-low patients if all would have followed the genomic low risk assignment and received no ACT (C-Low/G-Low, and C-High/G-Low randomized to no ACT double weighted, n=4130). We used Kaplan-Meier estimates for time to event endpoints and hazard ratios with 95%CI from Cox-regression models adjusted for stratification factors used for the randomization. **Results** C-low/G-low patients who were recommended endocrine therapy only (compliance > 79%, based on local guidelines) have excellent 5 and 8 year survival rates for all endpoints (Table 1). The estimated survival rates for all G-Low patients, if all would have followed the genomic low risk assignment and received no ACT, is excellent as well (Table 1), albeit this population includes both C-Low and C-High patients. The survival estimates for C-Low/G-High patients are for all endpoints a few percentage points lower than for the C-Low/G-Low group (Table 1). At 8 years of follow-up, in the relatively small subset of 690 patients with C-Low/G-High tumors assigned to ACT or not by randomization (ITT), a 1.5% (SE ±2.3%) higher DMFS is seen in the ACT group, and a 2.9% (SE ±2.0%) higher DMFI. This suggested benefit is mostly seen in patients under 50 years of age (absolute Δ in DMFS for ACT vs no ACT at 8 years: 5.4% for age ≤50 vs -0.3% for age >50). **Conclusion** Patients with a 70-gene G-Low risk tumor have an excellent 8 year outcome in the context of C-Low characteristics when recommended for endocrine therapy only, very close to the outcome in the larger group of all G-Low patients regardless of clinical risk. Stratification of C-Low patients in to G-Low and G-high provides meaningful information. The benefit of ACT in C-Low patients with a 70-gene G-High risk tumor needs further confirmation, especially relevant in younger women.

**Table1**

| | ***All Patients Population*** | ***Patients*** | ***Observed events*** | ***% at 5 years (95% CI)*** | ***% at 8 years (95% CI)*** |
|---|---|---|---|---|---|
| **DMFS** | **C-Low / G-Low** | 2744 | 170 | 97.3 (96.6-97.9) | 94.7 (93.8-95.6) |
| **C-Low / G-High** | 593 | 61 | 94.2 (92.0-95.9) | 91.1 (88.4-93.3) | |
| **DMFI** | **C-Low / G-Low** | 2744 | 103 | 98.5 (97.9-98.9) | 96.7 (95.9-97.3) |
| **C-Low / G-High** | 593 | 46 | 95.8 (93.8-97.2) | 93.5 (91.0-95.3) | |
| **OS** | **C-Low / G-Low** | 2744 | 122 | 98.2 (97.6-98.7) | 96.5 (95.7-97.2) |
| **C-Low / G-High** | 593 | 44 | 96.8 (94.9-98.0) | 93.1 (90.5-95.0) | |
| | ***Patients G-low (C-Low & C-High)*** | ***Patients*** | ***Estimated events*** | ***% at 5 years*** | ***% at 8 years*** |
| **DMFS** | **All G-Low - no ACT** | 4130 | 339 | 96.4 | 92.8 |
| **DMFI** | **All G-Low - no ACT** | 4130 | 244 | 97.4 | 94.6 |
| **OS** | **All G-Low - no ACT** | 4130 | 223 | 97.9 | 95.7 |

**2020 San Antonio Breast Cancer Symposium®**

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# Efficacy and safety of enobosarm, a selective androgen receptor modulator, to target AR in women with advanced ER+/AR+ breast cancer - final results from an international Phase 2 randomized study

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Introduction: Hormonal agents remain the most effective therapies for estrogen receptor positive (ER+) HER2- breast cancer. The androgen receptor (AR) is the most highly expressed steroid receptor found in up to 95% of ER+ breast cancer patients. Androgen agonists have antiproliferative activity in ER+ breast cancer and have been used in treatment, however their lack of availability and virilizing side effects have limited their use. Enobosarm is a non-steroidal tissue-selective AR modulator that that is being developed for AR targeted treatment of ER+/AR+ breast cancer.
Methods: An international, Phase 2, open label, parallel design, randomized study was conducted in 136 patients (pts) to investigate the efficacy and safety of enobosarm in postmenopausal women with metastatic ER+/AR+ breast cancer that progressed on previous endocrine therapy. Pts were randomized to receive 9 mg (n=72) or 18 mg (n=64) of oral daily enobosarm. The primary endpoint was clinical benefit rate (CBR) at 24 weeks (defined as CR, PR or SD) by RECIST 1.1. Secondary endpoints included objective response rate, best overall response rate (BOR), progression free survival (PFS), duration of clinical benefit.
Results: The study population consisted of heavily pre-treated pts with a mean of 4 (range 1-6) prior hormone therapies and >90% receiving one prior course of chemotherapy. Median age was 60.8 years (35-83) for 9 mg and 62.1 (42-81) for the 18 mg cohort. AR positivity was centrally confirmed in 73.6% and 81.2% in the 9 and 18 mg cohorts, respectively. Efficacy: In the evaluable pts, 50 in the 9 mg arm and 52 in the 18 mg arm (AR confirmed), 32% of the 9mg cohort met the primary endpoint of CBR at 24 weeks (95% CI, 19.5%; 46.7%) and 29% (95% CI, 17.1%; 43.1%) in the 18 mg cohort. The BOR was 2 CRs, 10 PRs in the 9 mg and 3 CRs,7 PRs in the 18 mg group by central review. Median PFS was 5.6 (2.9 to 27.5) and 4.2 (2.8 to 11) months (mo) in the 9 mg and 18 mg groups. The median duration of treatment was 4.0 months (0.23-30.3 months) in the 9 mg group and 3.8 months (0.5-16.7 months) in the 18 mg group. At the time the study was terminated, the median duration of clinical benefit was not reached (NR) in the 9 mg group (range 8.2 mo to NR) and 14.1 mo (range 11.0 to 16.5) in the 18 mg group.
QOL: Using a standardized instrument of generic health status (EQ-5D), a significant percentage of pts reported improvement in measurements including mobility (40%, 50%), anxiety/depression (50%, 29%) and pain discomfort (50%, 31%) for the 9 and 18 mg groups, respectively. Drug related severe adverse events (SAEs) (Grades 3-4) were observed in 6 (8.0%) at the 9 mg and 10 (16.4%) at the 18 mg dose. The SAEs (Grade 3-4) attributed to the study drug by the site investigator were for the 9 mg group: fatigue (1), elevated transaminases (2), headache (1), hypercalcemia (2) and anemia (1). For the 18 mg group the drug attributable SAEs (Grade 3-4) were: dry mouth (1), increased aminotransferase (2), decreased white blood cell count (1), fatigue (2), hypercalcemia (1), decreased appetite (1), headache (1), tumor flare (2), agitation (1), lymphadenopathy (1) and acute kidney injury (1).
Conclusions: In this Phase 2 parallel design study, enobosarm (9 mg and 18 mg) has significant clinical activity and was well tolerated in heavily pretreated patients with ER+/AR+ metastatic breast cancer. Given the limited options of hormonal therapy for metastatic ER+ breast cancer, enobosarm merits further clinical development in a Phase 3 clinical program as an AR targeted treatment for metastatic ER+AR+ breast cancer.

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# Identification of BBOX1 as a therapeutic target in triple-negative breast cancer

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Triple-negative breast cancer (TNBC), which accounts for 15-20% of breast cancers, causes the highest mortality rate among all breast cancer subtypes. Due to its heterogeneity and lack of estrogen and progesterone receptor or human epidermal growth factor receptor 2 expression, valuable targeted therapy is limited. Therefore, it is critical to identify novel therapeutic targets in TNBC. 2-oxoglutarate (2-OG)-dependent enzymes, including prolyl hydroxylases (EglN1-3), histone demethylases (for example, KDM5A) and DNA hydroxylases (such as TET1-3), are associated with cancer progression. However, the role of these enzymes in TNBC has never been systematically studied. Here, by performing a functional siRNA screening for 2-OG-dependent enzymes, we identified gamma-butyrobetaine hydroxylase 1 (BBOX1) as an essential gene for TNBC tumorigenesis. BBOX1 depletion inhibits TNBC cell growth, while not affecting normal breast cells. Mechanistically, BBOX1 binds with the calcium channel inositol-1,4,5-trisphosphate receptor type 3 (IP3R3) in an enzymatic-dependent manner and prevents its ubiquitination and proteasomal degradation. BBOX1 depletion suppresses IP3R3 mediated endoplasmic reticulum calcium release, therefore impairing calcium-dependent energy-generating processes including mitochondrial respiration and mTORC1 mediated glycolysis, which leads to apoptosis and impaired cell cycle progression in TNBC cells. Therapeutically, genetic depletion or pharmacological inhibition of BBOX1 inhibits TNBC tumor growth in vitro and in vivo. Our study highlights the importance of targeting previously uncharacterized BBOX1-IP3R3-calcium oncogenic signaling axis in TNBC.

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# Survival outcomes and prognosis for patients with triple negative breast cancer who received stereotactic radiosurgery for brain metastases

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**Background**: Triple-negative breast cancer (TNBC) has a high propensity for brain metastasis (BM) with poor prognosis. Stereotactic radiosurgery (SRS) has emerged as an effective treatment option for BM. However, clinical outcomes after SRS for BM from TNBC have not been well defined. We evaluated survival outcomes and prognostic factors among TNBC patients who received SRS for BMs.**Methods:** We retrospectively reviewed 99 patients with TNBC and BM who had received SRS at a single large-volume cancer center from May 2008 through April 2018. For the initial treatment of BM, 73 patients received SRS, 25 received whole-brain radiotherapy (WBRT), and 1 patient received surgery. Endpoints were overall survival (OS) from BM diagnosis, BM progression-free survival (BMPFS) from start of BM treatment, and times to intracranial local and distant failure from start of BM treatment. Both intracranial local and distant failure were considered BM progression. Local failure was defined as an increase in size of any treated lesions on imaging or assessment of treating physicians; enlargement attributable to radiation necrosis or post-radiation change was not counted as local failure. Kaplan-Meier analysis and Cox proportional hazard regression models were used to estimate survival curves and identify prognostic factors.**Results:** The median follow-up time from BM diagnosis was 12.7 months (95% confidence interval [CI] 1.3–52.1). The median age at BM diagnosis was 52 (range 24-82). The median interval between the diagnosis of primary breast cancer and BM was 25.8 months (95% CI 8.7–120.3). Of the 99 patients, 81 (81.8%) had 1-3 BMs and 18 (18.2%) had >3 BMs at diagnosis. The median OS time for all patients was 13.3 months (95% CI 10.3–16.4), and the cumulative survival rates were 55.1% at 1 year and 29.2% at 2 years. Factors independently associated with increased risk of death in multivariate analysis were Karnofsky performance score (KPS) ≤70 ($p$=0.01) and uncontrolled extracranial metastasis at BM diagnosis ($p$=0.05). No difference was found in OS according to type of initial treatment for BMs. Of the initial 99 patients, 12 were excluded from the evaluation of BMPFS, local and distant failure for missing follow-up imaging after initial treatment. The median BMPFS time was 7.2 months (95% CI 5.1–9.3). Of the 87 evaluable patients, 23 (26.4%) developed local recurrence after initial treatment, and among these 10 of 61 patients (16.4%) had received SRS and 13 of 25 patients (52%) had received WBRT. Patients initially treated with SRS had longer time to local failure than WBRT (50$^{th}$ percentile not reached vs. median 14.0 months, $p$=0.001). Multivariate analysis showed higher risk of local failure for patients who initially received WBRT versus SRS (hazard ratio [HR] 3.4, $p$=0.005). Forty-nine of 87 patients (56.3%) developed distant brain recurrence after initial treatment, and among these 35 of 61 patients (57.4%) had received SRS and 14 of 25 patients (56%) had received WBRT. No difference in risk of distant brain failure was found for patients initially treated with SRS versus WBRT ($p$=0.24). No difference was found in time to develop distant failure after initial treatment with SRS (median 18.4 months) versus WBRT (median 12.8 months, $p$=0.24).**Conclusion:** Patients with BM from TNBC had a median OS time of 13.3 months and a BMPFS time of 7.2 months. KPS≤70 and uncontrolled extracranial disease at the time of BM diagnosis were independent prognostic factors that increase risk of death. Patients initially treated with SRS had a longer time to develop intracranial local failure than those initially given WBRT, and this may be related to patient selection. Further prospective studies of larger numbers of
patients with BM from TNBC are needed for a more accurate comparison of treatment modalities

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# Impact of COVID-19 on study sites: Survey analysis from the noninterventional POLARIS study

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**Background:** The COVID-19 pandemic is negatively affecting patient enrollment, therapy administration, and patient visits in breast cancer clinical trials worldwide. COVID-19 may have a lasting impact on how clinical trials are conducted, and guidelines are necessary to inform trial design and patient safety. While many groups and journals have recently published guidelines, including NCCN, ESMO, IQVIA, and *Lancet Oncology*, there is no consensus on how to treat patients in the current environment. Understanding and quantifying the impact of the pandemic on clinical study sites will help inform the rational development of a consensus approach. The goal of this survey was to gather site-level data on the impact of COVID-19 from clinical sites participating in the POLARIS study (NCT03280303), an ongoing, prospective, real-world, noninterventional study in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer receiving palbociclib plus endocrine therapy. **Methods:** Two rounds of questionnaires were sent to investigators at POLARIS study sites: 1 via email March 26-27, 2020, and 1 via telephone from April 30-May 20, 2020. The questions on COVID-19 impact and management are shown in the **Table**. **Results:** Eighty of 122 POLARIS study sites contacted responded to the March questionnaire, and 86 responded to the April-May questionnaire. In March, 33% (26/80) of the surveyed population were working predominantly remotely, 26% (21/80) were working both onsite and remotely, and 31% (25/80) were working onsite. Approximately 24% of sites reported delayed data entry. The option of telemedicine or office visits was offered to subjects at approximately 73% (58/80) of sites, and 11% (9/80) of sites were restricted to telemedicine visits. In April-May, 36% (31/86) of respondents reported an impact on study management and 64% (55/86) reported no impact. Approximately 94% (81/86) of surveyed sites felt they were able to maintain clinical studies despite the challenges due to COVID-19, and 79% (68/86) of sites had the option for telemedicine and/or office visits, while 18% (16/86) had no telemedicine alternative. In April-May, 38% of sites reported an impact on patient visits. **Conclusion:** Although these findings must be interpreted with caution due to the limitations of survey studies, the results suggest that approximately 1/3 of the study sites will experience an impact on their responsiveness to correspondence, timely data entry, and subject management due to the COVID-19 pandemic. Telemedicine may be used to mitigate the effect of the pandemic on clinical trial execution. Pfizer (NCT03280303)

Table. Survey Questions

| **March Questionnaire (March 26-27, 2020)** | |
|---|---|
| Question | Responses |
| Working onsite or remotely? | 26 sites are predominately working remotely<br>21 sites are working a combination of onsite and remotely<br>25 sites are working onsite<br>7 sites provided inconclusive responses |
| Subject visits in office, by phone, by video, or a combination of 3 options? | 50 sites are using a combination of onsite and telemedicine<br>8 sites have onsite visits<br>9 sites have telemedicine visits only<br>8 sites provided inconclusive responses<br>4 instances where question was inapplicable due to no active subjects |
| Is data entry delayed? | 19 sites responded Yes<br>54 sites responded No<br>6 sites provided inconclusive responses |
| Is collection of biomarker blood samples impacted? | 11 sites indicated there will be impact to biomarker collection<br>28 sites indicated there will be no impact to biomarker collection<br>40 instances where question was inapplicable due to no subjects participating in collection |
| What other study areas are impacted? | 20 sites indicated impact due to financial challenges or limited abilities while working remotely<br>Remaining sites did not note any additional areas of impact |
| Patient-reported outcome questionnaire issues? | Most sites had not experienced any issues, but an overwhelming majority inquired about the ability to do them via phone or mail. Many sites and subjects expressed preference for the paper questionnaire instead of the electronic version. |
| **May Questionnaire (April 30-May 20, 2020)** | |
| Question | Responses |
| Has COVID-19 impacted your site's ability to execute a study?<br>• Clarify impact on your site | 55 sites responded No<br>31 sites responded Yes<br>• Subject visits impacted (limited onsite visits): 24<br>• Institutional restrictions/limited staff: 7 |
| Is there any impact on scheduled onsite standard of care patient visits? | 53 sites responded No<br>33 sites responded Yes |
| Please indicate which if any of the following apply to your site:<br>Process in place for remote patient study visits<br>Process is used for remote patient study visits<br>Alternative methods are available to deliver drug<br>Other | 67 sites responded that telemedicine is in place for subject visits<br>16 sites responded that there is no alternative for telemedicine<br>1 site noted that they have no active subjects<br>1 site noted that subjects are attending on site visits<br>1 site did not respond to question |
| How able are you to maintain ongoing studies at this time?<br>Extremely able to do so<br>Very able to do so<br>Moderately able to do so<br>A little able to do so<br>Not at all able to do so | 27 sites are extremely able to do so<br>42 sites are very able to do so<br>12 sites are moderately able to do so<br>5 sites are able to do so only a little<br>• COVID impact is felt more profoundly at 4 sites<br>• Financial barrier has limited one site's time on study<br>0 Sites unable to do so at all |

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# Can composite risk model help clinicians make adjuvant ovary function suppression dicision for breast cancer patients

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**Background:** Composite measure of recurrence risk with certain clinicopathologic characteristics provided prognostic and adjuvant ovarian function suppression (OFS) therapeutic effect information for patients in the TEXT and SOFT trials, but the role of this composite risk score (CRS) in OFS treatment decision-making has not been established. We carry out this study to evaluate the association of CRS with OFS treatment recommendation in our multidisciplinary team (MDT) treated patient cohort.**Methods:** Premenopausal patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative breast cancer who received surgery between April 2013 and December 2018 and had OFS decision-making made by MDT were included. The association of CRS with OFS recommendation and survival outcome were analyzed.**Results:** Totally 887 patients were identified, amongst which 239 (26.94%) were recommended to receive OFS. The median CRS was 1.92, 455 (51.3%) patients were categorized as low-risk and 432 (48.7%) as high-risk. Age < 35 years (OR = 24.68, 95% CI 12.97-46.95, P < 0.001), ≥ 4 ALNs metastasis (OR = 3.95, 95% CI 2.08-7.48, P < 0.001), ER ≥ 50% (OR = 5.45, 95% CI 2.16-13.75, P < 0.001) and CRS high-risk (OR = 2.82, 95% CI 1.62-4.91, P < 0.001) were independently predictive of OFS recommendation. CRS also served as an effective predictor of OFS recommendation in receiver operating characteristics (ROC) curve analysis (AUC = 0.775, P < 0.001). CRS high-risk was related to worse breast cancer-free interval (BCFI) (89% vs. 97.6%, HR 8.98, 95% CI 2.73-29.51, P < 0.001), no significant differences in overall survival (OS) were found between patients with CRS high and low-risk (96.5% vs. 99.8%, HR 5.5, 95% CI 0.66-45.73, P = 0.076).**Conclusions:** CRS was associated with OFS recommendation and BCFI in premenopausal patients with HR positive/HER2 negative breast cancer, which may be integral to their individualized OFS treatment decision-making.

Table 1. Clinicopathologic characteristics, CRS and OFS recommendation

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| characteristics | No-OFS N = (%) | OFS N = (%) | P value | OR | 95% CI | P value |
| Age (years) | | | < 0.001 | | | < 0.001 |
| < 35 | 21 (23.33) | 69 (76.67) | | 24.68 | 12.97-46.95 | < 0.001 |
| 35-39 | 40 (30.77) | 90 (69.23) | | 22.87 | 13.59-38.48 | < 0.001 |
| ≥ 40 | 587 (88.01) | 80 (11.99) | | 1 | | |
| Histologic grade | | | < 0.001 | | | 0.054 |
| I | 84 (94.38) | 5 (5.62) | | 1 | | |
| II | 409 (73.96) | 144 (26.04) | | 3.69 | 1.28-10.65 | 0.016 |
| III | 155 (63.27) | 90 (36.73) | | 3.48 | 1.11-10.86 | 0.032 |
| Tumor size | | | 0.012 | | | 0.172 |
| ≤ 2cm | 428 (75.89) | 136 (24.11) | | 1 | | |
| > 2cm | 220 (68.11) | 103 (31.89) | | 0.72 | 0.45-1.15 | |
| ALN status | | | < 0.001 | | | < 0.001 |
| 0 | 421 (80.04) | 105 (19.96) | | 1 | | |
| 1-3 | 171 (68.95) | 77 (31.05) | | 1.9 | 1.14-3.17 | 0.014 |
| ≥ 4 | 56 (49.56) | 57 (50.44) | | 3.95 | 2.08-7.48 | < 0.001 |
| ER | | | 0.022 | | | < 0.001 |
| < 50% | 53 (85.48) | 9 (14.52) | | 1 | | |
| > 50% | 595 (72.12) | 230 (27.88) | | 5.45 | 2.16-13.75 | |
| PR | | | 0.052 | | | |
| < 50% | 202 (68.94) | 91 (31.06) | | | | |
| ≥ 50% | 446 (75.08) | 148 (24.92) | | | | |
| Ki67 | | | < 0.001 | | | 0.466 |
| < 14% | 270 (84.38) | 50 (15.63) | | 1 | | |
| 14%-19% | 48 (70.59) | 20 (29.41) | | 1.65 | 0.77-3.53 | 0.202 |
| 20%-25% | 127 (73.84) | 45 (26.16) | | 1.11 | 0.6-2.06 | 0.747 |
| ≥ 26% | 203 (62.08) | 124 (37.92) | | 1.43 | 0.8-2.56 | 0.231 |
| CRS | | | < 0.001 | | | < 0.001 |
| ≤ 1.92 | 405 (89.01) | 50 (10.99) | | 1 | | |
| > 1.92 | 243 (56.25) | 189 (43.75) | | 2.82 | 1.62-4.91 | |

Table 2. ROC analysis for prediction of OFS recommendation

| characteristics | AUC | P value |
|---|---|---|
| Age (years) | 0.109 | < 0.001 |
| Histologic grade | 0.601 | < 0.001 |
| Tumor size | 0.596 | < 0.001 |
| ALN status | 0.624 | < 0.001 |
| ER | 0.514 | 0.53 |
| PR | 0.442 | 0.008 |
| Ki67 | 0.622 | < 0.001 |
| CRS | 0.775 | < 0.001 |

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Trends in incidence and stage of male breast cancer, 2004-2016: An analysis from the national cancer database

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**Background:** Male breast cancer has been less well studied due to the rarity of this condition compared with female breast cancer. Men have traditionally presented at later stages than women, leading to disparities in outcomes. Our aim was to identify the incidence of male breast cancer in recent years and determine trends in clinical and pathologic stage that could be utilized to improve breast cancer care. **Methods:** Patients diagnosed with primary breast cancer between 2004 and 2016 were identified using the National Cancer Database (NCDB), which collects hospital registry data from over 1,500 Commission on Cancer (CoC)-accredited facilities and represents more than 70% of newly diagnosed cancer cases in the United States. Patient, tumor, treatment, and facility data was compared between male and female patients. Incidence of male and female breast cancer was stratified by both AJCC clinical stage and pathologic stage (I-IV) and evaluated over the study period. **Results:** 17,814 male breast cancer patients and 2,001,551 female patients with breast cancer were identified. The incidence of male breast cancer increased by 1.5-fold from 1044 cases per year in 2004 to 1565 cases per year in 2016. The number of female breast cancer cases was 123,799 in 2004 and reached the highest annual volume of 184,718 in 2015. In 2010 incident male breast cancer cases rose by nearly 100% compared with the prior year, the majority of which represented early stage disease. In that year alone, for males there was a 99.6% increase (276 vs. 556 cases) in pathologic stage I disease, 89% increase (200 vs. 378 cases) in pathologic stage II disease and 94.7% increase (68 vs. 132 cases) in patients diagnosed with in situ disease. After 2010, incidence patterns for male breast cancer stabilized with ratio changes for Stage I or II at the level of only 1% to 7.3% per year. Interestingly, the proportion of male to female breast cancer incident cases remained constant over the study period, with males representing 0.8-0.9% of the total cases. Overall, a minority of patients presented with Stage III (6.6%) and Stage IV (4.6%) disease, though a greater proportion of males than females had advanced stage disease at diagnosis (16.88% of males vs. 11.14% females, $p< 0.001$). The incidence of clinical Stage I and II disease increased over time for both genders, though a greater proportion of female breast cancer was Stage I (43.2% female vs. 35.93% male, $p<0.001$), and Stage II disease was more common in men (33.83% male vs 24.22% female, $p<0.001$). When pathologic stage was considered, Stage I and II represented the majority of male breast cancer cases, 74.7% to 80% per year, and was slightly higher than the combination of Stage I and II at clinical diagnosis, 65.7% to 78.7% per year. **Conclusions:** Over past 15 years, the incidence of male breast cancer has increased substantially, yet remains a stable proportion of total breast cancer cases. The greater frequency of Stage II, III and IV disease in men likely reflects the difference in diagnosis by clinical exam or symptoms in men vs. screening programs in women. Education to increase awareness of male breast cancer, promote symptom recognition, and encourage appropriate use of genetic testing should be emphasized to improve early diagnosis of breast cancer in men.

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# Patient perspectives on chemotherapy de-escalation: “Don’t de-escalate! I don’t want to die!”

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**Introduction:** Given excellent survival outcomes in breast cancer and new methods to predict treatment response, oncologists are interested in de-escalating the amount of chemotherapy delivered to patients. This is particularly important in the setting of COVID-19, where patient perspectives of de-escalation may be altered by perception of COVID-19 risk.**Methods:** This concurrent mixed methods study included (1) semi-structured interview data from patients with breast cancer treated at the University of Alabama at Birmingham and patient advocates from nationally representative advocacy organizations (10/2019-5/2020) and (2) cross-sectional survey data from a nationwide sample of women with breast cancer (11/19-12/2019). Questions evaluated interest in de-escalation study participation, perceived barriers/facilitators to participation, and language describing de-escalation. Participant perspectives surrounding COVID-19 impact on de-escalation were elicited in interviews post 3/2020.**Results:** Quantitative and qualitative findings were synergistic. Interviews were conducted with 40 female participants (24 patients, 16 patient advocates). Participant ages ranged from 33-79 years old; 30% were minorities; 35% didn’t have a college degree. Common barriers to acceptance of de-escalation included fear of recurrence, worry about decision regret, lack of clinical trial interest, and dislike for the focus on less treatment. Fear of recurrence was the most commonly expressed barrier, with one participant stating, “I’m just afraid it wouldn’t get it all”. Common facilitators included trust in the physician, toxicity avoidance, monitoring with the option of increasing treatment intensity, perception of good prognosis, and impact on daily life. Participants interviewed during the COVID-19 pandemic (n=16) expressed substantial virus-related fear, including fear of exposure, fear of infecting their personal contacts or health care team, fear of cancer-related complications, and fear about their immunocompromised state. These fears contributed to participants perspective on de-escalation, as highlighted by participants stating, “I wouldn't worry about getting the chemo as much as I would worry about getting the virus” and “Less is more for me right now”.Of 91 survey respondents (69% response rate), median age was 58 years (interquartile range [IQR] 48-69), 86% had early stage breast cancer. Many (43%) patients were not interested in participation in a study testing lower doses of chemotherapy than standard of care. Patients not interested in participating were more often unmarried (55% vs. 32%, V=.23), disabled (56% vs. 40%, V=.17), or diagnosed with early stage cancer (45% vs. 22%, V=.14). Barriers to participation included fear of cancer recurrence (85%) and regret about the decision to receive less chemotherapy if the cancer were to recur (79%). Few patients (19%) considered clinical trials themselves as a barrier. Patients were interested in participation due to lessened physical side effects of treatment (82%), lessened long-term problems related to treatment (76%), and lessened impact on daily life (72%). The most popular terminology describing chemotherapy de-escalation was “lowest effective chemotherapy dose” (53%); no patients preferred the term “de-escalation.”
**Conclusion:** Fear of recurrence is a common barrier to de-escalation clinical trial participation in patients with breast cancer. Fears may be altered for patients considering treatment during the COVID-19 pandemic. Trust in the physician and use of patient-generated language, such as “customized” instead of “de-escalation”, are potential areas for future interventions engaging patients in trials.

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# Ribociclib + letrozole in premenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Subgroup analysis of the phase IIIb CompLEEment-1 trial

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**Background:** The oral, selective cyclin-dependent kinase 4/6 inhibitor, ribociclib (RIB), has demonstrated significant overall survival benefit in combination with endocrine therapy (ET) in premenopausal patients with HR+, HER2- ABC. Here, we present a subgroup analysis of premenopausal patients from the Core Phase of CompLEEment-1 (NCT02941926), a Phase IIIb trial of RIB in combination with letrozole (LET) in patients with HR+, HER2- ABC, which included a more diverse and broader patient population, reflecting a real-world clinical setting. **Methods:** CompLEEment-1 included women of any menopausal status and men with HR+, HER2- ABC treated with ≤1 line of prior chemotherapy and no prior hormonal therapy for advanced disease. Pts received RIB (600 mg QD, 3 weeks on/1 week off) in combination with LET (2.5 mg QD, continuous). Men and premenopausal women received a luteinizing hormone-releasing hormone agonist (3.6 mg goserelin or 7.5 mg leuprolide, Q28D). This subgroup analysis assessed the primary outcomes (safety and tolerability) and secondary outcomes of time to progression (TTP), overall response rate (ORR), and clinical benefit rate (CBR) in premenopausal women. Baseline and end-of-treatment patient quality of life (QoL) was also measured in patients from selected countries as a secondary endpoint using the FACT-B questionnaire. **Results:** At the data cutoff date (November 8, 2019), 722 premenopausal patients (22.2%; N = 3,246) had been evaluated, with a median duration of exposure to RIB of 18.3 months. Adverse events (AEs) were reported in 710 (98.3%) patients; 681 (94.3%) patients had treatment-related AEs. Grade ≥ 3 AEs were reported in 519 (71.9%) patients; severe treatment-related AEs were reported in 26 (3.6%) patients. There were no treatment-related fatal AEs. The most common all-grade AEs were neutropenia (76.9%), nausea (36.0%), and leukopenia (27.6%). The most common grade 3/4 AEs were neutropenia (57.9%), leukopenia (10.4%), and increased alanine aminotransferase (5.7%). Overall, 242 (33.5%) patients had ≥ 1 dose reduction of RIB, 170 (23.5%) due to AEs. 413 (57.2%) patients permanently discontinued treatment, 67 (9.3%) due to AEs. In this subgroup analysis, median TTP was 25.1 months (95% confidence interval [CI], 22.1-not estimable). For the 458 patients with measurable disease, ORR was 49.3% (95% CI, 44.7-54.0%) and CBR was 69.7% (95% CI, 65.2-73.8). FACT-B questionnaire assessments showed a trend that patient QoL was maintained while on treatment (n = 290). **Conclusions:** This subgroup analysis from CompLEEment-1 supports the use of RIB + LET in premenopausal patients. ORR was similar to that seen in the Phase III MONALEESA-7 trial which studied RIB + ET in a premenopausal patient population, validating the efficacy of RIB in a close-to-real-world setting. The safety profile associated with RIB + LET was manageable and consistent with previous Phase III trials of RIB + LET.

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# Phase II study of nivolumab in combination with abemaciclib plus endocrine therapy in patients with HR+, HER2- metastatic breast cancer: WJOG11418B NEWFLAME trial

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**Background:** Currently, the standard immunotherapy treatment for anti-programmed death-ligand 1 (PD-L1)-positive triple-negative breast cancer is a combination of PD-L1 antibody and nab-paclitaxel. PD-1/PD-L1 antibody was investigated as a treatment for hormone receptor positive (HR+) breast cancer; however, the efficacy of single agents is poor. In pre-clinical studies, anti-PD-1/PD-L1 antibody, CDK4/6 inhibitors, and endocrine therapy (ET) have synergistic effects. We initiated this investigator-initiated trial to evaluate the efficacy and safety of the combination of nivolumab, abemaciclib, and ET (fulvestrant [FUL] or letrozole [LET]) as a first- or second-line treatment for patients (pts) with HR+, human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC). **Methods:** This multicenter, multi-cohort, nonrandomized, open-label phase II study evaluated the efficacy and safety of nivolumab, abemaciclib, and ET (FUL or LET) in pts with HR+, HER2- MBC. Key eligibility criteria for the FUL cohort were: HR+, HER2- MBC with ECOG PS ≤ 1; measurable disease; no more than one ET; no prior chemotherapy for MBC; and had exhibited disease progression while receiving ET, adjuvant ET, or ≤ 12 months after adjuvant ET. Key eligibility criteria for the LET cohort were: postmenopausal HR+, HER2- MBC with ECOG PS ≤ 1; measurable disease; and no prior systemic therapy. ET as an adjuvant was permitted if the patient had a disease-free interval > 12 months after the completion of ET. Patients received 240 mg nivolumab on days 1 and 15, 150 mg abemaciclib twice daily, and either 500 mg FUL on days 1, 15, 29, and every 4 weeks thereafter (FUL cohort) or 2.5 mg LET once daily (LET cohort) until disease progression or unacceptable toxicity. The primary endpoint was the objective response rate (ORR). Key secondary endpoints included toxicity, disease control rate (DCR: CR+PR+SD), progression-free survival (PFS), and the overall survival (OS). The threshold and expected ORR of the FUL cohort were 45% and 60%, respectively; and 32 pts would ensure a statistical power of 80% ($\alpha = 0.20$). The threshold and expected ORR of the LET cohort were 55% and 75%, respectively; and 16 pts would ensure a statistical power of 80% ($\alpha = 0.20$). **Results:** Between June and December 2019, 17 pts were enrolled (FUL cohort: n = 12, LET cohort: n = 5). One patient in the FUL cohort was excluded due to prior treatment history. Enrollment was closed and combination treatment was discontinued mid-study due to safety concerns. All pts had ≥ 1 adverse event (AE). AEs ≥ Grade 3 were observed in 91.7% and 100% of pts in the FUL and LET cohorts, respectively. Immune-related AEs ≥ Grade 3 were observed in 66.7% and 60.0% of pts in the FUL and LET cohorts, respectively. The most frequent AEs ≥ Grade 3 were elevated liver function tests (LFT; FUL cohort: 50.0%, LET cohort: 60.0%). Immune-related (elevated LFT) AEs ≥ Grade 3 were observed in 50.0% and 40.0% of pts in the FUL and LET cohorts, respectively. Severe AEs (SAEs) were observed in 50.0% and 60.0% of pts in the FUL and LET cohorts, respectively. One treatment-related patient death occurred in the LET cohort due to interstitial lung disease (ILD). ORR was 54.5% (6/11) and 20% (1/5) in the FUL and LET cohorts, respectively. DCR was 90.9% (10/11) in the FUL cohort and 80.0% (4/5) in the LET cohort. Due to the discontinuation, PFS and OS were undetermined. **Conclusions:** Although nivolumab + abemaciclib + FUL appeared to have activity, our findings do not support further investigation of this combination therapy due to toxicity. Toxicity profiles vary with CDK4/6 inhibitors; therefore, a different inhibitor may improve tolerability. Results of the ongoing nivolumab, palbociclib, and ET trial are awaited (CheckMate 7A8, NCT04075604). Clinical trial information: JapicCTI-194782.

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# Tao kinase 3 augment the resistance to microtubule-disrupting agents in breast cancer cells

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Breast cancer is the leading type of cancer in women worldwide. It is a heterogeneous disease that contains several subtypes with substantial differences in pathology and clinical outcome. With the advancements in imaging and targeted therapy, many patients with early stages of this disease have a great opportunity to be cured. However, recurrence or metastasis of tumor still occurs in patients even after successful primary treatment. Chemotherapy remains one of the most important treatment for advanced breast cancer. Anti-microtubule agents including taxanes, eribulin and vinca-alkaloids constitutes the major anti-breast cancer chemotherapeutic category, while chemoresistance remains a thorny issue for advanced disease. We aimed to discover novel candidate regulators for chemoresistance in breast cancer. A lentiviral-based, high-throughput shRNA platform was developed for screening the variation of global kinome to find new therapeutic targets in paclitaxel-resistant breast cancer cells. The underlying molecular mechanisms was further explored by global phosphoprotein array and expression microarray. The serine/threonine kinase, TAO Kinase 3 (TAOK3), was identified from 724 kinase genes. Knockdown of TAOK3 exhibited the most profound reduction of IC50 values in response to paclitaxel treatment in breast cancer cells. High expression of TAOK3 was related to poor prognosis in breast cancer patients after adjuvant chemotherapy. Furthermore, the expression of TAOK3 also decreased the sensitivity to other anti-microtubule drugs, including eribulin and vinorelbine. Expression microarray analysis revealed that NF-κB signaling plays the major regulation roles in TAOK3-associated resistance. Taken together, our results showed that TAOK3 increases resistance to anti-microtubule drug through upregulating the NF-κB signaling in breast cancer. Inhibitors that disrupt TAOK3 and NF-κB signaling pathway may overcome the drug resistance for patients treated with anti-microtubule agents.

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# Risk estimation of locoregional recurrence, distant metastasis and second primary breast cancer in early stage breast cancer patients: The INFLUENCE 2.0 nomogram

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**Background** Breast cancer follow-up aims at early detection of locoregional recurrences (LRR) and second primary breast cancer (SP). Predicting a patient's time-dependent risk for such an event may improve follow-up strategies. Furthermore, many clinicians and patients are interested in the risk of distant metastasis (DM) as well, as it provides additional information on prognosis. The existing INFLUENCE nomogram predicts the yearly risk of LRR up to five years from diagnosis using logistic regression analyses. However, this model was based on patients diagnosed between 2003 and 2006 and lacked information on HER2 status, which is nowadays an important prognostic variable. In this population-based study, we aimed to improve the INFLUENCE model with more flexible predictions over time, more recent information and additional outcomes - risk of LRR, distant metastasis (DM) and SP - using different underlying models.
**Methods** Patient-, tumor- and treatment-related characteristics of all female patients diagnosed with invasive adenocarcinoma of the breast in 2007, 2008 and 2012, of who active 5-year follow-up was performed, were selected from the Netherlands Cancer Registry. Models were developed for LRR, DM and SP as a first event separately, and for each three-monthly time interval to predict time-dependent risks as accurately as possible. Follow-up was calculated from date of definite surgery to date of event or last observation. We compared three different models to estimate the three outcomes: a Cox regression model, a flexible parametric spline model and a random survival forest (RF) model. To assess calibration of each outcome, three-monthly risk predictions during the 5-year follow-up period were compared to corresponding observed event rates. To assess discrimination, the areas under the curves (AUC) were calculated for each timeframe in the 5-year period and averaged to one combined measure (average 5-year AUC). To correct for optimism we performed bootstrapping on the entire cohort with 200 replicates and updated the calibration measures and AUCs accordingly.
**Results** In total, 13,494 patients were included. LRR, DM and SP within five years were experienced by 2.8%, 6.3% and 3.1% of the patients, respectively. The following variables were included in the final models: age, tumor grade, tumor stage, nodal stage, multifocality, HER2 status, hormonal receptor status, type of surgery, chemotherapy, radiotherapy, hormonal therapy, anti-HER2 therapy. The optimism-corrected mean time-dependent prediction errors for individual risk predictions ranged between 0.12% and 0.46% for all three models and all three month timeframes. The average 5-year AUCs for LRR, SP and DM using the Cox model were 0.71, 0.63 and 0.77, respectively. The average 5-year AUCs for LRR, SP and DM using the parametric spline model were 0.71, 0.63 and 0.78, respectively. When using the RF model, the average 5-year AUCs were 0.74, 0.68 and 0.77 for LRR, SP and DM, respectively (Table).
**Conclusion** Although differences were very small, the RF model had the best performance overall. This INFLUENCE 2.0 model provides us with updated information on the individual time-dependent risks of LRR, DM and SP within five years following surgery. This model is freely accessible at https://tinyurl.com/influence-2 and can be used as an instrument to improve follow-up strategies and to give patients better insights in their prognosis.

Table. Optimism-corrected average AUCs over the 5-year follow-up period

| **Model type** | **LR** | **DM** | **SP** |
|---|---|---|---|
| Cox regression | 0.71 | 0.77 | 0.63 |
| Flexible parametric spline | 0.71 | 0.78 | 0.63 |
| Random survival forest | 0.74 | 0.77 | 0.68 |

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# Epithelial proliferation score as an independent breast cancer risk predictor in benign breast disease

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*Background*: Women with benign breast disease (BBD) experience an increased risk of breast cancer (BC). Histologic classification of BBD, as non-proliferative disease (NP), proliferative disease without atypia (PDWA) or atypical hyperplasia (AH), stratifies groups of patients into progressively higher categories of BC risk. However, this classification does not comprehensively assess the proliferative state of the epithelium throughout the biopsy. In addition, while AH is considered the most high-risk class of BBD, it is not always a highly proliferative lesion; atypical ductal lesions may reflect focal cytologic and architectural changes. We evaluated the association of an alternative classification of BBD severity and BC risk based on subjective grading of: 1) the maximal degree of epithelial proliferation and 2) multifocality of epithelial proliferation. *Methods*: Pathologists reviewed biopsies from participants aged 18 to 85 years in the Mayo BBD cohort (2002-2013), masked to BC outcomes, ascertained via questionnaires, tumor registry data and medical record review. Biopsies were classified as NP, PDWA or AH and semi-quantitatively scored for: 1) maximal degree of epithelial proliferation within a focus (DP) (0-3; none to severe) and 2) multifocality of proliferation (MP) (0-3; none to multiple foci). DP and MP scores were also summed to give a DP+MP score (0-6). Associations of DP and MP with BC risk were examined using Cox proportional hazards regression analyses, adjusting for age at BBD biopsy. Women were followed from date of initial biopsy to date of BC, death or last follow-up. *Results*: Of the 1529 assessable biopsies, 544 (35.6%) were classified as NP, 708 (46.3%) as PDWA and 277 (18.1%) as AH. Both DP and MP scores had significant positive correlation with increasing BBD severity (DP: r=0.51, p< 0.001; MP: r=0.52, p< 0.001). Mean (SD) DP scores were 0.6 (0.6) for NP, 1.6 (0.9) for PDWA, and 1.8 (0.7) for AH (ANOVA p<0.001). Mean (SD) for MP scores were 0.6 (0.6) for NP, 1.4 (0.8) for PDWA, and 1.8 (0.8) for AH (ANOVA p<0.001). Mean (SD) for DP+MP scores were 1.2 (1.2) for NP, 2.9 (1.5) for PDWA, and 3.6 (1.2) for AH (ANOVA p<0.001). With median follow-up of 8.8 years for controls and 5.3 years for cases, 10.6% of the women in the cohort developed BC. Compared to those with DP scores of 0, women with DP scores of 3 had significantly increased BC risk (HR 1.42, 95% CI: 1.16, 1.74, p=0.003). MP was associated with a non-significant increase in BC risk for scores of 3 versus 0 (HR: 1.20, 95% CI: 0.97,1.49, p=0.11). DP+MP scores of 6 conferred the highest BC risk (HR (score 6 vs. 0): 1.62, 95% CI 1.18,2.21, p=0.02). Results did not substantively differ after adjusting for BBD severity as NP, PDWA or AH. *Conclusions*: In this preliminary analysis within the Mayo BBD cohort, both proliferative degree (DP) and multifocality (MP) scores were correlated with histologic severity of BBD. DP and DP+MP scores were each associated with increased BC risk. We conclude that improved characterization of epithelial proliferation in BBD biopsies may enable refined prediction of individual BC risk.

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Preclinical head-to-head comparison of CDK4/6 inhibitor activity toward CDK4 vs CDK6

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**Background:** The cyclin-dependent kinase (CDK) 4/6 inhibitors ribociclib, abemaciclib, and palbociclib have been established as effective treatment options for hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2–) breast cancer. While these agents have not been evaluated head-to-head in clinical studies, they have all demonstrated significant progression-free survival improvements; however, only two of these, abemaciclib plus endocrine therapy (ET; MONARCH 2) and ribociclib plus ET (MONALEESA-3 and MONALEESA-7), achieved significant overall survival (OS) to date prompting closer examination of how these CDK4/6 inhibitors are distinct. Preclinical studies revealed differences in how these molecules interact with various kinases. These studies indicated that ribociclib and palbociclib exhibited greater selectivity for CDK4 and CDK6 relative to other human kinases than abemaciclib. In addition, studies suggested that these molecules displayed different relative activity against their primary targets CDK4 and CDK6. Although intriguing, these latter studies either used purified proteins without the accompanying cellular context or used proliferation as a proxy for target engagement. Here, we sought to extend the body of evidence created by the prior analyses by constructing cellular model systems where the effects of each CDK4/6 inhibitor on CDK4 or CDK6 could be studied in isolation.**Methods:** MEL-JUSO (an *NRAS* mutant melanoma cell line) and MIA PaCa-2 (a *KRAS* mutant pancreatic ductal adenocarcinoma cell line) cells were selected for this analysis after being identified as lacking dependence on either CDK4 or CDK6, as indicated by short hairpin RNA knockdown. Isogenic variants of each cell line lacking either CDK4 or CDK6 expression were generated by ablating CDK4 or CDK6 expression using CRISPR/CAS9 genome editing techniques and single-cell clonal selection. Levels of phosphorylated RB (phospho-RB) protein were used as a readout for target inhibition and were measured by Fast Scan phospho-RB (ppRB807/811) enzyme-linked immunosorbent assay (ELISA). Half-maximal inhibitory concentrations (IC50) for each CDK4/6 inhibitor were calculated in parental cells, as well as variant cell lines expressing only CDK4 or CDK6. Additionally, measurement of phospho-RB was performed in T47-D cells (an estrogen receptor–positive breast cancer cell line) to confirm results of prior analyses.**Results:** The level of phospho-RB inhibition in T47-D cells was similar to what has been described previously (Chen P, et al. *Mol Cancer Ther*. 2016). In MEL-JUSO cells, ribociclib, abemaciclib, and palbociclib inhibited CDK4 at 11-, 22-, and 2-fold lower drug concentrations than CDK6, respectively. In MIA PaCa-2 cells, ribociclib, abemaciclib, and palbociclib inhibited CDK4 at 9-, >47-, and 2-fold lower drug concentrations than CDK6, respectively. **Conclusions:** Consistent with prior biochemical studies and cell proliferation assays, our findings indicate that both ribociclib and abemaciclib more potently inhibit CDK4 than CDK6, whereas palbociclib has similar activity against both targets in cells. Understanding the importance of CDK4 relative to CDK6 in the etiology of breast cancer and possible implications for increased CDK4 target engagement is an emerging topic of discussion in the field. Given that CDK4 has been shown to be expressed at higher levels in breast tumor samples, and many breast cancer cell lines have demonstrated greater dependence on CDK4 vs CDK6, the differential inhibition of the CDK4/6 inhibitors may have important implications.

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# Targeting insulin receptor in estrogen receptor positive breast cancer

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Obesity and metabolic dysfunction are on the rise in the United States. Hyperinsulinemia, frequently seen in these conditions, correlates with an increased risk of development of and mortality from estrogen receptor (ER) positive breast cancer. Expression of components of the insulin and insulin-like growth factor (IGF) family of proteins promote cancer cell growth *in vitro*, is linked to shorter progression-free survival, and is associates with an increased risk of metastatic disease and death in breast cancer patients. Previously our lab found that development of resistance to the commonly used ER-targeting drug tamoxifen (Tam) *in vitro* is associated with a loss of the type I IGF receptor expression with an increased dependence on the homologous insulin receptor (IR). These data argue for targeting IR in breast cancer, but concern has been raised due to the potential of disrupting glucose homeostasis in patients with or without existing metabolic disease. To address this concern, a novel insulin-Fc fusion protein (AKS-130) was developed to lower blood glucose levels without causing clinical hypoglycemia with a potential to target tumor IR. AKS-130 was found to downregulate IR expression in models of colorectal cancer (HCT-116) and malignant melanoma (WM266.4). Further, AKS-130 suppressed xenograft growth in fed and fasted states.

We examined if AKS-130 had similar effects on ER positive breast cancer cells. To test the hypothesis that resistance to endocrine therapy increases the reliance of ER positive breast cancer cells on IR signaling, we utilized the ER positive breast cancer cell lines (MCF-7, T47D) and their Tam resistant derivatives (MCF-7 TamR, T47D TamR). Similar to in HCT-116 and WM266.4 cells, we found that AKS-130 is a modest agonist of IR in ER+ breast cancer cells. Exposure to AKS-130 led to a marked reduction in IR expression in both parental and TamR cell lines, and was associated with partially suppressed downstream signaling to Akt. Interestingly, AKS-130 induced proliferation at similar levels to insulin treatment in parental and TamR cells at 3 and 5 days post treatment, however AKS-130 prevented further insulin-stimulated proliferation. *In vivo*, AKS-130 treatment by itself did affect MCF7 parental xenograft growth however AKS-130 in combination with Tam trended toward extending time to a tumor size of $500mm^3$. In MCF7 TamR xenografts, addition of AKS-130 to Tam treatment also trended toward delaying xenograft growth. Importantly, prolonged treatment with AKS-130 did not lead to significant changes in weight or blood glucose.

Taken together these data show that novel agents, such as AKS-130, may serve as way to disrupt IR signaling in cancer cells without affecting host glucose metabolism. Addition of AKS-130 to Tam treatment trended toward delaying xenograft growth though further studies are needed. These data indicate that IR signaling may represent a target to overcome or delay endocrine therapy resistance in breast cancer.

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Impact of Medicaid expansion on racial disparities in time to adjuvant chemotherapy administration among breast cancer (BC) patients

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**BACKGROUND:** Delays in adjuvant chemotherapy initiation have a detrimental effect in outcomes and are more frequently seen among racial/ethnic minorities, uninsured patients and those with low socioeconomic status. A provision in the Affordable Care Act called for expansion of Medicaid eligibility in order to cover more low-income Americans. In this study we evaluate the impact of Medicaid expansion on racial disparities in time to adjuvant chemotherapy administration in a large cohort of BC patients.**METHODS:** Women (aged 40-64) diagnosed with primary invasive BC (stage I-III) between 01/01/2007 and 12/31/2016 were identified in the National Cancer Database. All patients underwent surgery as initial treatment modality and received adjuvant chemotherapy within 6 months of surgery. Chemotherapy delay was defined as >60 days from surgery to the first dose of chemotherapy. The cohort was limited to those residing in states that underwent Medicaid expansion in 2014 (KY, NV, CO, OR, NM, WV, AR, RI, AZ, MD, MA, ND, OH, IA, IL, VT, HI, NY, DE). For comparison purposes, 2007-2013 was considered the pre-expansion period and 2014-2016 the post-expansion period. We calculated difference-in-difference (DID) estimates using multivariable linear regression models. Results are presented as adjusted differences (in % points) between race/ethnicity groups in the pre and post-expansion periods, and as adjusted DID with 95% CI. A negative DID estimate indicates that Medicaid expansion reduces the racial/ethnic disparity in chemotherapy administration delay. The parallel trend assumption was tested. Variables in the final model included age, comorbidities, BC subtype, insurance status, distance to treatment facility, region, education, household income, facility type and facility case volume. **RESULTS:** 105,385 patients were included (median age 53), of them 75,663 (71.8%) were diagnosed in the pre- and 29,722 (28.2%) in the post-expansion period. 77.5% of the patients were White, 11.7% Black and 4.9% Hispanic. The proportion of patients experiencing chemotherapy initiation delays was greater among Blacks and Hispanics in both study periods compared to Whites. The proportion of chemotherapy delays decreased for all races between the pre and the post-expansion period. We observed a statistically significant decrease in the chemotherapy initiation racial disparity. The adjusted DID was -2% (95%CI -3.8 to -0.3, P=0.02) between Whites and Blacks was and -3% (95%CI -5.5 to -0.5, P=0.02) between Whites and Hispanics. In a subgroup analysis among 10,777 Medicaid patients the parallel trend assumption was not valid, therefore we estimated the DID between Whites and Blacks using a propensity-score based weight sample, identifying a reduction in the racial disparity of even greater magnitude (DID -9.1% [-14.4 to -3.8, P<0.001]).

| | Pre-Expansion | | | Post-Expansion | | | | |
|---|---|---|---|---|---|---|---|---|
| Race | N | Adjusted Rate of Delayed Chemo > 60 days | Adjusted Difference Between White Race (% points) | N | Adjusted Rate of Delayed Chemo > 60 days | Adjusted Difference Between White Race, (%points) | Adjusted DID (95% CI), Percentage Points | P |
| White | 59305 | 27.2 | 0 | 22325 | 24.2 | 0 | Ref | Ref |
| Black | 8560 | 36.1 | 8.9 | 3720 | 31.1 | 6.9 | **-2.0 (-3.8 to -0.3)** | **0.02** |
| Hispanic | 3432 | 32.3 | 5.1 | 1704 | 26.3 | 2.1 | **-3.0 (-5.5 to -0.5)** | **0.02** |

**CONCLUSIONS:** We demonstrate that Medicaid expansion reduced racial disparities by decreasing the proportion of Blacks and Hispanics experiencing delays in adjuvant chemotherapy initiation and decreasing the gap that exists when compared to Whites. These important results highlight the positive impact of policies aimed at improving equity and increasing access to health care.

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# Intratumoural heterogeneity in PgR expression: Molecular and prognostic significance

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Background: PgR is only expressed significantly in ER+ breast cancers and is generally considered a classical estrogen-sensitive protein, however, while ER+ cells are almost always expressed in a non-clustered pattern across the tumour bed, PgR+ cells form clusters or clumps with surrounding areas of PgR- cells when assessed by IHC in about 20-25% of PgR+ tumours. This is an ill-described and unexplained feature of intratumoural heterogeneity of a widely measured biomarker. The prognostic significance of the PgR clumpiness is also unknown.
Aims: to determine the (i) biologic and (ii) prognostic significance of PgR clumpiness in ER+ primary breast cancer.
Methods: (i) Biologic study: 40 primary ER+PgR+ tumours were identified with distinct PgR clumpiness by IHC. Areas of PgR+ and PgR- cells (PgR-rich and PgR-poor areas, respectively) were needle microdissected from unstained sections by juxtaposing them with PgR-stained sections from the same tumour. Areas were also dissected from 8 homogeneous PgR+ and 8 PgR- tumours for reference. NanoString gene expression analysis using a 50-gene code set (45 oestrogen-responsive or proliferation genes + 5 housekeeping genes) was performed on RNA extracts from the samples. (ii) Prognostic study: we developed a PgR heterogeneity score (PgR Het-score, range 0-18) as the product of (A) the number of PgR+ clumps/cm2 of tumour area (range 0 to 6) and (B) the level of overall PgR-positivity (0-4% or 96-100%, score 0; 5-19% or 80-95%, score 1; 20-39 or 60-79%, score 2; 40-59%, score 3). PgR Het-scores were derived from images (Hamamatsu NanoZoomer-XR) of PgR-stained sections from two sets of tumour biopsies taken at diagnosis after which all patients received adjuvant endocrine therapy: 322 tumours from the Royal Marsden and from Southern Sweden collected for a case:control study of risk of recurrence (recurrence:no recurrence, 1:1) and 591 patients from the TransATAC cohort study with time to recurrence as the end-point.
Results: (i) Biologic study: In unsupervised hierarchical clustering of RNA expression from all samples, 33/40 pairs of PgR-rich and PgR-poor areas from a single tumour paired together and all 8 positive and negative control samples were grouped separately. Eight genes were differentially expressed between the PgR-rich and -poor areas (FDR<0.05: PGR, SERPINA3, AURKA, MSMB, PDZK1, IGSF1, FKBP5, SLC2A3). PGR had a 35-fold difference indicating that transcriptional differences explained the PgR IHC differences. The progesterone-regulated genes FKBP3 and SERPINA3 both showed significantly higher expression in PgR-rich areas consistent with the PgR differences having functional impact. AURKA was also more highly expressed in the PgR-rich areas indicating that the PgR-rich areas may also be more proliferative. ER and most of known estrogen-regulated genes were not differentially expressed and therefore show an unexpected divergence from PgR expression and regulation downstream of ER. (ii) Prognostic study: The PgR Het-score showed no consistent association with clinical factors including tumour size, nodal status, grade, age. Each of the individual components as well as the composite PgR Het score were significantly associated with risk of recurrence in POLAR: (A) p=0.02; (B) p=0.002; (PgR Het score) p=0.008. However, there was no association of the PgR Het score with risk of recurrence in TransATAC.
Conclusion: Major, functionally significant differences in PgR expression occur within some ER+ tumours that are not explained by differences in ER expression and are not associated with differences in expression of most other estrogen-dependent genes. Further work is on-going to provide a mechanistic explanation for the PgR heterogeneity. Given the discordance in results from the two clinical studies its prognostic significance is uncertain.
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Hormone receptor positive breast cancers and Black race: Does gender matter?

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**Introduction:** Male breast cancer (MBC) patients present with later disease stages and have higher mortality rates than female breast cancer (FBC) patients. Additionally, black breast cancer patients, regardless of gender, consistently have worse clinical outcomes than their white counterparts. To date, there are few studies exclusively comparing clinical outcomes between black MBC and black FBC patients. The objective of this study is to understand the differences in presentation, treatment and mortality between black MBC and black FBC patients with hormone receptor positive breast cancer using the National Cancer Database (NCDB).
**Methods:** The NCDB was queried for all black MBC and FBC patients, ages 18-90, with hormone receptor positive breast cancer diagnosed between 2010-2016. Hormone receptor positivity was defined as estrogen receptor positive, progesterone positive and HER 2-negative cancer. Sociodemographic and clinical variables were compared between MBC and FBC patients on univariate analysis. For stages I-III patients, a propensity score (PS) was generated by a logistic regression model including the following covariates: age at diagnosis, tumor size, nodes removed, node positivity, resection margin status, hormonal treatment, chemotherapy treatment, and radiation treatment. MBC patients were matched to FBC patients using PS 2:1 nearest-neighbor matching. A log rank test was used to determine differences in survival between the matched cohort.
**Results:** There were 994 black MBC and 65,931 black FBC patients that met study criteria. MBC patients were older at diagnosis than women (age, MBC 63 ± 12.5, FBC 60.6± 13.3). Compared to FBC patients, more MBC patients had lower oncotype scores (RS 0-10, MBC 39.7%, FBC 24%, $p<0.001$). Additionally, MBC patients were more likely to present with metastatic disease (stage 4, MBC 4.4%, FBC 2.6%, $p<0.001$), had fewer smaller tumors (tumor size <2cm, MBC 32.1, FBC 49.1%, $p<0.001$) and a higher percentage of poorly differentiated tumors (grade 3, MBC 28.5%, FBC 21.4%, $p<0.001$). Notably, MBC patients had lower rates of hormone therapy (MBC 66.4%, FBC 80.7%, $p<0.001$) and neoadjuvant chemotherapy (MBC 5.8%, FBC 7.5%, $p=0.05$) utilization than their female counterparts. On propensity score matched analysis black MBC patients had a higher overall mortality compared to FBC patients ($p=0.026$).
**Conclusion:** Hormone receptor positive black MBC patients in the NCDB present with more advanced stages of disease, are less likely to receive endocrine therapy and have worse overall mortality compared to their black FBC counterparts. These results indicate that significant gender-based disparities exist in presentation, treatment and mortality among black breast cancer patients. Future studies should evaluate how biologic sex and tumor biology intersect to affect these intra-racial differences in clinical outcomes.

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# A Phase 1b/2 Study of the BET inhibitor ZEN003694 in combination with talazoparib for treatment of patients with TNBC without gBRCA1/2 mutations

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**Background:** Metastatic triple-negative breast cancer (TNBC) is an aggressive and heterogeneous cancer with limited therapeutic options. PARP inhibitors (PARPi) are approved to treat breast cancer harboring germline BRCA1/2 *(gBRCA1/2)* mutations and have not shown efficacy in homologous recombination DNA repair (HRR) proficient tumors. In pre-clinical models, the BET inhibitor (BETi) ZEN003694 sensitizes wild-type *BRCA1/2* tumors to PARPi through downregulation of HRR gene expression, providing a rationale for combination therapy. We report initial results from a Ph 1b/2 trial evaluating the combination of ZEN003694 and the PARPi, talazoparib, in TNBC patients without *gBRCA1/2* mutations.
**Methods:** A Ph 1b dose-finding segment will be followed by a single-arm Ph 2 Simon 2-stage segment. Ph 1b evaluated several dose combinations of ZEN003694 and talazoparib, with safety and recommended Ph 2 dose (RP2D) as primary endpoints and pharmacokinetics (PK), pharmacodynamics (PD), and clinical benefit rate (CBR = Objective response rate (ORR) + stable disease ≥ 4 months) as secondary endpoints. The Ph 2 segment has CBR as the primary endpoint and progression free survival (PFS) and duration of response as secondary endpoints. Eligibility criteria included TNBC (ER/PR < 10% and not a candidate for endocrine therapy), HER2-, wild-type *gBRCA1/2*, and ≥ 1 prior chemotherapy regimen for metastatic disease. Patients were dosed daily in continuous 28-day cycles until disease progression or unacceptable toxicity. Dose limiting toxicity (DLT) period was one cycle. Adverse events (AE), PK, and PD in whole blood and tissue biopsies were assessed. Response endpoints were assessed per RECIST 1.1 every 2 cycles.
**Results:** Findings of the Ph 1b are reported. 15 patients with a median 3 lines of prior therapy in the metastatic setting were enrolled in 3 dose-finding cohorts. RP2D was determined to be 48mg ZEN003694 plus 0.75mg talazoparib. Across the cohorts, the most common AE was thrombocytopenia (TCP) (73%) with 53% G3/4 (Table 1). G4 TCP was the DLT and 1 DLT patient required a platelet transfusion. TCP could be managed to G1/2 levels with intermittent dose holds and reductions. Other G1/2 AEs included fatigue, anorexia, neutropenia, nausea, dysgeusia, and photophobia. Dose intensity analysis showed average daily doses of ZEN003694 and talazoparib could be maintained above 40mg and 0.5mg, respectively, over 4 cycles. Exposures of ZEN003694 and talazoparib were dose proportional with no drug-drug PK interactions. At RP2D, PD assessment by a whole blood mRNA assay for BET-dependent genes demonstrated robust down-regulation of *CCR1*, *IL1RN*, and *IL8* to < 50% of baseline for > 8 h. Expression of HRR genes, *RAD51 and BRCA1*, in whole blood also decreased for > 8 h. Analysis of an on-treatment biopsy showed robust and durable BET target modulation assessed by comparing RNA sequence data with a reference BET dependent signature. Across the 3 cohorts, ORR by Investigator was 38% (5/13), including 1 CR and 4 PRs, and CBR was 57% (8/14). 6 of the 15 patients are ongoing as of data analysis date (2-9 cycles), with 1 patient responding for > 6 months.
**Conclusions:** Combination of ZEN003694 and talazoparib demonstrated anti-cancer activity in pretreated metastatic TNBC patients without *gBRCA1/2* mutations. TCP is frequent but manageable with dose adjustments. PK is predictable, and PD data show meaningful target engagement. The Ph 2 part of the trial is currently ongoing.

| Grade 3/4 Adverse Events | Cohort 1(1mg talazoparib + 48mg ZEN003694)N=6 | Cohort 2(0.75 mg talazoparib + 48mg ZEN003694)N=6 | Cohort 3(1mg talazoparib + 36mg ZEN003694)N=3 |
|---|---|---|---|
| Thrombocytopenia | 3 (G3), 2 (G4, DLT) | 1 (G3), 1 (G4, DLT) | 1 (G3) |
| Diarrhea | 1 (G3) | 0 | 0 |
| Neutropenia | 0 | 1 (G3) | 0 |

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# Molecular characterization of advanced breast cancer according to site of metastasis

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**Background**: There is an increasing need in the clinic to biopsy metastatic disease in patients with advanced breast cancer (ABC). However, the microenvironment and tumor cell biology of breast cancer metastasis is largely unknown. Here, we report a molecular characterization of ABC according to the site of metastasis. **Methods**: RNA from 184 FFPE metastatic samples were evaluated using the nCounter BC 360 Panel, which includes the expression of 689 BC-related genes and 82 immune-related genes. PAM50 subtypes (Basal-like, HER2-enriched [HER2-E], Luminal A, Luminal B and Normal-like) were also determined. HER2 protein expression was assessed by immunohistochemistry (IHC) in 115 tumor samples, and HER2-low tumors (i.e. 1+ or 2+ and ISH-negative) were identified. Descriptive statistics, significance analysis of microarrays (using False Discovery Rate [FDR]) and logistic regressions were used to identify organ-specific gene expression profiles. Finally, we derived an organ-specific predictor of 209-genes from our cohort, and applied it to the RNAseq-based TCGA PanCancer dataset, which includes 174 glioblastomas multiforme, 424 liver hepatocellular carcinomas and 576 lung adenocarcinomas, among other cancer-types. **Results**: A single metastatic tumor sample from 184 individual patients with ABC was obtained from bone (18%), liver (17%), skin (15%), brain (12%), breast (13%), lymph nodes (9%), lung (7%), pleura (5%), ovary (2%), muscle (1%) and peritoneum (1%). All PAM50 subtypes were identified across the main organ sites; however, significant differences in subtype distribution were observed ($p<0.001$). Basal-like subtype was more prevalent in brain, lung and skin metastasis (FDR=0.3%). Unsupervised analysis and principal component analysis revealed brain and liver metastasis as the most distinct. Supervised analysis identified organ-specific genes independently of PAM50 subtype, i.e.: bone-specific genes (*WIF1, IBSP, MMP9* and *ITGB3)*; brain-specific genes (*CRYAB, SOX10, FGF1* and *CHI3L1*); liver-specific genes *(ALDH1A1, CYP4F3, PCK1,* and *SFRP2)*; lung-specific genes *(CAV1, WNT5A, PTGS2* and *IL6*); skin-specific genes (*KRT14, KRT5, S100A7* and *SERPINB5*). Among the organ-specific gene list, 15 (30%) of the 50 PAM50 genes were identified, including up-regulation of *FGFR4* in liver, *ESR1* in bone, *ERBB2* in lung and *KRT5* and *KRT14* in skin. Regarding ERBB2, a high correlation between *ERBB2* mRNA and HER2 IHC expression (0, 1+, 2+ and 3+) was observed ($p<0.001$). Interestingly, HER2-low disease was identified across all PAM50 subtypes and organ sites, including bone metastasis. Regarding immune-genes, all were found differentially expressed across the main organ sites (FDR<5%) with lung metastasis showing the highest expression (i.e. *PDCD1, CD8A, GMZA, IL1B*) and liver and brain metastasis the lowest. Finally, the 209-gene organ-specific predictor in PanCancer TCGA identified 96% of glioblastomas multiforme as brain, 98.6% of liver hepatocellular carcinomas as liver and 57.1% of lung adenocarcinoma as lung. **Conclusions**: The main sites of metastasis in ABC have unique biological features independently of tumor molecular subtype. Our results suggest that treatment strategies based on the site(s) of metastasis should be explored.

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# Phase 1b clinical trial of HX008, a novel anti-PD-1 monoclonal antibody, Combined with gemcitabine and cisplatin in the first-line treatment of metastatic triple-negative breast cancer

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**Background** HX008 is a humanized IgG4S228P anti-PD-1 monoclonal antibody with an engineered Fc domain. Gemcitabine plus cisplatin (GP) has shown satisfying antitumor activity as first-line therapy for metastatic triple-negative breast cancer (mTNBC) in CBCSG 006 trial (ClinicalTrials.gov, NCT01287624). The phase 1b study was conducted to assess the safety and preliminary antitumor activity of HX008, combined with GP in patients with mTNBC in first-line setting. **Methods** Eligible patients are mTNBC with ≥6 months DFI who never receive antitumor therapy for metastatic disease. Participants received HX008 at 3mg/kg (d1, q3w) plus gemcitabine at 1250mg/m2 (d1, 8, q3w) and cisplatin 75mg/m2 (d1, q3w). At most 6 cycles of GP chemotherapy were given, while HX 008 could be maintained until disease progression or unacceptable toxicity occurred. **Results** Between July 2019 and March 2020, a total of 31 patients were enrolled in this study. Median (range) age was 50 (29-69) years. Among 31 patients who were evaluated, 25 (80.6%) experienced objective response and the other 6 (19.4%) experienced stable disease (SD). The median progression free survival (PFS) was 9.07 months (95%CI,7.29m-13.01m). The PFS data was not yet mature, for nearly half of the intent-to-treat population has not progressed by October 9, 2020. The most common treatment-related adverse events of grade 3 or 4 included neutropenia (71.0%), anemia (55.5%), thrombocytopenia (32.3%), hypocalcemia (9.68%), hypokalemia (6.45%), and Alanine aminotransferase increased (6.45%). There were no treatment-related deaths. **Conclusion** HX008 plus GP demonstrated promising activity and manageable safety in patients with mTNBC in first-line setting. Clinical trial information: CHINADRUGTRIALS.ORG, CTR 20191353.

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Correlation of pathological complete response and radiological response with Contrast-enhanced mammography in breast cancer patients after neoadjuvant chemotherapy

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**Background:** Pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) has been reported as a surrogate endpoint for prediction of disease-free survival (DFS) and overall survival (OS) particularly in HER2-positive and triple-negative (TN) breast cancer . NAC requires imaging techniques to accurately predict pathological response and subsequently surgical planning. Magnetic resonance imaging (MRI) has been the most sensitive technique to assess response to NAC, although it is expensive and time consuming. In our hospital we use Contrast-enhanced mammography (CEM) that is easy to perform, fast, reproducible and its signs are superimposable to the MRI, with the advantages of lower cost. It allows diagnosing multifocal, multicenter and bilateral involvement, and monitoring the response to treatment with NAC.**Aims**: Analyze the correlation between complete radiological response (rRC) with CEM and pCR in patients treated with NAC. Analyze this correlation based on the different immunophenotypes (IF)**Methods:** Retrospective analysis of 112 patients with stage II-III breast cancer treated with NAC , from January 2018 to April 2020, in the Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, with CEM performed before and after NAC. pCR categorization using the Miller and Payne system, defined pCR as a non-invasive tumor in the breast and axilla (ypT0/is N0).**Results:** Of 112 analyzed patients, 8 did not undergo surgery (6 patients with T4d tumors received radical radiotherapy, 1 progressed during NAC and 1 did not undergo surgery for liver failure). Median age 53 years (range 31-89). Stages: IIA 26%, IIB 47%, IIIA 16%, IIIB 10%, IIIC 1%. IF: Luminal A: 11%, Luminal B Her2-: 33%, Luminal B Her2 +: 23%, pure HER2: 21%, TN: 12%. NAC received: doxorubicin-cyclophosphamide (AC)-weekly paclitaxel 53%, Taxanes + pertuzumab + trastuzumab (PT) 39%, AC-paclitaxel + PT 4%, other 4%. 99 patients obtained radiological response: 60 (54%) rRC and 39 (35%) partial response. In 14 patients (12%) there was no response. 36% pCR (N = 37). The sensitivity (S) and specificity (E) of CEM for the evaluation of pCR were 67% and 95% respectively. S was 100% in pure HER2 and 78% in TN. The positive and negative predictive values (PPV and NPV) were 96% and 61% respectively. After a median follow-up of 19 months, 6 patients have relapsed and 2 have died.**Conclusion:** CSEM has an S and E to detect pCR after NAC of 67 and 95% respectively; rates higher than those offered in other series by the MRI. S and E are higher in pure HER2 and TN tumors.

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# Oral paclitaxel and encequidar (oPac+E) in the treatment of metastatic breast cancer (mBC): Management of gastrointestinal adverse events (GI AE). Study KX-ORAX-001

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**Background:** There is a need for more effective and less toxic treatments for patients with mBC. Patients may prefer oral vs IV cytotoxic therapies to avoid frequent hospital visits. In addition, oral therapies allow frequent or metronomic dosing regimens which may alter the toxicity or activity profile of agents vs infrequent IV administration. oPac+E is oral paclitaxel combination with Encequidar, a specific, minimally absorbed, oral p-glycoprotein inhibitor that facilitates the absorption of oral paclitaxel. mBC patients who received oPac+E had significantly greater confirmed tumor response and longer survival with lower rates and severity of neuropathy but increased GI AE compared to IV paclitaxel (IVPac) (Study KX-ORAX-001 presented at SABCS, 2019, Abstract # GS6-01).
**Methods:** Study KX-ORAX-001 was a phase III, randomized, study in women with mBC for whom treatment with IVPac was recommended. Patients were randomized 2:1 to receive oPac+E or IVPac. Patients continued treatment until discontinuation due to progressive disease or toxicity. oPac 205 mg/m$^2$ was given once daily for 3 days weekly. E 12.9 mg was given 1 hour before each dose of oPac. IVPac 175 mg/m$^2$ was infused over 3 hours every 3 weeks. The primary endpoint was efficacy defined as tumor response confirmed by BICR at two consecutive evaluations. Key secondary endpoints included PFS, OS. Safety was monitored throughout the study.
**Results:** All IVPac patients received high-dose dexamethasone and antihistamine premedication, which have significant anti-emetic activity and may have received additional anti-emetic agents as needed. The protocol did not allow any prophylaxis for GI AE for oPac+E patients nor were they to receive predose corticosteroids, nor antihistamines.
The protocol was amended after approximately 30% of patients were enrolled to allow prophylactic anti-emetic medications for patients randomized to oPac+E. Patients were also given loperamide to take at home and were instructed to initiate loperamide with the onset of diarrhea. The rates of Grade ≥2, vomiting and diarrhea for patients treated with IVPac, the patients treated with oPac+E prior to after the amendment are summarized in the table below.

| | IVPac | | | oPac+E Pre-Amendment | | | oPac+E Post Amendment | | |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 | Grade 2 | Grade 3 | Grade 4 |
| Vomiting | 4% | 1% | 0% | 24% | 7% | 0% | 7% | 4% | 0% |
| Diarrhea | 7% | 1% | 0% | 27% | 9% | 0% | 16% | 3% | 0.5% |

Prophylactic anti-emetic therapy and early use of loperamide markedly decreased the incidence of ≥Grade 2 vomiting and diarrhea although there was a greater incidence than IVPac.
The most frequently prescribed anti-emetic agents for oPac+E treated patients were ondansetron (54%), metoclopramide (21%), domperidone (4%) and aprepitant (3%). For patients randomized to IVPac, the most frequently prescribed agents were ondanesteron (59%), granisetron (24%), palenosetron (7%) and aprepitant (2%). Oral administration of the oral NK1 inhibitor aprepitant appeared to be associated with increased incidence of oral paclitaxel systemic toxicity, potentially due to inhibition of metabolism of oPac by cytochrome P450 3A4.
**Conclusions:** oPac+E was associated with greater efficacy in the treatment of mBC and lower rates and severity of peripheral neuropathy, but increased GI AE compared to IVPac 175mg/m$^2$. GI AE in oPac+E treated patients can be managed by prophylactic use of anti-emetics, primarily 5-$HT_3$ inhibitors and early intervention with the anti-diarrhea agent loperamide. The use of the oral NK1 inhibitor aprepitant in combination with oPac+E is not recommended.(NTC02594371)

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Recruitment strategies for enrollment of high-risk women to a randomized controlled trial of web-based decision support tools to increase breast cancer chemoprevention

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**Background**: Less than 10 % of those identified as eligible for clinical trials are recruited. Recruitment for chemoprevention trials poses challenges as it is often difficult to identify unaffected patients at high risk for cancer. Barriers to recruitment include personal perceptions of the benefits, fear of trials, low recruitment of minorities, language barriers, transportation costs, and complex study designs. In this study, we identified five potential sources of recruitment that could be collectively leveraged to identify women at high risk for breast cancer to improve recruitment yield.
**Methods**: A total of 300 high-risk women and 50 healthcare providers were recruited and randomized to access web-based decision support tools in combination with standard educational materials or standard educational materials alone. Patient inclusion criteria included: 1) women, age 35-75 years; 2) English or Spanish-speaking; 3) no previous breast cancer diagnosis; 4) no prior use of selective estrogen receptor modulators (SERMs) or aromatase inhibitors (AIs). Five broad strategies were considered for identification and recruitment of women at high risk for breast cancer: 1) in-person recruitment during routine screening mammography with survey administration for breast cancer risk assessment according to the Gail model; 2) collection of breast cancer risk factors from the electronic health record (EHR) for risk assessment according to the Breast Cancer Surveillance Consortium (BCSC) risk calculator; 3) identification of women with atypical hyperplasia (AH) or lobular carcinoma *in situ* (LCIS) using ICD-9/10 diagnostic codes from the EHR; 4) high-risk women with clinic appointments and referred by enrolled providers; 5) women who responded to recruitment flyers and online recruitment distributed throughout the medical center and community.
**Results**: A total of 6229 high-risk women were identified using these recruitment sources, of which 3663 were contacted by email, mailed letter, and/or phone for participation in our clinical trial. Of these contacted women, 16.4% were identified through in-person recruitment during screening mammography, 35.8% through breast cancer risk factors in the EHR, 14.5% had a diagnosis of AH or LCIS identified in the EHR, 28.7% had appointments with enrolled providers, and 4.5% responded to recruitment flyers or online recruitment. Women from the different recruitment sources varied by mean age (64.7 years for mammography and 44.9 years for recruitment flyers), race/ethnicity (73.7% non-white from mammography and 45.5% from breast cancer risk factors in the EHR), and mean 5-year breast cancer risk (2.56% identified from the EHR and 1.34% from recruitment flyers). Of 300 consented patients, 44.7% came from provider referrals (12.7% recruitment yield [number consented/number contacted]) and 27.3% from mammography (13.6% recruitment yield). Comparing enrolled to unenrolled patients, there were significant differences in mean age (57.3 vs. 58.7 years, $p=0.027$), proportion of non-whites (41.5% vs. 54.7%, $p<0.001$), and mean 5-year breast cancer risk (3.0% vs. 2.2%, $p<0.001$).
**Conclusions:** We were able to identify a large cohort of women at high risk from breast cancer from multiple different recruitment sources. Our recruitment yield was highest among direct referrals from healthcare providers and in-person recruitment from mammography. Consented patients tended to be younger, include more non-Hispanic whites, and have a higher risk of breast cancer compared to the overall pool of high-risk women identified. We were able to successfully recruit a racially-ethnically diverse study population to a randomized controlled trial of decision support for breast cancer chemoprevention.

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# Intraoperative radiation therapy (IORT) for1200 early breast tumors

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**Introduction:** Two prospective randomized trials, TARGIT-A and ELIOT, have shown intraoperative radiation therapy (IORT) to be a safe alternative with a low-risk of local recurrence compared to whole breast radiation therapy following breast conserving surgery for selected low-risk patients. We report the first 1200 tumors treated with this modality at our facility.**Methods:** 1200 distinct breast cancers in 1169 patients (31 bilateral) were treated with breast conserving surgery and X-ray IORT, using the Xoft Accent System from June 2010 to November 2018. Patients were enrolled in an IORT registry trial and data were collected at 1 week, 1 month, 6 months, 1 year, and yearly thereafter. The primary endpoint was local recurrence.**Results:** To date, there have been 61 events in 54 patients: 50 ipsilateral local recurrences (14 DCIS and 36 invasive), 7 regional nodal recurrences and 4 distant recurrences. Of local recurrences, 9 were within the IORT field, 21 outside of the IORT field but within the same quadrant as the index cancer, and 20 were new cancers in different quadrants. There has been no breast cancer related deaths and 27 non-breast cancer deaths. Currently, with a median follow-up of 52 months, Kaplan Meier analysis projects 5.2 % local recurrence rate at 5 years. In the table below, the five-year probability of local recurrence is analyzed by quadrant and/or type of
recurrence (all recurrences or just invasive). Using the 2017, ASTRO Categories, 520 patients (43%) were suitable for IORT, 415 (35%) were cautionary, and 265 (22%) were unsuitable for IORT after final histopathology was evaluated.**Conclusion:** IORT is profoundly convenient. When used as the only adjuvant breast irradiation, it eliminates approximately 15-35 outpatient visits. This has become increasingly important during the current COVID-19 pandemic. In the group of patients described here, more that 100,000 patient-hours were saved. The local, regional, and distant recurrence rates observed in this trial were slightly higher than those of the prospective randomized TARGIT-A and ELIOT Trials. This may be explained by 22% of our patients being considered unsuitable for IORT by ASTRO Criteria. The low complication rates previously reported by our group as well as the low recurrence rates reported in this study support the cautious use and continued study of X-ray IORT in women with low-risk breast cancer.

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# Factors associated with chronic breast lymphedema after adjuvant radiation in women undergoing breast conservation therapy

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Purpose/Objective(s):Unlike temporary breast edema caused by post-lumpectomy radiation therapy (RT), the edema that persists beyond one year is not well defined and difficult to treat. The aim of this study is to define the incidence and risk factors for the development of chronic breast lymphedema in women undergoing lumpectomy with RT at a large metropolitan cancer center.
Materials/Methods:A retrospective chart review was performed on all patients who underwent lumpectomy from 2014 to 2018. Women who did not undergo RT at our institution and those with stage IV disease were excluded from the analysis. Patient demographics, comorbidities, operative data, RT data and postoperative complications were obtained. Chronic breast lymphedema (CBL) was defined as edema that persisted beyond one year post completion of radiation therapy. Breast volumes were determined by contoured breast volumes or, if unavailable, estimated by the 95% isodose volumes from the RT treatment planning system. Using a density curve, the distribution of breast volumes was plotted for patients with and patients without CBL. Univariate analysis was used to evaluate factors associated with CBL. Multivariate regression analysis was used to evaluate factors associated with the risk of CBL while accounting for potential confounding variables as defined by the univariate analysis.
Results:A total of 1173 patients were included for analysis. Seventy-four (6.3%) patients developed breast lymphedema beyond one year. For the entire cohort, mean age was 63 years old (SD=11.17), mean BMI was 31.15 kg/m2 (SD=7.17), mean breast volume was 1198.54 $cm^3$ (SD=645.82 $cm^3$), mean total radiation was 59.18 Gy (SD=16.76), and 139 (11.8%) patients underwent ALND. Compared to the cohort that did not develop CBL (n=1099), the CBL cohort (n=74) had a higher median BMI (33.23 $kg/m^2$ vs. 29.81 $kg/m^2$, P<0.001), higher percentage of African Americans (56.8% vs. 37.9%, P=0.004), larger median breast volume (1502.33 $cm^3$ vs. 1083.59 $cm^3$, P<0.001), higher percentage that underwent ALND (23% vs. 11.1%, P=0.005), and larger median size of lumpectomy specimen (128.00 $cm^3$ vs. 94.57 $cm^3$, P=0.002). When accounting for potential confounding variables, multivariate regression analysis revealed when breast volume was evaluated as a continuous variable, for every 1 $cm^3$ increase in breast volume, the risk of breast lymphedema increases by 0.1% (OR=1.001, P<0.001). When breast volume was analyzed as a categorical variable using 1300 $cm^3$ as the optimal cutoff (based on density curve evaluations), patients whose breast volume was greater than 1300 $cm^3$ had nearly 3 times the risk of developing CBL (OR=2.976, P<0.001) compared to those with less than 1300 $cm^3$ breast volume. The multivariate regression also demonstrated that CBL was associated with total radiation dose (OR=1.02, P=0.015) and African American race (OR=1.705, P=0.037).
Conclusion:Chronic breast lymphedema presents a clinical concern for women undergoing lumpectomy with postoperative radiation, particularly in women with larger breasts. Further studies should focus on preventative strategies, as well as the psychosocial and economic impact of this morbidity.

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Patient-reported outcomes from the Phase III IMpassion031 trial of neoadjuvant atezolizumab + chemotherapy in early triple-negative breast cancer

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**Background:** In the IMpassion031 study (NCT03197935) of patients (N = 333) with invasive stage II or III early triple-negative breast cancer (eTNBC), neoadjuvant treatment with atezolizumab vs placebo, each combined with nab-paclitaxel followed by doxorubicin + cyclophosphamide, significantly improved pathologic complete response in the intent-to-treat population. Patient-reported outcomes (PROs) were collected to document patient perspectives on overall treatment burden and clinical benefit of atezolizumab + chemotherapy for neoadjuvant treatment of eTNBC. **Methods:** Patients received either atezolizumab 840 mg or placebo every 2 weeks (q2w) with nab-paclitaxel 125 mg/m$^2$ every week for 12 weeks followed by atezolizumab 840 mg or placebo q2w with doxorubicin 60 mg/m$^2$ + cyclophosphamide 600 mg/m$^2$ q2w for 4 cycles. After surgery, patients in the atezolizumab arm were unblinded and continued to receive atezolizumab 1200 mg every 3 weeks for 11 doses, while patients in the control arm did not receive any study treatment. Patients completed the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and single-item GP5 from the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire at baseline and day 1 of each cycle of neoadjuvant and adjuvant treatment, at end of treatment and during follow-up every 3 months during year 1, every 6 months during years 2-3, and then annually. Mean and mean change from baseline scores (with changes ≥ 10 considered clinically meaningful) in function (role and physical) and global health status/health-related quality of life (GHS/HRQoL) were predefined secondary endpoints. Mean and mean change from baseline scores in disease and treatment-related symptoms, as well as an assessment of overall side-effect bother, were exploratory endpoints. **Expected results:** The PROs will be compared between the atezolizumab and placebo arms to assess overall treatment burden and the effect of adding atezolizumab to neoadjuvant chemotherapy for the treatment of eTNBC.

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# Health-related quality of life for margetuximab + chemotherapy vs. trastuzumab + chemotherapy in the phase 3 SOPHIA trial of patients with pretreated HER2+ metastatic breast cancer

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Background: Margetuximab (M), an investigational Fc-engineered, immune-activating, HER2-targeted monoclonal antibody, shares specificity with trastuzumab (T) and is being studied in HER2 overexpressing tumors including MBC. The randomized phase 3 SOPHIA trial (NCT02492711) in pretreated HER2+ MBC demonstrated PFS superiority by blinded analysis of M + chemotherapy over T + chemotherapy. M demonstrated a tolerable safety profile. Here, patient-reported health-related quality of life (HRQOL) is reported. Methods: In SOPHIA, 536 patients with HER2+ MBC and ≥ 2 prior HER2+ directed therapies, including pertuzumab, were randomized 1:1 to M (15mg/kg IV q3w) or T (6 [8 for loading dose] mg/kg IV q 3wk). Each antibody was given with physician's choice chemotherapy (standard dose capecitabine, eribulin, gemcitabine, or vinorelbine). HRQOL was measured at baseline and on D1 of each odd cycle using the Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI) - 16 and EuroQol 5-Dimension 5 level (EQ-5D-5L) questionnaires. Descriptive statistics were performed on NFBSI-16 total score (possible score range: 0 [most symptomatic] - 64 [least symptomatic]), EQ-5D-5L overall score (possible score range: 0 [most symptomatic] - 100 [least symptomatic]), and subscales of each measures. Lower scores reflect a higher impact on HRQOL domains. Changes from baseline in NFBSI-16 total score and in EQ-5D-5L utility score were assessed using mixed model repeated measures analysis (MMRM) with treatment group, stratification factors, time, and treatment group by time interaction as covariates. Each analysis used an unstructured covariance matrix, and least square mean estimates were calculated at each time point. A Cox proportional hazard model was used to assess time to symptom progression, defined as a ≥ 5-point decrease from baseline in NFBSI-16, using the same covariates as in MMRM analyses.Results: HRQOL questionnaire completion rates were comparable between M and T treatment groups. Mean NFBSI-16 total scores and EQ-5D-5L overall scores were similar between treatment arms at baseline and at end of treatment. During cycles 11-17, a greater proportion of patients in the M group reported being bothered by side effects and fatigue “quite a bit” or “very much” on the NFBSI-16. However, adverse event assessments at corresponding time points were largely attributed to concomitant chemotherapy. Also, a smaller proportion of patients on T completed these measures at these times. Overall, least mean square estimates (95% CIs) of change from baseline NFBSI-16 total scores were -1.99 (-3.395, -0.594) in the M group, and -2.13 (-3.794, -0.469) in the T group. A slightly higher proportion of patients in the M group had ≥ 5-point decrease from baseline NFBSI-16 total score compared to those in the T group (M: 105 [39.5%]; T: 100 [37%]). However, this difference was neither prespecified nor statistically significant (Cox model HR: 0.88, 95% CI: 0.672, 1.164; p=0.382). Overall least square mean estimates (95% CIs) of change from baseline in EQ-5D-5L total scores were -0.93 (-4.493, 2.637) in the M group, and -3.93 (-8.253, 0.387) in the T group, suggesting that patients on M had less signs of deterioration compared to the T group; statistical significance testing was not prespecified. Conclusions: Overall, HRQOL domains, including symptoms and functioning, were maintained. Changes from baseline were similar between the 2 treatment groups. Treatment-specific symptoms were consistent with side effects associated with chemotherapy, not antibody study therapy. Findings support similar, acceptable safety profiles demonstrated previously for margetuximab and trastuzumab.

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# Her2-xpat, a novel protease-activatable prodrug t-cell engager (tce), exhibits potent t-cell activation and efficacy in her2 tumors, yielding large predicted safety margins based on non-human primate (nhp)

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Background
TCEs are effective at inducing remissions in hematologic cancers but have been challenging in solid tumors due to *on*-target, *off*-tumor toxicity. Attempts to circumvent CRS include fractionated or step-up dosing and/or complex molecular designs, but these have been unsuccessful due to toxicity and/or enhanced immunogenicity. Amunix has developed a conditionally active TCE, XPAT or **X**TENylated **P**rotease-**A**ctivated bispecific **T**-Cell Engager, that exploits the protease activity present in tumors vs. healthy tissue to expand the therapeutic index (TI). The core of the HER2-XPAT (PAT) consists of 2 tandem scFVs targeting CD3 and HER2. Two unstructured polypeptide masks (XTEN) are attached to the core that sterically reduce target engagement and extend T1/2. Protease cleavage sites at the base of the XTEN masks enable proteolytic activation of XPATs in the tumor microenvironment, unleashing a highly potent TCE with a short T1/2 and further improving the TI. Although checkpoint inhibitors have been ineffective in HER2+ or HR+ breast cancer, TCEs can co-opt T-cells regardless of their antigenic specificity, providing the potential to introduce effective T-cell immunity against tumors expressing HER2. HER2-XPAT, as a tumor protease-activatable prodrug with a wide safety margin, offers the potential to induce effective T-cell cytotoxicity against HER2$^{hi}$ tumors and HR+/HER2 1-2+ tumors.
Methods
Preclinical studies were conducted to characterize the activity of HER2-XPAT, HER2-PAT (cleaved XPAT), and HER2-NonClv (a non-cleavable XPAT) for cytolytic activity in vitro, for anti-tumor efficacy in xenograft models, and for stability and safety in NHPs.
Results
HER2-PAT (cleaved XPAT) demonstrated potent *in vitro* tumor-directed T-cell cytotoxicity (EC50 1-2pM) and target-dependent T-cell activation and production of cytokines by PBMCs. HER2-PAT also exhibited cytotoxicity in HR+, HER2 1+ MCF7s at higher doses (EC50 0.13nM). HER2-XPAT provided up to 14,000-fold protection against killing of HER2 tumor cells and exhibited no cytotoxicity against cardiomyocytes at concentrations up to 1uM. *In vivo*, HER2-XPAT induced complete tumor regressions in BT-474 tumor models with equimolar dosing to HER2-PAT, whereas non-cleavable HER2-NonClv had no efficacy, supporting tumor protease cleavage requirement for T-cell activity. In NHP, HER2-XPAT has been dose-escalated safely up to 42mg/kg (MTD) but was not tolerated at 50mg/kg. HER2-XPAT demonstrated early T-cell margination at 2mg/kg but largely spared CRS, cytokine production, and tissue toxicity at doses up to 42mg/kg. PK profiles of HER2-XPAT and HER2-NonClv were comparable in NHP, indicating minimal systemic cleavage of XPAT, consistent with its *ex vivo* stability when incubated in the plasma of cancer pts for 7 days at 37°C. Given by continuous infusion, HER2-PAT induced lethal CRS and cytokine spikes at 0.3mg/kg/d, but was tolerated at 0.2mg/kg/d, providing HER2-XPAT with >3000-fold protection in tolerated Cmax versus HER2-PAT, >4 logs over cytotoxicity EC50s for HER2 and HR+ cell lines, and a 20-fold margin of safety over the dose required for pharmacodynamic activity.
Conclusions
HER2-XPAT is a potent prodrug T-cell engager with promising evidence of activity at low doses while exhibiting minimal CRS and a potentially wide TI based on NHP tolerability at doses up to 42mg/kg. With XTEN's prior clinical data demonstrating low immunogenicity, the XPAT TCEs provide a promising solution. IND studies are currently ongoing. Additional PK, PD, cytokines, safety, and efficacy data will be presented.

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# Differential gene expression analysis and clinical utility of MammaPrint and BluePrint in male breast cancer patients

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**Background:** Male breast cancer (MaBC) is rare, comprising <1% of all breast cancers in the United States. The low incidence of MaBC limits the ability to conduct clinical trials specifically for this population. Due to the paucity of research on MaBC, current understanding regarding MaBC biology, pathology, and treatment strategies has been primarily based on evidence extrapolated from research on female breast cancer (FBC) patients. Traditional diagnostic biomarkers such as ER, PR, and HER2, as well as newer multi-gene prognostic signatures, are employed when making treatment decisions for both MaBC and FBC. However, limited empirical data is available to support the use of identical laboratory biomarkers and molecular signatures in both MaBC and FBC. The 70-gene risk of distant recurrence signature, MammaPrint (MP), and the 80-gene molecular subtyping signature, BluePrint (BP), are commonly used to help make treatment decisions for both MaBC and FBC patients. To support the clinical utility of MP and BP in MaBC, this study aims to elucidate whether significant molecular biological differences exist between MaBC and FBC. To address this knowledge gap, we evaluated and compared 1) MP index results within Low Risk (LR) and High Risk (HR) groups, 2) MP and BP gene expression, and 3) differentially expressed genes within the full genome and their associated biological pathways between tumors from MaBC and FBC.

**Methods:** This analysis included a total of 817 breast tumor samples sent to Agendia, Inc. (Irvine, CA) for MP and BP testing. Full-transcriptome microarray data were available for 1) a subset of 400 post-menopausal FBC patients enrolled in the FLEX Registry (NCT03053193) and 2) 80 MaBC pateints, 32 of whom enrolled in the FLEX registry and 48 non-study patients for whom data were limited to metadata and quality metrics routinely captured for diagnostic testing. Data from all patients were de-indentified.

Differences in mean MP indices between FBC (N=400) and MaBC (N=417) according to MP Risk classification (LR or HR) were analyzed using a Z-test. Differential gene expression analysis was performed using the R-limma package in which gene expression data were quantile normalized. Pathway analyses were performed using GOseq. Differentially expressed genes (DEGs) were identified between FBC (N=400) and MaBC (N=80) for whom full transcriptome microarray data were available. DEGs were defined as those with a fold change of > 2 and an adjusted *P* value of < 0.05.

**Results:** All patients in this study had hormone positive, HER2 negative early-stage breast cancer. There was no statistical difference in the average MP index between MaBC and FBC classified as MP LR ($P$=0.273) or those classified as MP HR ($P$=0.692). Gene expression comparison revealed 166 DEGs between MaBC (N=80) and FBC (N=400), 99 DEGs between MP HR MaBC (N=42) and MP HR FBC (N=200), and 290 DEGs between MP LR MaBC (N=38) and MP LR FBC (N=200). Pathway analyses revealed that downregulated genes in MaBC compared to FBC enriched to immune-related functions, including B-cell mediated immunity, whereas upregulated genes were associated with hormone metabolic processes. In all comparisons, expression of MP or BP genes was not significantly different.

**Conclusions:** We found similar MP index distributions between MaBC and FBC. Importantly, differential gene expression between MaBC and FBC provides novel insight into the mechanisms underlying MaBC. Although these data reveal biological distinctions between male and female breast cancer, MP and BP assay performance is preserved across both groups. Further studies are needed to assess clinical outcomes; however, these findings support the use of MP risk of recurrence assay and BP molecular subtyping assay for prognosis and informing treatment decisions in MaBC.

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# Efficacy of Platinum-based first-line chemotherapy among metastatic breast cancer (MBC) patients according to the germline BRCA1/2 mutational status: An analysis of the French ESME MBC database

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**Background:** Platinum-based chemotherapy regimens (PtCT) have been shown to increase treatment efficacy when combined to neoadjuvant standard of care treatment of triple negative breast cancers (TNBC). In the metastatic breast cancer (MBC) setting, preclinical and clinical data suggest that PtCT could be more efficient than non-platinum based ones (non-PtCT) among patients (pts) with germline BRCA1/2 mutations (gBRCAm). However, published data remain controversial on this topic, particularly for MBC. We evaluated the progression-free (PFS) and overall survival (OS) under first-line PtCT and non-PtCT among gBRCAm carriers in ESME, a nationwide real-life MBC database. **Methods:** ESME MBC database (NCT03275311), is a unique national cohort of all consecutive pts who initiated a first-line treatment for MBC between 2008 and 2016 in one of the 18 French Comprehensive Cancer Centers. Women with HER2- MBC and known hormone receptors (HR) and gBRCA1/2 (before or in the 6 first months of metastatic disease, gBRCAm / wild type / not tested) status, who received a first-line MBC CT were selected. Patients with other germinal mutations were considered as wild type. Primary objectives were OS and PFS under first-line CT (PtCT vs. non-PtCT) in the TNBC gBRCA1/2m population.Secondary objectives were OS and PFS during first-line CT (PtCT vs. non-PtCT) in the TNBC wild-type and “not tested” population, as well as among the HR+/HER2- pts.To avoid guarantee time bias related to oncogenetic testing, analyses were performed at baseline (CT initiation) and different landmark time points (3-month or 6-month after CT initiation). Thus, BRCA status was defined according to oncogenetic testings performed before the landmark time, and patients who progressed or censored before the landmark time were excluded. **Results:** 10,164 pts (2,794 TNBC; 7,370 HR+/HER2-) were included in this analysis. Pts who received PtCT were significantly younger, affected by a gBRCA1/2m, had a high histological grade and/or TNBC tumor, with more frequent visceral and central nervous system spreading than non PtCT ones. Median follow-up was 51.1 months [95%CI 49.6; 52.6]. All reported results were based on the gBRCA status defined at CT initiation and on multivariable analysis adjusted on age at MBC diagnosis, de novo MBC status, type and number of metastases. In the gBRCA1/2m TNBC population (N=132), PtCT was independently associated with a better PFS compared to non-PtCT (HR=0.56, 95%CI 0.38-0.84, p=0.005), without significant difference in OS (HR=0.79, 95%CI 0.51-1.23, p=0.29).No difference was seen in wild-type BRCA1/2 TNBC pts (N=269) according to the CT regimen, while, in the larger population of untested TNBC (N=2,393), PtCT was associated with worse OS (HR=1.18, 95%CI 1.03-1.34, p=0.016) compared to non-PtCT regimens, without significant difference in PFS (HR=1.07, 95%CI 0.95-1.22, p=0.26). No significant difference was seen regarding PFS nor OS in gBRCA1/2m HR+/HER2- pts (N=124) and in the wild-type BRCA1/2 HR+/HER2- population.However, in the larger population of untested HR+/HER2- pts (N=6,836), PtCT was independently associated with worse OS (HR=2.15, 95%CI 1.79-2.59, p<0.001) and PFS (HR=1.57, 95%CI 1.33-1.86, p<0.001) compared to non-PtCT regimens. Results were similar in landmark analyses at 3-month or 6-month after CT initiation. **Conclusions:** This large-scale real-life analysis suggests higher efficacy of PtCT in term of PFS in gBRCA1/2m TNBC pts. The small sample size and post-1$^{st}$ line treatments may preclude observing a significant OS difference. PtCT appeared however associated with worse outcomes in untested TNBC and HR+/HER2- pts. These results emphasize the need for BRCA1/2 characterization before considering these regimens in the MBC setting.

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# Comprehensive analysis of health services, sociodemographic, clinical, and genomic factors driving locally advanced breast cancer mortality via a first-in-kind linkage of SEER-Medicare data with physical tumor samples

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**Background:** There continues to be an active debate as to the relative contribution of health services, sociodemographic, clinical, and genomic factors in breast cancer disparities. Efforts to understand the contributions of each of these factors have historically focused on separate investigations of socioeconomic, demographic, and genomic elements. However, true multidisciplinary investigation of these factors requires the existence of datasets that combine each of these elements together into population-level, real world cohorts. To this end we created the first-in-kind linkage of SEER-Medicare data to physical tumor samples to combine clinical, health services, and genomic data into a single cohort and used it to investigate the impact of screening and socioeconomic status on early stage breast cancer biology and mortality.**Methods:** This retrospective study used formalin-fixed, paraffin-embedded (FFPE) breast cancer (BC) tissue collected between 1992-2006 within the Iowa and Hawaii SEER Residual Tissue Repositories (SEER-RTR). Medicare fee-for-service claims data were linked for participating patients age 65 and older. Molecular subtyping and exploratory genomic analyses were completed using the NanoString Breast Cancer 360 (BC360) gene expression panel containing the PAM50 classifier. Screening status was assessed by validated claims-based algorithms. Factors associated with overall (OS) & breast cancer-specific (BCS) survival were analyzed in women aged 66-75 with clinically high risk ER+ disease (M0, T1b+, LN+) using Cox proportional hazards models combining sociodemographic, clinical, and genomic data.**Results:** SEER-Medicare data were available for 1,232 women, of which 379 (30.7%) were diagnosed by screening mammogram. Screen-detected disease was associated with lower T stage, N stage, and improved OS (HR 0.72) & BCS (HR 0.68) in multivariable analysis. Molecular analysis of 130 luminal A/B cases revealed superior outcomes of luminal A and luminal B tumors compared to symptom detected tumors of the same molecular subtype (p = 0.02). In multivariable cox proportional hazards models increased overall mortality was associated with impoverished neighborhoods, PR- receptor status, upregulation of TGF-beta and p53 dysregulation, whereas protective factors included upregulation of androgen receptor (AR), stromal, and cytotoxicity signaling (all P<0.05; **Table 1**). T2 vs. T1 tumor stage was associated with the largest observed differences in gene expression, and was associated with distinct changes in gene expression in luminal A vs. B disease including down regulation of interferon gamma signaling and MHCII expression in luminal B, but not luminal A, tumors.**Conclusions and Relevance:** Linkage of SEER, Medicare, and physical tumor specimen data is feasible and allows the combination of genomic analyses with clinical and health services data within population-level cohorts and may provide a novel means to elucidate links between biology, access, and disparities in breast cancer outcomes. Future research is warranted to conduct analogous prospective investigations of cancer disparities.

**Table –** Cox multivariable survival model

| *Parameter* | *All-cause mortalityHR (95% CI)* |
|---|---|
| Symptomatic tumor | 1.59 (0.70 - 3.64) |
| Stage N2+ vs N1 | 2.67 (0.48 -14.83) |
| Stage T2 vs T1 | **3.49 (1.42 - 8.58)** |
| Aged 71-76 vs 66-70 | **2.30 (1.05 - 5.01)** |
| Comorbidity Score (ref=0) | |
| 2+ | **8.85 (1.88-41.73)** |
| High school dropout rate | **3.72 (1.36 -10.17)** |
| PR- vs PR+ | **7.25 (1.96 -26.77)** |
| Luminal B vs Luminal A | 0.99 (0.40 - 2.49) |
| AR signature | **0.21 (0.09 - 0.48)** |
| TGF beta signature | **6.97 (2.00 -24.33)** |
| Macrophages signature | **0.22 (0.08 - 0.60)** |
| BC cytotoxicity signature | **0.61 (0.43 - 0.88)** |
| p53 signature | **3.12 (1.51 - 6.47)** |

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Identification and validation of stromal immunotype predict survival and benefit from neoadjuvant chemotherapy in patients of breast cancer

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**Background** Immune infiltration of breast cancer is associated with clinical outcome. A growing number of research suggests the immune response were composed by variously functionally distinct immune cell. But it's not clear which kinds of cell play the important role. The aim of this study was to determine whether differences in the cellular composition of the immune infiltrate in breast cancer influence survival and treatment response, and construct a stromal immunotype which could predict the response of neoadjuvant therapy and survival. **Patients and Methods** A total of 1502 ER negative breast cancers from TCGA and METABRIC cohort were used to infer the proportions of 22 subsets of immune cells, Another 320 ER negative breast cancer patients from Guangdong Provincial People's Hospital in the validation cohort were also included in the study. Immune cell infiltration was evaluated by immunohistochemical staining or CIBERSORT method, Five immune features were selected out of 22 immune features to construct immunotype based on LASSO Cox regression model.
**Result**Of the cell subsets investigated, CD8+ T cells (hazard ratio [HR] = 0.064, 95% CI 0.018-0.234; p < 0.001), CD4+ T cells (HR 0.072, 95% CI 0.013-0.382; p = 0.002), B cells (HR 0.04, 95% CI 0.005-0.340; p = 0.003) , M1 macrophages(HR 0.09, 95% CI 0.016-0.502; p = 0.006) were associated with favourable outcome. T regulatory cells(HR 10.791, 95% CI 2.059-58.444; p = 0.005) emerged as the most strongly associated with poor outcome. Using the LASSO model, we classified ER negative breast cancer patients into stromal immunotype A subgroup (CD8+T cells$^{high}$ CD4+T cells$^{high}$ B cell$^{high}$ M1 macrophages$^{high}$ Treg$^{low}$) and stromal immunotype B subgroup (CD8+T cells$^{low}$ CD4+T cells$^{low}$ B cell$^{low}$ M1 macrophages$^{low}$ Treg $^{high}$). Significant differences were found
between immunotype A and immunotype B in the combined cohort with 10-year overall survival (66.2% vs. 49.8%; P<0.001) and 10-year disease-free survival (63.8% vs. 44.4%; P<0.001). Stromal immunotype was revealed to be an independent prognostic indicator in multivariate analysis in all cohorts separately, and also showed to be related to pCR in neoadjuvant chemotherapy. Finally, stromal immunotype A showed higher immune checkpoint molecules (PD-L1, PD-1, CTLA-4) expression and three important cytokines expression profiles (IL-2, INF-γ and TGF-β). **Conclusion** The stromal immunotypes could predict survival and recurrence of ER negative breast cancer patients effectively. Furthermore, the immunotypes might be a practical predictive tool for immunotherapy and neoadjuvant chemotherapy.

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Associations with response to poly(ADP-ribose) polymerase (PARP) inhibitors in patients with BRCA mutated metastatic breast cancer: Results of a meta-regression analysis

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**Background:** PARP inhibitors (PARPi), when given as single agents, have modest antitumor activity in patients with advanced breast cancer and mutation in BRCA1 or BRCA2. It is unclear whether some subgroups derive greater benefit from treatment.**Methods:** Two electronic databases (MEDLINE, CENTRAL) and one registry (Clinicaltrials.gov) were searched from inception to June 2020 to identify trials of PARPi in patients with metastatic breast cancer. Objective response rate (ORR) and disease control rate (DCR) to PARPi were extracted and pooled in a meta-analysis using the Mantel Haenszel random effects model. Analyses were performed for patients with a BRCA mutation exclusively. Meta-regression explored the influence of patient and tumor characteristics and previous chemotherapy on ORR and DCR as reported in individual studies. Analysis comprised of a linear regression weighted by individual study sample size using the weighted least squares (mixed effect) method. Quantitative significance was defined using methods described by Burnand et al.
**Results:** Twenty-two studies comprising 1627 patients were identified and among these 1466 (90%) patients had a germline (n=1451) or a somatic (n=15) BRCA mutation and were included in the analysis. In 7 of these studies (32%; n=680 patients), the PARPi was given in combination with a platinum-based chemotherapy.; 54% of breast cancers were triple-negative. 81% of patients had received at least 1 prior line of chemotherapy in the metastatic setting and 28% were previously exposed to a platinum-based chemotherapy in the metastatic setting. Pooled ORR was 46%; 66% when combined with platinum vs 36% with PARPi alone (OR 3.44, 2.77-4.29, p0.001). Meta-regression results are shown in the Table. Previous chemotherapy in the metastatic setting, especially platinum-based chemotherapy, was associated with highly significantly lower ORR as defined by by Burnand et al. Age and hormone receptor status were not associated with response. Quantitatively similar results were observed for DCR.
**Conclusion:** PARPi therapy is associated with lesser response in patients with prior chemotherapy exposure, especially platinum-based treatment. There was no association between ORR and hormone receptor status or age.

| Dependent variable | Variable | Coefficients Bêta | Signifiance |
|---|---|---|---|
| **ORR BRCA1/2**n = 146645.67 % | Age | -0.32 | 0.34 |
| | Previous chemotherapy in metastatic setting | **-0.70** | **0.004** |
| | Previous platinum in metastatic setting | **-0.62** | **0.02** |
| | Platinum refractory | -0.39 | 0.22 |
| | Hormone receptor positive | 0.19 | 0.48 |
| | Triple negative | -0.12 | 0.66 |
| **DCR BRCA1/2**n = 126071.47 % | Age | -0.24 | 0.53 |
| | Previous chemotherapy in metastatic setting | **-0.74** | **0.006** |
| | Previous platinum | -0.42 | 0.21 |
| | Platinum refractory | -0.07 | 0.83 |
| | Hormone receptor positive | -0.12 | 0.69 |
| | Triple negative | 0.23 | 0.47 |

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# Targeted safety events from a phase I/Ib study evaluating GDC-0077 alone and in combination with endocrine therapy (ET) ± palbociclib (palbo) in patients (pts) with *PIK3CA*-mutant (mut), hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC)

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**Background**
Activating mutations in *PIK3CA*, encoding the p110α subunit of phosphatidylinositol 3-kinase (PI3K) occur in ~40% of HR+/HER2- BCs. GDC-0077, a PI3Kα-selective inhibitor and mutant PI3Kα degrader, is being developed as an anticancer agent. A phase I/Ib study of GDC-0077 alone and combined with other therapies is ongoing in pts with locally advanced or metastatic *PIK3CA*mut, HR+/HER2- mBC (NCT03006172). Targeted safety events are presented here.

**Methods**
Safety was assessed via NCI-CTCAE v4 for GDC-0077 administered alone (Arm A), with letrozole and palbo (Arm B), with letrozole (Arm C), with fulvestrant (Arm D), or with fulvestrant and palbo (Arm E, plus metformin in Arm F for pts with body mass index ≥ 30 and/or HbA1c ≥ 5.7%), in 28-day cycles until intolerable toxicity or disease progression. GDC-0077 was administered orally daily at 3, 6, 9, or 12 mg; letrozole, at 2.5 mg orally daily; palbo, at 125 mg orally 21/28 days; and fulvestrant, at 500 mg intramuscularly every 4 weeks. Targeted adverse events (AEs) included hyperglycemia, diarrhea, stomatitis (includes stomatitis, mucosal inflammation, mouth ulceration, glossitis, lip ulceration, palatal ulcer, and tongue ulceration), rash (includes rash, maculopapular rash, dermatitis acneiform, erythema, and erythematous rash), neutropenia (includes neutropenia and neutrophil count decreased), thrombocytopenia, and pneumonitis.

**Results**
As of clinical data cutoff (03/20/2020), 157 pts were enrolled and treated (Arm A: 20; Arm B: 33; Arm C: 37; Arm D: 39; Arm E: 13; Arm F: 15). Median cumulative dose intensity was 97.2% for GDC-0077, 90.6% for palbo, 99.9% for letrozole, and 100% for fulvestrant.

| **Pts, n (%)** | **Treatment-related AEs** | **Treatment-related grade ≥ 3 AEs** |
|---|---|---|
| | **All arms; N = 157** | **All arms; N = 157** |
| Hyperglycemia | 98 (62) | 36 (23) |
| Stomatitis (grouped terms) | 69 (44) | 2 (1) |
| Diarrhea | 68 (43) | 0 |
| Rash (grouped terms) | 19 (12) | 1 (1) |
| | **Palbo arms (B/E/F); N = 61** | **Palbo arms (B/E/F); N = 61** |
| Neutropenia | 45 (74) | 36 (59) |
| Stomatitis (grouped terms) | 41 (66) | 2 (3) |
| Thrombocytopenia | 19 (31) | 4 (7) |

Pneumonitis was reported in 2 pts, both in palbo-containing arms (grade 1 in Arm B; grade 2 in Arm F). Hyperglycemia required antihyperglycemic treatment in 69 pts (44%), and the most frequent agents used were metformin (39%; except Arm F where this was required as part of study treatment), empagliflozin (16%), and sitagliptin (15%). Fifteen pts (10%) required GDC-0077 dose reductions due to hyperglycemia. Stomatitis treatment was administered in 51 pts (32%), with dexamethasone mouthwash used most frequently (22%). Neutropenia and thrombocytopenia were managed with palbo dose reduction in 13 pts (21%) and 1 pt (2%), respectively. Overall, treatment-related AEs led to GDC-0077 discontinuation in 2 pts (1%) (grade 3 hyperglycemia in Arm B; grade 2 panniculitis in Arm F).

**Conclusion**
Targeted safety events with GDC-0077 alone and in combination ET ± palbo were manageable and required minimal GDC-0077 dose modifications or discontinuations. No unexpected safety events were reported in combination with palbo. A phase III study of GDC-0077 in combination with palbo and fulvestrant is enrolling currently (NCT04191499).

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# Identifying breast cancer survivors with dormant disseminated tumor cells: The PENN-SURMOUNT screening study

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**Background:** Patients (pts) treated for early stage breast cancer have a 30% lifetime risk of developing incurable, distant metastatic disease. Current models suggest that this occurs through escape of cells from the primary tumor into the circulation and subsequent sequestration of “disseminated tumor cells” (DTCs), in the bone marrow and other sequestration sites, where they enter dormancy. DTCs identified by immunohistochemistry (IHC) are associated with poor prognosis in longitudinal studies and meta-analyses, increasing odds of recurrence by approximately 2 to 5-fold. However, little is known about the test characteristics of the DTC-IHC assay, clinical DTC detection rates over time, and patient and disease risk factors that can identify pts harboring these cells.
**Methods:** The PENN-SURMOUNT Screening Study (NCT 02732171) is a prospective, longitudinal study examining bone marrow and blood biomarkers of recurrence among pts within 5 years of diagnosis who have completed therapy for primary breast cancer (with the exception of endocrine therapy). Pts with positive lymph nodes, triple negative receptors, ER-positivity with RS ≥ 25 and/or high-risk MammaPrint (MP), or residual disease after neoadjuvant chemotherapy were screened with bone marrow aspirate (BMA) for presence of DTCs. A positive DTC-IHC result is defined by the presence of at least one pancytokeratin-DAB positive cell utilizing the methods of Naume et al. Cytospin slides prepared from the BMA are independently reviewed by two pathologists with adjudication for the presence of DTCs; Pts who screen negative for DTCs are offered repeat screening annually. Pts who screen positive are referred to an interventional clinical trial (CLEVER, NCT 03032406).
**Results:** A total of 194 pts screened eligible for enrollment on PENN-SURMOUNT between 6/2016 and 3/2020. Of these, 158 consented and 151 underwent BMA with successful IHC analysis on 100%. Pts came from 22 U.S. states; ≥ 1/3 traveled over 50 miles to the study center. At baseline BMA, 36/151 (24%) had at least 1 measurable DTC by IHC. Patient characteristics and DTC distribution among subpopulations are shown in Table 1. Of the 78/115 who were initially DTC negative and continued to be eligible for repeat screening, as of 3/2020, 46 (59%) returned for at least one repeat BMA. 13/46 (28%) had at least 1 detectable DTC on 1 of up to 3 subsequent follow up assessments for a total DTC positivity rate of 32.5% (49/151). 48 (98%) DTC+ pts have subsequently enrolled on the CLEVER trial.
**Conclusions:** BMA assessment for DTCs is feasible in pts with high risk, early stage breast cancer. DTCs are detected in up to a third of breast cancer survivors with repeat assessment during the surveilance period. DTC positivity rates are relatively similar across all receptor subtypes, and after both neoadjuvant and adjuvant chemotherapy. Pts harboring DTCs are highly likely to enroll on interventional trials designed to reduce recurrence risk.

Table 1. Patient characteristics and distribution of % DTC positivity among subpopulations

| | | **DTC+ (N=49)** | **DTC- (N=102)** | **Total (N=151)** | **DTC+ Rate (Overall: 32.5%)** |
|---|---|---|---|---|---|
| **DEMOGRAPHICS** | | | | | |
| **Median Age at BMA (yrs)** | | 51.9 (43.9-60.6*) | 50.5 (42.9-58.1) | 50.5 (43.8-58.8) | **N/A** |
| **Race** | **Caucasian** | 44 (89.8%) | 91 (89.2%) | 135 (89.4%) | **32.6%** |
| | **African American** | 5 (10.2%) | 9 (8.8%) | 14 (9.3%) | **35.7%** |
| | **Other** | 0 (0%) | 2 (2.0%) | 2 (1.3%) | **0%** |
| **Menopausal Status** | **Pre-** | 15 (30.6%) | 34 (33.3%) | 49 (32.5%) | **30.6%** |
| | **Post-** | 34 (69.4%) | 68 (66.7%) | 102 (67.5%) | **33.3%** |
| **BMI at BMA (kg/m$^2$)** | | 24.2 (21.9-28.9*) | 26.9 (23.4-31.4) | 26.1 (22.8-30.4) | **N/A** |
| **RECEPTOR STATUS** | | | | | |
| **ER/PR+ HER2neg (by ASCO/CAP)** | | 24 (49.0%) | 51 (50.0%) | 75 (49.7%) | **32.0%** |
| **HER2+ (any ER/PR)** | | 9 (18.4%) | 12 (11.8%) | 21 (13.9%) | **42.9%** |
| **ER/PRneg HER2neg** | | 23 (46.9%) | 48 (47.1%) | 71 (47.0%) | **32.4%** |
| **RISK CRITERIA** | | | | | |
| **Lymph Node Positive** | | 24 (49.0%) | 65 (63.7%) | 89 (58.9%) | **27.0%** |
| **Triple Negative (ER/PR<10%)** | | 27 (55.1%) | 50 (49.0%) | 77 (51.0%) | **35.0%** |
| **Non-pCR** | | 11 (22.4%) | 25 (24.5%) | 36 (23.8%) | **30.6%** |
| **RS ≥ 25 and/or High Risk MP** | | 6 (12.2%) | 8 (7.8%) | 14 (9.3%) | **42.9%** |
| **Median T size (cm) -excluding NACT** | | 2.1 (1.5-2.9*) | 1.8 (1.3-2.8) | 1.8 (1.3-2.9) | **N/A** |
| **PRIOR THERAPY** | | | | | |
| **Adjuvant Chemo** | | 25 (51.0%) | 60 (58.8%) | 85 (56.3%) | **29.4%** |
| **Neoadjuvant Chemo** | | 22 (44.9%) | 41 (40.2%) | 63 (41.7%) | **34.9%** |
| **Endocrine Therapy** | | 19 (38.8%) | 47 (46.1%) | 66 (43.7%) | **28.8%** |
| **XRT** | | 29 (59.2%) | 75 (73.5%) | 104 (69.3%^) | **27.9%** |

* Ranges represent interquartile range^ XRT data not available on 1 patient; n=150 was used to figure percentage

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Benign breast disease: Temporal trends from 1967 to 2013

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*Background*: Women with benign breast disease (BBD) are at increased risk of breast cancer (BC). Classic studies based on film-based mammographic screening and pathology diagnosis of surgical biopsies conducted in the 1980s established a hierarchy of increasing BC risk: non-proliferative (NP) BBD, proliferative BBD without atypia (PDWA) and atypical hyperplasia (AH). Given changes in epidemiological BC risk factors and introduction of percutaneous core needle biopsy (CNB) in mid-1990s, and later, digital mammography, we hypothesized that the patient characteristics and relative frequency of BBD diagnoses have changed over time. Accordingly, we performed a longitudinal analysis of the frequency of patient characteristics and BBD diagnoses in the Mayo BBD cohort.
*Methods*: Utilizing the Mayo Clinic Surgical and Pathology Indices, women ages 18 to 85 who had a BBD biopsy between 1/1/67 and 12/31/13 were identified. Breast pathologists reviewed biopsies masked to diagnoses of incident BC diagnosed in follow-up. Demographic characteristics and BC events were obtained by query of institutional data sources and participant surveys. Trends were evaluated for the following eras: 1: pre-mammogram (1967-1981), 2: pre-CNB (1982-1992), 3: CNB Transition (1993-2001), and 4: CNB (2002-2013). Demographics were formally compared across eras using chi-square tests for categorical variables and analyses of variance (ANOVAs) for continuous variables.
*Results*: From 1967-2013, the cohort includes 19,582 unique women with BBD. The frequency of CNB increased from eras 1-4: 0.04%, 0.6%, 51.3 %, and 88.9%, respectively. Mean age at BBD diagnosis was younger in era 1 (48.0 years) vs eras 2-4 (53.2, 52.0, and 51.8, respectively, $p<0.001$). The percentage of biopsies diagnosed as PDWA increased from era 1-4 (25.7%, 34.3%, 35.2%, 46.2%, $p<0.001$), as did the percentage with AH (2.4%, 5.1%, 8.6%, 12.3%, $p<0.001$). Over eras 1-4, the percentages of women with a strong family history of BC increased (9.9%, 12.7%, 17.1%, and 29.0%, $p<0.001$) as did mean BMI (24.8, 26.4, 27.4, and 28.6, $p<0.001$). With a median follow-up of 10.9 years, 1,719 breast cancers have developed, with increasing proportion of noninvasive (DCIS-only) disease across eras 1-4: 15.0%, 21.1%, 21.2%, and 33.2%, $p< 0.001$.
*Conclusions*: Analysis of this large, single institution BBD cohort for the 46 year period 1967-2013 demonstrates that BC risk factors among BBD patients has changed over time, with subjects demonstrating increasing age, BMI, and family history, and that the percentages of BBD classified as PDWA and AH have increased. Impact on BC risk will be further investigated.

**Publication Number:** PS16-11

Potential therapeutic effects of HDACi FK228 on TNBC using various models

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Breast cancer is the most prevalent type of cancer among women. Most breast cancers are hormone sensitive, however triple negative breast cancer (TNBC), a more aggressive subtype of breast cancer is characterized by its negative expression of estrogen and progesterone receptors, and lack of Her2/NEU amplification. Because of its receptor status, hormone receptor targeted treatments are ineffective against TNBC making it difficult to treat. FK228, known as Romidepsin, is a histone deacetylase inhibitor (HDACi) that specifically targets the enzymes HDACs 1 and 2, tumor suppressor and other proteins exerting epigenetic changes on tumor cells resulting in anticancer activity. FK228 has not been studied in TNBC, but has been approved by the FDA for the treatment of peripheral T-cell lymphoma (PTCL), where the mechanism of action has demonstrated cell cycle arrest and apoptosis [1,2]. To assess the preliminary role of FK228 in breast cancer, a number of TNBC cell lines were treated with the drug and analyzed for suppression of cell cycle genes. Similar to PTCL, TNBC cell lines showed an increase in cell cycle arrest genes such as p21 and others subsequent to treatment. Moving forward, to recapitulate the tumor microenvironment we have utilized 2D and 3D culture, while PDXs (patient derived xenografts), an excellent translational tool. We first identified changes in morphology and migration in 2k1, MDA-MB 231 and HS-578t cell lines treated with FK228 under in-vitro conditions. Additional molecular studies also show a reversal of the epithelial to mesenchymal transition (EMT) in FK228 treated BC cell lines; specifically in relation to EMT genes CDH1 and ZEB2, both directly connected to HDAC1/2 activity. To further study the effects of FK228, PDXs are implanted into mice to study growth patterns, recurrence, metastatic potential and response to FK228 in different patient tumor models. FK228 showed a drastic suppression in tumorigenesis in model TU-BCX-2O0, prompting the study of several other models in tumorigenesis including TU-BX-4IC, 4M4 and 4QX. Metastasis was also monitored by H&E staining lung and liver tissue for analysis for each model, and using an in vivo model consisting of GFP/luciferase transfected breast cancer cells MDA-MB-231 and SUM-159 to monitor both the proliferation and spread of disease in mice. Ultimately this study aims to characterize the FK228 alteration of pathways involved in tumorigenesis, metastasis and resistance within TNBC.

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**Publication Number:** PS2-11

Ctc-her2+ a novel subset in stage $IV_{aggressive}$: Molecular correlations, outcome and clinical characteristics in metastatic breast cancer

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**Background** The enumeration of Circulating Tumor Cells (CTCs) in the peripheral blood of patients (pts) with metastatic breast cancer (MBC) showed prognostic value independent of clinic-pathological characteristics and proposed as a new tool for Stage IV stratification. Molecular characterization of CTCs with analysis of standard HER2 and estrogen-receptor (ER) status provides additional predictive value. The presence of HER2 positive CTCs (CTCs-HER2+) has been documented in pts with HER2 negative MBC and suggestive of tumor heterogeneity. The molecular features associated with the detection of these cells and the clinical significance of CTCs-HER2+ remains of unclear clinical significance. The lack of validated prospective trials limits the use of this immunophenotypic characterization as a prognostic and predictive factor. We conducted an analysis of a large cohort of patients with MBC evaluated for CTCs enumeration (CTCs+), molecular analysis of CTCs (CTCs-HER2+) and ctDNA. **Methods** The IRB-approved study prospectively analyzed blood samples of pts with MBC enrolled before starting a new line of therapy. Samples were collected from pts treated at Northwestern University (Chicago, IL) between 2016 and 2020. ctDNA was analyzed using the Guardant360 NGS assay (Guardant Health) with a specific focus on the detection of *ERBB2* mutations. CTCs were enumerated through CellSearch™ (Menarini Silicon Biosystems, Bologna, Italy), and characterized for HER2 expression using the CellSearch CXC Kit. HER2+ CTCs were divided in 4 different categories (0,1+,2+,3+), leaning on fluorescence intensity, as previously reported by Riethdorf et al. Pts with <5 CTCs (stage $IV_{indolent}$ ) were excluded from the analysis. The cHER2 ratio, defined as the sum of 2+ CTCs and 3+ CTCs divided by the total number of HER2+ CTCs was used to split the remaining pts in 2 different subgroups: cHER2 ratio> 0.75 ($cHER2_{high}$), cHER2 ratio<0.75 ($cHER2_{low}$). Pts' characteristics and genomic alterations were compared between these two subgroups and a long-rank test was performed to analyze the outcome (progression-free survival, PFS). **Results** A total of 247 pts with MBC about to start new therapy were enrolled. 136 patients (55%) demonstrated CTCs count ≥ 5 (stage $IV_{aggressive}$). Of these, 111 pts had a blood sample bearing HER2+ CTCs. 88 pts were classified as $cHER2_{low}$, while 32 were allocated in the second subgroup ($cHER2_{high}$). The clinic subtype distribution of the two groups was as follows: 65% ER+, 19% HER2+ and 16% TNBC among $cHER2_{low}$, compared to 55% ER+, 38% HER2+ and 7% TNBC among $cHER2_{high}$ pts. The HER2+ subtype was significantly more represented in the $cHER2_{high}$ group ($p<0.05$), along with *ERBB2* mutations ($p<0.05$). We observed a total of 89 events (progression to treatment), 67 and 22 respectively. The median PFS was 87 days in the $cHER2_{low}$ and 209 days among $cHER2_{high}$ pts (log Rank test, $p<0.001$). **Conclusion** This study shows a significant association between the cHER2 ratio and outcome in pts with Stage $IV_{aggressive}$ disease, suggesting a potential predictive/prognostic role of this biomarker among MBC pts bearing CTC-HER2+. $cHER2_{high}$ pts, in which blood was collected a prevalent number of CTC-HER2+ 2+ and 3+, were more likely to have a HER2 FISH amplification by tissue biopsy and *ERBB2* gene alteration by ctDNA. These findings, taken together, suggest a potential role of these subsets of CTC-HER2+ in the characterization of the HER2+ metastatic disease. The $cHER2_{low}$ is intrinsically characterized by a higher percentage of CTC-HER2+ 1+. This CTC-HER2+ subset of cells is commonly detected among all subtypes but, more frequently in ER+ disease and their significance remains unclear. Exploring the underlying biological nature of the CTC-HER2+ 1+ could allow to better understand the role these cells in the natural evolution of the MBC.

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Targetable *ERBB2* mutation status is an independent marker of adverse prognosis in estrogen receptor positive, *ERBB2* non-amplified primary lobular breast carcinoma: Validation using a novel gene signature of HER2 activation

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Invasive lobular carcinoma (ILC) accounts for 10-15% of primary breast cancer and is typically ER+ and *ERBB2* non-amplified. There is preclinical evidence that somatic *ERBB2* mutation may provide an alternative and tractable mechanism for upregulation of HER2 activity in tumors that do not express HER2 by current clinical criteria. Using large public datasets, we previously demonstrated that targetable *ERBB2* mutations are enriched in ILC *versus* invasive ductal carcinoma (IDC) and are an independent prognostic factor in ILC (HR=3.7, 95% CI 1.2-11.0; *p*=0.021)*. We next hypothesized that a gene expression signature incorporating HER2 activity due to *ERBB2* mutation and / or amplification would validate the prognostic signal we found in ILC.

To derive a novel gene expression signature of HER2 activity that accounted for the effect of potentially targetable *ERBB2* mutations in *ERBB2* non-amplified tumors, we applied a weighted average difference method to gene expression data in cases from the METABRIC 2012 (N=1,980) and TCGA 2015 (N=817) cohorts. To compare our novel gene expression signature with an established signature of HER2 activity, we performed multivariate regression modeling of response to neratinib, a small molecule tyrosine kinase inhibitor of HER1, 2 and 4, using pharmacogenomic data accessed *via* the CellMinerCDB online portal.

We show that our novel HER2 pathway signature score uniquely enriches for *ERBB2* mutated tumors. Using a Cox regression model and stratifying gene expression scores into upper *versus* lower quartiles, we were able to validate the prognostic signal of *ERBB2* mutations in ILC tumors (HR for 10-year OS in ILC=2.3, 95% CI 1.04-5.05; *p*=0.040). In contrast, no relationship was found between *ERBB2* mutation status or novel HER2 pathway enrichment score and patient outcome in cases of IDC.

We conclude that *ERBB2* mutations that are enriched in ILC provide a robust biomarker of HER2 pathway activation and can be detected *via* gene expression signature. Novel clinical trials of HER2-targeted therapy in *ERBB2* non-amplified primary ILC are warranted.

*Reference: Kurozumi S *et al*, Cancer Research 2019, 80(4) suppl: SABCS 2019 Abstract P1-18-06 and medRxiv 2020.01.24.20018622

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**Publication Number:** PD3-11

# A randomized, open-label, phase III trial of pertuzumab re-treatment in HER2-positive, locally advanced/metastatic breast cancer patients previously treated with pertuzumab, trastuzumab, and chemotherapy: The Japan Breast Cancer Research Group-M05 (PRECIOUS) study

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**Background:** Patients (pts) with HER2-positive locallyadvanced/metastatic breast cancer (LA/MBC) previously treated with pertuzumab(P)-containing regimens have few therapeutic options. The efficacy of Pre-treatment combined with trastuzumab (T)+chemotherapy as 3 or 4 -line chemotherapy was examined in such pts. **Methods:** Pts previously treated with P-containing regimens as1st/2nd-line treatment for LA/MBC were randomly assigned 1:1 to two groups(P+T+chemotherapy based on physicians' choice (C) (PTC), and T+C (TC)),stratified by estrogen receptor status, previous P treatment duration, numberof previous chemotherapy regimens, and presence or absence of visceralmetastasis. The primary endpoint was investigator-assessed progression-freesurvival (PFS). Superiority of PTC to TC will be tested using a stratifiedlog-rank test that accounts for all stratification factors, and a one-sidedP-value of less than 0.05 will be considered an indicator of superiority. Thedistribution of PFS will be estimated using the Kaplan-Meier method. In addition,the hazard ratio and one-sided 95% CI of the therapeutic effect between thegroups will be calculated using the Cox proportional hazard model. Secondaryendpoints included independent reviewer assessed PFS, PFS in pts treated withT-DM1 as the latest regimen (PFS after T-DM1), objective response rate (ORR),overall survival (OS), safety, and health-related quality of life (HR-QoL). **Results:** Of the 219 pts enrolled, 217 (108 PTC, 109 TC) wereincluded in the intent-to-treat analysis. At the data cutoff (July 31, 2019),PFS and OS events were 184 (84.8%) and 84 (38.7%), respectively. Medianfollow-up time was 14.2 months (mo). Investigator-assessed PFS wassignificantly better in the PTC group (median PFS 5.3 vs. 4.2 mo; HR = 0.755[One-sided 95%CI upper limit, 0.967]; One-sided stratified log-rank test p =0.0217). Median PFS after T-DM1 (5.3 vs. 4.2 mo; HR = 0.801 [One-sided 95%CIupper limit, 1.061]; One-sided log-rank test p = 0.0952) and OS (28.8 vs. 23.4mo; HR = 0.713, [One-sided 95%CI upper limit, 1.026], One-sided log-rank test p= 0.062) tended to be longer in the PTC group, though further follow-up isneeded. The ORR with measurable disease (PTC (n = 90) 18.9% vs. TC (n = 92)19.6%) did not differ between the groups. The serious adverse event rate didnot differ between the groups (17.9% vs. 21.3%). There were no new safetysignals included cardiac events in the groups. In the comparison of HR-QoL bytime to deterioration analysis, there was no significant difference between thegroups in FACT-B trial outcome index (PTC 2.8 mo vs. TC 4.3 mo; HR = 1.274,log-rank test p = 0.2289).**Conclusions:** P re-treatment as 3 or 4 -line chemotherapy wasactive and feasible. P re-treatment can be a standard treatment option forpatients with HER2-positive LA/MBC previously treated with P.(ClinicalTrials.gov number: NCT02514681)

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Prospective HER-2 testing using simultaneous immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH): Experience of dual testing in a single academic institution

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Background: HER-2 testing informs prognosis and critically guides therapy in breast cancer. Current guidelines for immunohistochemistry (IHC) testing define 3+ as positive, 0 and 1+ as negative, and 2+ as equivocal with additional testing recommended. Guidelines for *in situ* hybridization (ISH) testing are more complex and generally define a HER-2/CEP17 ratio of ≥2.0 with average HER-2 copy number of ≥4.0 copies/cell as HER-2 positive. Further, HER-2 copy number between 4 and 6 per cell, with a ratio of <2.0, is considered equivocal while ≥6 per cell is frequently confirmed positive. Limited data suggest that an elevated HER-2 copy number alone has clinical relevance, however most clinical trials addressing HER-2 targeted therapeutics define HER-2 positive based on HER-2/CEP17 ≥2.0.
Design: From 2013-2016, all new invasive breast cancer cases diagnosed at the University of Vermont Medical Center were prospectively tested for HER-2 using both IHC and chromogenic *in situ* hybridization (CISH) simultaneously. All testing was performed on formalin-fixed paraffin-embedded tissue, using the 4B5 Rabbit Monoclonal Antibody (Ventana) for IHC and the INFORM dual ISH DNA probe (Ventana) for CISH. Interpretation was performed using published criteria, and all cases were independently analyzed by two experienced reviewers.
Results: 1906 patients underwent HER-2 testing by both IHC and CISH. 1671 (87.7%) patients had a HER-2/CEP17 ratio of <2.0. Of patients considered to be non-amplified by the CISH ratio, 55 (3.2%) had a HER-2 copy number ≥4. In IHC 0 and 1+ cases with HER-2/CEP17 ratio of <2, 0.4% and 2.3% have equivocal and excess HER-2 copies/cell, respectively, compared to 10.8% for IHC 2+. Additionally, 17 (8.6%) of the IHC 3+ cases had a CISH ratio of <2, of which 41.2% had ≥4 HER-2 copies/cell (see table).
Table. Simultaneously tested IHC and CISH data for new invasive breast cancer cases

| | IHC | CISH ratio ≥2.0 | CISH ratio <2.0 | HER-2 copies/cell (CISH ratio <2.0 cohort) | | | CISH ratio <2.0 with ≥4 HER-2 copies/cell |
|---|---|---|---|---|---|---|---|
| IHC | n | n (%) | n (%) | <4 (n) | 4-6 (n) | >6 (n) | |
| 0 | 501 | 0 (0.0) | 501 (100.0) | 499 | 2 | 0 | 0.4% |
| 1+ | 942 | 21 (2.2) | 921 (97.8) | 899 | 20 | 1 | 2.3% |
| 2+ | 265 | 33 (12.5) | 232 (87.5) | 206 | 25 | 0 | 10.8% |
| 3+ | 198 | 181 (91.4) | 17 (8.6) | 10 | 6 | 1 | 41.2% |
| Total | 1906 | 235 (12.3) | 1671 (87.7) | 1614 | 53 | 2 | 3.2% |

Conclusion: To our knowledge, this is the largest study to date that has examined the concurrent use of both IHC and ISH HER-2 assays prospectively in a real-time clinical setting. In the IHC 2+ cohort, only 12.5% were amplified by ISH testing. Interestingly, of those in the IHC 2+ cohort not amplified by CISH, 10.8% had an equivocal or excess HER-2 copy number. Further, while based on a very small sample size, 41.2% of IHC 3+ patients with a CISH ratio of <2.0 had an equivocal or excess HER-2 average copy number. Finally, data on the clinical outcome and therapeutic benefit of HER-2 targeted therapy in patients with non-amplified ISH testing and equivocal or excess HER-2 copy number remains limited, and warrants further evaluation.

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# Altered regional cerebral blood flow in adjuvant-treated breast cancer survivors after chemo- and endocrine therapy

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**Objectives:** In the first published observation of altered brain metabolism in patients exposed to chemotherapy (*Breast Cancer Res Treat.* 2007; 103:303-311), we described diminished metabolism in prefrontal cortex in proportion to magnitude of diminishment of short-term memory performance, 5-10 years following patients' last chemotherapy dose. Subsequently, at least 7 other groups of investigators have independently demonstrated altered cerebral metabolism of frontal cortex as assessed by FDG-PET (*J Nucl Med.* 2019; 60:16821690). We now offer the first report of regional cerebral blood flow (rCBF) changes assessed by [O-15]water PET in prospectively recruited subjects with newly diagnosed breast cancer, longitudinally followed from time of initial therapy for one year.

**Methods:** A total of 204 brain [O-15]water PET scans were obtained of 17 right-handed female subjects newly diagnosed with breast cancer, with near-equal portions of 10 chemo-exposed ***(C)*** and 7 unexposed ***(U)*** subjects undergoing endocrine therapy in the ensuing year (5/10, 3/7). For each subject, 12 scans were obtained -- 6 during short-term memory, long-term memory, and control tasks presented in counterbalanced order soon after completion of any adjuvant chemotherapy but prior to initiation of any endocrine therapy (baseline), and repeating one year later. PET data were assessed through paired t statistical tests at the voxel level, after Family Wise Error (FWE)-based corrections for multiple comparisons.

**Results:** Across all subjects, scans at baseline during short-term recall revealed most marked activation of bilateral temporal-occipital cortex (peak voxel t=7.20; size 4,649 voxels, p<.0005 $FWE_{corr.}$) and similar activation occurred during long-term recall (t=6.48; 6,446 voxels, p<.0005 $FWE_{corr.}$). One year later, left prefrontal cortex, including Broca's area, activated during short-term recall (t=5.74; 227 voxels, p=.02 $FWE_{corr}$), as did bilateral medial occipital cortex (t=5.45; 908 voxels, p<.0005 $FWE_{corr.}$); during long-term recall, prefrontal cortex activated with greater bilaterality, but with an extent in left frontal lobe (1031 voxels, p=.008 $FWE_{corr.}$) about double the size of right (452 voxels), and with less occipital activation. In therapy-stratified analyses, baseline short-term recall of left prefrontal cortex, including Broca's area, activated more extensively (3253 voxels, p<.0005 $FWE_{corr.}$) in ***U***, while ***C*** showed more extensive activation in medial occipital cortex (5670 voxels, p<.0005 $FWE_{corr.}$vs. 423 voxels, p=.001). One year later, short-term recall in ***U*** continued to activate left prefrontal cortex including Broca's area (4035 voxels, p<.0005 $FWE_{corr.}$), while ***C*** still primarily activated medial occipital cortex (976 voxels, p=.008 $FWE_{corr.}$), though demonstrating a shift of activation away from this region relative to one year prior, with more voxels of activation tending to appear in left prefrontal cortex over that interval. Similar, though less striking, differences were observed during long-term recall.

**Conclusions:** Activation of rCBF during recall of verbal associative memories was diminished in left prefrontal brain areas critical to verbal memory performance in ***C*** relative to ***U***. Concomitantly, ***C*** demonstrated apparent compensatory activation of primary visual cortex, involved in perceiving the visually presented verbal memory cues, in lieu of specific activation of the prefrontal cortical regions in the dominant hemisphere involved in processing language information. The strengths of these therapy-associated differences were generally diminished one year later, consistent with partial interim recovery in ***C*** of cerebral processing by language-specialized areas.

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# A Phase 2, open-label study to evaluate the safety and efficacy of the probody therapeutic (Pb-Tx) CX-2009 in metastatic HR-Positive/HER2-negative breast cancer (mHR+/HER2− BC) and of CX-2009 as monotherapy and in combination therapy with CX-072 in metastatic triple-negative breast cancer (TNBC)

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**Background:** Probody® therapeutics (Pb-Tx) are masked antibodies designed to be selectively activated in the tumor microenvironment by tumor-associated proteases, while remaining largely inactive in normal tissue and in circulation. This allows Pb-Tx to address previously undruggable targets that are highly expressed in both tumor and normal tissue, such as the activated leukocyte cell adhesion molecule (ALCAM) CD166. CX-2009 is an investigational Probody drug conjugate consisting of an anti-CD166 monoclonal antibody conjugated to the microtubule inhibitor DM4. A Phase 1 study demonstrated safety and durable clinical activity in patients with mHR+/HER2− BC and in mTNBC patients who had received a median of 7 prior regimens. In the efficacy evaluable subgroup receiving doses of at least 4 mg/kg Q3W, the overall response rate (ORR; includes confirmed and unconfirmed responses) was 11% (HR+/HER2−; n=18) and 38% (TNBC; n=8), with a clinical benefit rate at 24 weeks (CBR24) of 35% in all breast cancer patients. Gr ≥3 DM4-associated ocular toxicities related to CX-2009 ≤7mg/kg were reported in 2%. In this Phase 2 study, CX-2009 monotherapy will be evaluated in patients with mHR+/HER2− BC and mTNBC. In addition, CX-2009 will be combined with CX-072, a Probody therapeutic directed against PD-L1, to evaluate the safety of the combination and whether the cytotoxic activity of the DM4 payload is additive with PD-L1 blockade via CX-072 in patients with mTNBC. CD166 expression in patients with HR+/HER2− BC was high (>90%) in the Phase 1 study; this cohort will enroll without screening for CD166. CD166 expression in patients with TNBC was variable and, as such, patients will undergo screening for CD166 positivity.

**Methods:** This Phase 2, open-label noncomparative study with 3 parallel arms (n≈40/arm) is investigating the safety and activity of CX-2009 monotherapy (7 mg/kg Q3W) and the combination of CX-2009 (7 mg/kg Q3W) + CX-072 (1200 mg Q3W) in patients with previously treated locally advanced or metastatic HER2− BC. All patients will be adults with an ECOG status of 0-1, acceptable end-organ function, measurable disease, and willingness to receive ocular prophylaxis for DM4 related toxicities. Tumor tissue is required for CD166 expression analysis. Key eligibility criteria for the mHR+/HER2− BC cohort include 2-4 prior regimens (not including single-agent hormonal therapy). Patients with mTNBC must be CD166 positive by IHC and have received 1-3 regimens. For mTNBC patients who receive the doublet, key exclusion criteria include known PD-L1-negative tumor status, history of or active autoimmune disease, and progression within 120 days of first dose of an IO agent. Patients with active or chronic corneal disorders will be excluded from the study. All treatments will be given until disease progression or unacceptable toxicity. Radiology assessments will be done Q6W. The primary endpoint will be ORR assessed by an independent radiology committee per RECIST v1.1. Secondary endpoints will include ORR, DoR, CBR16 and CBR24, and PFS by investigator, OS will also be assessed. This study will also evaluate tolerability, pharmacokinetics, and antidrug antibodies with CX-2009 as monotherapy and in combination with CX-072. Exploratory endpoints will include potential predictive markers of response or toxicity. This trial is actively enrolling.

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# Integrated safety summary of single agent and combination margetuximab in phase 1, 2, and 3 studies of HER2-positive advanced cancers and metastatic breast cancer (MBC)

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**Background** Margetuximab (M) is an investigational Fc-engineered anti-HER2 monoclonal antibody that targets the same epitope as trastuzumab (T). Compared with T, M has higher affinity for both the 158V (high-binding) and 158F (low-binding) allotypes of the activating Fc receptor CD16A. M enhances innate immunity more effectively than T in vitro, including CD16A-mediated antibody-dependent cellular cytotoxicity. Samples collected from patients (pts) before and after single-agent treatment also demonstrate that M induces HER2-specific adaptive immune responses, including both T- and B-cell responses. The SOPHIA trial (NCT02492711) in pts with pretreated HER2+ MBC showed that M+chemotherapy (chemo) improved progression-free survival vs T+chemo, with comparable safety. A pooled analysis of M safety across 3 clinical trials is presented. **Methods** Study 01 (NCT01148849), an ongoing Phase 1 dose-finding/safety study of M monotherapy, enrolled 66 pts with advanced HER2+ carcinomas, including 27 with MBC. Study 02 (NCT01828021), a completed Phase 2 study of M monotherapy in low-expressing HER2+ MBC, enrolled 25 pts. Study 04 (NCT02492711), an ongoing Phase 3 study in pts with pretreated HER2+ MBC to compare M + chemo vs T + chemo, randomized 536 pts, of whom 264 and 265 received M and T, respectively. The pooled safety population includes all pts who received any M in Study 01 (cutoff 01Oct2015), Study 02 (cutoff 02Aug2017), and Study 04 (cutoff 10OCT2018). Treatment-emergent adverse events (AEs), defined as AEs that began or worsened in severity on or after first dose of study drug through an End of Treatment Visit or 28 days after last study treatment, are reported. **Results** Of 355 pts that received at least 1 dose of M, 295 received 15 mg/kg Q3W, and 60 received other doses from 0.1 - 18 mg/kg. Median (mean, range) number of cycles for all dose levels was 5.0 (6.6, 1-43), higher on Study 04 (6.0) than Study 01 (1-3 across dose groups) or Study 02 (2.0). Most pts (347 [97.7%]) experienced at least 1 AE, and about half (173 [48.7%]) had at least 1 Grade >/= 3 AE. Serious AE (SAE) incidence across studies was low (58 [16.3%]), and 21 pts (5.9%) discontinued M due to AEs. Most frequently reported AEs (>/= 20%) were fatigue (124 [34.9]), nausea (103 [29.0%]), diarrhea (75 [21.1%]), and neutropenia (75 [21.1%]). Blood/lymphatic system disorders were the most frequent events by SOC, and largely restricted to Study 04. Increased neutropenia on M (26.1%), relative to T (20.4%), was observed in Study 04 yet both febrile neutropenia (M 3.0%, T 4.5%) and infections (M 36.4%, T 39.6%) were higher on T. By contrast, Study 01 and Study 02 revealed no tendency of M monotherapy to cause neutropenia. Overall, infusion related reactions (IRRs) were observed in 51 pts (14.4%), primarily at first infusion, including serious IRRs in 5 (1.4%). Also, 34 pts (9.6%) had > 15% reduction in LVEF with a median time to > 15% reduction of 49 days. In all pts with complete follow-up, these LVEF reductions were asymptomatic and reversible. No M-induced cardiac conduction abnormalities were noted. In Study 04, similar proportions in both groups experienced AEs (M 97.7%, T 96.2%), including Grade >/= 3 AEs (M 52.3%, T 48.3%), SAEs (M 14.8%, T 17.4%), discontinuations due to AEs (M 3.0%, T 2.6%), and deaths due to AEs (M 0.8%, T 0.8%). As of the 23Feb2020 safety update, 2 pts remain on M in Study 01, after 116 and 109 cycles (6.7 and 6.3 years), respectively. In Study 04, 16 pts (6%) continued on M, and 7 (2.6%) remained on T. **Discussion** M has demonstrated an acceptable safety profile across Phase 1, 2, and 3 studies. It has been administered for over 6 years without long-term cumulative safety issues. Combined M plus chemotherapy Q3W demonstrated acceptable safety and tolerability, similar to that for T plus chemotherapy Q3W in Study 04.

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# Trastuzumab deruxtecan (T-DXd; DS-8201) vs investigator's choice of chemotherapy in patients with hormone receptor-positive (HR+), HER2 low metastatic breast cancer whose disease has progressed on endocrine therapy in the metastatic setting: A randomized, global phase 3 trial (DESTINY-Breast06)

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**Background:** HER2 directed therapies have substantially improved clinical outcomes in patients with HER2 positive (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH] positive) metastatic breast cancer. However, no HER2 directed therapies are currently available for breast cancer with lower HER2 expression (IHC 2+/ISH− or IHC 1+). Patients with HER2 low and HR+ breast cancer typically receive initial treatment with endocrine therapy ± targeted therapies (CDK4/6, PI3K, or mTOR inhibitors). After disease progression, patients are treated with chemotherapy, which has shown limited clinical benefit. There is an unmet need for treatments that provide a superior risk-benefit profile compared with standard chemotherapy. T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a membrane permeable topoisomerase I inhibitor payload. Results from a phase 1 study demonstrated promising antitumor activity with a confirmed objective response rate (ORR) of 37.0% (20 of 54) per independent central review (ICR) and a median progression-free survival (PFS) of 11.1 months in patients with heavily pretreated (median 7.5 prior regimens) HER2 low metastatic breast cancer. Among patients with HR+ disease, the ORR was 40.4% (19 of 47) per ICR (Modi S, et al. *J Clin Oncol*. 2020;38:1887-1896). Here, we describe a phase 3 trial evaluating the efficacy and safety of T-DXd vs chemotherapy in patients with HR+, HER2 low metastatic breast cancer that has progressed on prior endocrine therapy. In addition to the primary population of patients with HER2 low disease being studied, this trial will also study the efficacy and safety of T-DXd in an IHC > 0 < 1+ (detectable HER2 staining < 1+) population.
**Study Description:** DESTINY-Breast06 is a global, randomized, multicenter, open-label, phase 3 trial designed to demonstrate superiority of T-DXd vs investigator's choice of chemotherapy in patients with HR+, HER2 low metastatic breast cancer who had prior progression on endocrine therapy. Approximately 850 patients (HER2 low, n = 700; IHC > 0 < 1+, n = 150) from ≈ 300 centers globally will be randomized 1:1 to receive T-DXd 5.4 mg/kg every 3 weeks or investigator's choice of chemotherapy (paclitaxel, nab-paclitaxel, or capecitabine) until disease progression, discontinuation due to intolerable toxicity, or death. Patients must have progression on ≥ 2 prior lines of endocrine therapy and cannot have received prior chemotherapy or any anti-HER2 therapy for metastatic disease. Randomization will be stratified by prior CDK4/6 inhibitor use (yes vs no), HER2 IHC expression (IHC2 +/ISH− vs IHC 1+ vs IHC > 0 < 1+), and prior taxane use in the non-metastatic setting (yes vs no). The primary endpoint is PFS per blinded ICR (BICR) in the HER2 low population. Key secondary endpoints are overall survival in the HER2 low and intent-to-treat (ITT; HER2 low and HER2 IHC > 0 < 1+) populations and PFS by BICR in the ITT population. Primary and key secondary endpoints will be tested in a hierarchical order. Other secondary endpoints are ORR by BICR and investigator assessment (according to RECIST 1.1), duration of response by BICR and investigator, time to second progression or death per investigator, time to first subsequent treatment or death, and time to second subsequent treatment or death (all in the HER2 low and ITT populations); PFS per investigator assessment in the HER2 low population; and safety, pharmacokinetics, patient-reported outcomes, and immunogenicity.

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# Impact of race/ethnicity on triple negative breast cancer molecular features, treatment response and clinical outcomes in patients receiving neoadjuvant therapy

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Background: Triple negative breast cancer (TNBC) disproportionally impacts Black and Hispanic women and is suggested to be partly responsible for disparities observed in breast cancer mortality. We sought to evaluate the impact of race/ethnicity on TNBC molecular subtype, immune profile, pathologic complete response (pCR) and recurrence free survival (RFS).
Methods: The ARTEMIS trial (NCT02276443) uses imaging response and molecular profiling to personalize neoadjuvant chemotherapy in early stage TNBC. After 4 cycles of AC, patients with chemo-sensitive disease receive standard taxane-based therapy, while those with chemo-resistant disease are offered therapeutic trials based upon molecular profiling. Pathologic response was assessed at surgery. Patients self-reported race/ethnicity was categorized as Asian, Black/African-American, Hispanic/Latino and White (non-Hispanic). Patients were excluded if no race or ethnicity was reported. Clinical and pathologic factors were recorded and compared. Gene expression profiling was performed by RNAseq to determine Vanderbilt signature. PD-L1 and Androgen Receptor (AR) were determined by immunohistochemistry. Frequencies at which various factors were observed by race/ethnicity were calculated and Fisher's exact test performed to determine statistical significance. Kaplan-Meier analysis was used to estimate survival stratified by pCR status and race/ethnicity.
Results: Among 321 women enrolled in ARTEMIS, 26 (8.1%) were classified as Asian, 50 (15.6%) as Black, 59 (18.4%) as Hispanic and 186 (57.9%) as White. Demographic and clinical features were similar, except Black women were more likely to have BMI ≥30 (70.0%, p<0.001). Comparing by race/ethnicity, there was no statistically significant difference in tumor histology, tumor size, nodal status, clinical stage, chemo-resistant disease, type of surgery or receipt of radiation. A trend toward higher proportion of N3 disease was observed in Black women (24.0%) compared to other groups (p=0.054). Tumor profiling results are listed in Table 1. No statistically significant difference was observed by race/ethnicity in Vanderbilt signature, presence of PD-L1 or stromal tumor infiltrating lymphocytes (sTIL) status. More AR-positive tumors were identified in Asian women (64%, p=0.007). pCR and RCB status did not significantly vary by race/ethnicity however, higher proportion of RCB-III disease was identified in Black (14%) and Hispanic women (16.9%) as compared to Asian (3.8%) and White (8.6%) women (p=0.164). At median follow up of 23.8 months (range 3.4-51.1), there was no statistically significant difference in RFS by race/ethnicity.
Conclusion: Among this population of patients with TNBC treated with neoadjuvant chemotherapy there was no statistically significant difference observed in TNBC Vanderbilt signature, PD-L1 staining, sTIL, pCR or RFS by race/ethnicity. Asian women were found to have a higher incidence of AR-positive subtype. Numerically higher rates of N3 stage in Black women and RCB-III classification in Black and Hispanic women were identified, however not statistically significant. Larger cohorts of patients are needed to further investigate these findings.

Table 1. TNBC profiling compared by race/ethnicity.

| | Total n (%) | Asian n (%) | Black n (%) | Hispanic/Latino n (%) | White n (%) | p value |
|---|---|---|---|---|---|---|
| **Vanderbilt signature** n (%) Basal like (BL1) Basal like 2 (BL2) Immunomodulatory (IM) Luminal androgen receptor (LAR) Mesenchymal (M) Mesenchymal stem-like (MSL) Unstable (UNS) | 231 50 (21.6) 25 (10.8) 42 (18.2) 22 (9.5) 48 (20.8) 14 (6.0) 30 (13.0) | 21 (9.1) 0 (0.0) 4 (19.0) 5 (23.8) 3 (14.3) 5 (23.8) 1 (4.8) 3 (14.3) | 35 (15.2) 9 (25.7) 5 (14.3) 6 (17.1) 2 (5.7) 7 (20.0) 1 (2.9) 5 (14.3) | 43 (18.6) 14 (32.5) 3 (7.0) 10 (23.2) 5 (11.6) 6 (14.0) 2 (4.7) 3 (7.0) | 132 (57.1) 27 (20.5) 13 (9.8) 21 (15.9) 12 (9.1) 30 (22.7) 10 (7.6) 19 (14.4) | NS |
| **Androgen Receptor** n (%) Positive (>=10%) Negative (<10%) | 311 109 (35.0) 202 (65.0) | 25 (8.0) 16 (64.0) 9 (36.0) | 49 (15.8) 11 (22.4) 38 (77.6) | 57 (18.3) 19 (33.3) 38 (66.7) | 180 (57.9) 63 (35.0) 117 (65.0) | 0.007 |
| **PD-L1** n (%) None >1 | 298 212 (71.1) 86 (28.9) | 24 (8.1) 15 (62.5) 9 (37.5) | 47 (15.8) 33 (70.2) 14 (29.8) | 57 (19.1) 40 (70.2) 17 (29.8) | 170 (57.0) 124 (72.9) 46 (27.1) | NS |
| **Stromal tumor infiltrating lymphocytes (sTIL)** n (%) High (>=20%) Low (<20%) | 319 107 (33.5) 212 (66.5) | 26 (8.1) 12 (46.2) 14 (53.8) | 50 (15.7) 13 (26.0) 37 (74.0) | 58 (18.2) 21 (36.2) 37 (63.8) | 185 (58.0) 61 (33.0) 124 (67.0) | NS |

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# Preliminary correlative analysis of clinical outcomes with *PIK3CA* mutation (mut) status from a phase I/Ib study of GDC-0077 in patients (pts) with hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC)

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**Background**
Mutations in p110α, encoded by *PIK3CA*, are present in ~40% of HR+/HER2- BCs. GDC-0077, a PI3Kα-selective inhibitor and mutant PI3Kα degrader, elicits antitumor activity in *PIK3CA*mut preclinical models as a single agent and when combined with endocrine therapy (ET). New evidence suggests BCs harboring multiple *PIK3CA*mut exhibit increased signaling through the PI3K/AKT pathway and are more sensitive to PI3Kα inhibitors compared with BCs with a single *PIK3CA*mut. We report a preliminary analysis of *PIK3CA*mut status with clinical outcomes from an ongoing study of GDC-0077 alone or with ET (letrozole/fulvestrant) ± palbociclib (palbo) in pts with *PIK3CA*mut HR+/HER2- mBC (NCT03006172).

**Methods**
Detectable *PIK3CA*mut from local tumor tissue/blood-based assay or tumor tissue by cobas *PIK3CA* assay were required to enroll. Plasma-derived circulating tumor (ct) DNA was collected at baseline (BL), cycle 1 day 15 (C1D15), and C2D1 (in the cohort where GDC-0077 starts at C1D15) to detect *PIK3CA*mut. Paired tumor samples were analyzed for Ki67 and pAKT/pS6 expression by immunohistochemistry. Single vs multiple *PIK3CA*mut was correlated with the percentage of pharmacodynamic (PD) inhibition of Ki67/pAKT/pS6 expression; with the *PIK3CA*mut allele frequency ratio between BL and C1D15 or C2D1 (MAFr15); with best overall response (BOR, RECIST v1.1); and with time on treatment (TOT) in days. Statistical analyses: Kruskal-Wallis and Mann-Whitney-Wilcoxon for group and pairwise comparisons, respectively, and two-sample proportion testing for categorical comparisons.

**Results**
Data cutoff was 03/20/2020. *PIK3CA*mut were detected in 87/103 (84.5%) pts with BL ctDNA available for sequencing. Multiple *PIK3CA*mut were detected in 21/87 (24.1%) BL ctDNA samples: 9 from pts treated with single-agent GDC-0077; 8 from pts treated with GDC-0077 + letrozole/fulvestrant; and 4 from pts treated with GDC-0077 + letrozole/fulvestrant + palbo. The median number of lines of prior therapy for metastatic disease was not different between pts with multiple (3.0 lines) vs single (2.5 lines) *PIK3CA*mut detected at BL (p = 0.205). Median percentage inhibition of Ki67/pAKT/pS6 expression was greater in pts with multiple (-65.8, -70.3, -66.8%, respectively) vs single (-42.1, -34.1, -29.5%) *PIK3CA*mut detected at BL (p = 0.095, 0.002, 0.056). Median MAFr15 was lower in pts with multiple (MAFr15 0.01) vs single *PIK3CA*mut (MAFr15 0.15) detected at BL (p = 0.004). Of 73 pts with both BL ctDNA-detected *PIK3CA*mut and BOR data, 16/16 (100%) with multiple *PIK3CA*mut experienced BOR of partial response (PR) or stable disease (SD) while 42/57 (73.7%) with single *PIK3CA*mut experienced BOR of PR or SD (p = 0.051). No pts with multiple *PIK3CA*mut detected experienced a BOR of progressive disease. Median TOT was greater in pts with multiple *PIK3CA*mut (196 days) vs single *PIK3CA*mut (140.5 days) detected at BL, but this was not significant (p = 0.1804).

**Conclusions**
The fraction of pts in which multiple *PIK3CA*mut were identified from BL ctDNA in this HR+/HER2- mBC dataset (24.1%) was slightly higher than reported elsewhere. This may be due to the method of detection (blood vs tissue) and/or the definition of multiple *PIK3CA*mut used. Pts in which multiple *PIK3CA*mut were detected by ctDNA exhibited greater depth of PD biomarker inhibition in tumors and experienced PR/SD more often compared with pts in which only one *PIK3CA*mut was detected. However, no significant associations were observed with the number of prior lines of therapy for metastatic disease or TOT. The dataset is currently too small to assess the impact of different treatment regimens in this study but will be re-evaluated as the data mature.

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Can oncotype Dx risk categories be predicted in invasive lobular carcinoma?

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**Background** Oncotype Dx Recurrence Score (ODX-RS) is a 21-gene assay used to predict recurrence in early stage breast cancer and guide chemotherapy decisions. Invasive lobular carcinomas (ILC) represent approximately 10-15% of all breast cancers. Many prior studies have shown that they have unique clinicopathologic features when compared to other histological subtypes. Therefore, the aim of this study was to first assess whether ODX-RS can be predicted using clinicopathologic factors in ILC and secondly, to compare these factors in invasive ductal carcinoma (IDC) and invasive carcinoma with mixed ductal and lobular features (IMC). **Materials and Methods** With IRB approval, the CoPath pathology database was queried for patients who were newly diagnosed with either IDC, ILC or IMC from 2010-2018 and had available Oncotype scores. For ILC cases, the subtype and presence or absence of LCIS was documented. The original pathology report was reviewed, and a chart review was performed to assess treatment decisions, locoregional and or distant recurrences and duration of follow-up. Patients with hormone receptor negative, HER2 positive or lymph node macrometastatic disease were excluded. **Results** A total of 582 patients were identified. The mean age was 60.1 years (range, 25-80 years). The median follow-up was 49 months (range, 0-145 months). There were 414 (71%), 102 (18%) and 66 (11%) cases of IDC, ILC and IMC, respectively. For ILC, there was a statistically significant relationship between ODX-RS and tumor grade, tubule formation, nuclear pleomorphism, mitotic count, modified Magee score (MME) and associated LCIS (Table 1). When compared to IDC and IMC, ILC had the lowest percentage of Grade 3 tumors, PR expression and high-risk patients by ODX. Factors predictive of high-risk ODX-RS in ILC were nuclear pleomorphism, mitotic count, ER H-score, PR H-score and MME, while for IDC, predictive factors included tumor grade, PR H-score, and MME using TAILORx cutoffs (Table 2). The rate of locoregional recurrences was similar between ILC and IDC (Table 1). No statistically significant correlation was found between ILC variants and RS. Disease free survival (DFS) was best in patients with IMC compared to IDC and ILC. DFS was also significantly better in patients with classic variant of ILC compared to pleomorphic variant.**Conclusion** We found that although ILC was similar to IDC and IMC based on tumor stage, tumor grade, risk category distribution, they demonstrated different predictors of high-risk ODX. Overall DFS was best in patients with IMC and patients with ILC, classic variant, however, when stratified based on RS scores the results were variable. Table 1. Clinicopathologic features of patients with ILC based on risk categories.

| | **ODX based on TAILORx** | | | | |
|---|---|---|---|---|---|
| | **<11** | **11-25** | **>25** | **Total** | ***p*-value** |
| **Age** | | | | | **0.534** |
| **<50** | 2 (14) | 12 (86) | 0 | 14 | |
| **>50** | 18 (20) | 65 (74) | 5 (6) | 88 | |
| **Race, n (%)** | | | | | **0.551** |
| **Caucasian** | 20 (23) | 62 (72) | 4 (5) | 86 | |
| **African American** | 0 | 12 (92) | 1 (8) | 13 | |
| **Asian** | 0 | 2 (100) | 0 | 2 | |
| **Not reported** | 0 | 1 (100) | 0 | 1 | |
| **T stage, n (%)** | | | | | **0.187** |
| **1** | 11 (21) | 35 (69) | 5 (10) | 51 | |
| 2 | 7 (16) | 36 (84) | 0 | 43 | |
| **3** | 2 (25) | 6 (75) | 0 | 8 | |
| **Tumor Grade, n (%)** | | | | | **<0.0001** |
| **1** | 3 (22) | 11 (78) | 0 | 14 | |
| **2** | 16 (19) | 66 (78) | 3 (3) | 85 | |
| **3** | 1 (33) | 0 | 2 (67) | 3 | |
| **Tubule formation, n (%)** | | | | | **<0.0001** |
| **Not reported** | 3 (50) | 2 (33) | 1 (17) | 6 | |
| **1** | 0 | 0 | 0 | 0 | |
| **2** | 0 | 0 | 1 | 1 | |
| **3** | 17 (18) | 75 (79) | 3 (3) | 95 | |
| **Nuclear pleomorphism, n (%)** | | | | | **<0.0001** |
| **Not reported** | 3 (50) | 2 (33) | 1 (17) | 6 | |
| **1** | 2 (14) | 12 (86) | 0 | 14 | |
| **2** | 14 (19) | 58 (80) | 1 (1) | 73 | |
| **3** | 1 (11) | 5 (56) | 3 (33) | 9 | |
| **Mitotic count, n (%)** | | | | | **<0.0001** |
| **Not Reported** | 3 | 2 | 1 | 6 | |
| **1** | 16 | 70 | 1 | 87 | |
| **2** | 1 | 5 | 3 | 9 | |
| **ER %, mean (SD)** | 95 (4) | 92.6 (10) | 95.6 (1.3) | 93.2 (8.5) | **0.426** |
| **PR %, mean (SD)** | 74.3 (31.6) | 54.6 (37) | 62.2 (19) | 58.8 (36) | **0.09** |
| **Modified Magee Score, mean (SD)** | 13 (6.5) | 17.3 (5) | 16.7 (9.8) | 16.4 (5.8) | **0.010** |
| **ILC Variants, n (%)** | | | | | **0.169** |

| | | | | | |
|---|---|---|---|---|---|
| **Classic** | 18 (20) | 68 (77) | 3 (3) | 89 | |
| **Pleomorphic** | 2 (15) | 9 (70) | 2 (15) | 13 | |
| **Associated LCIS Variants, n (%)** | | | | | **<0.0001** |
| **Classic** | 15 (19) | 62 (79) | 2 (2) | 79 | |
| **Solid** | 0 | 0 | 1 (100) | 1 | |
| **Pleomorphic** | 0 | 8 (80) | 2 (20) | 10 | |
| **Mixed Pleomorphic and Classic** | 5 (42) | 7 (58) | 0 | 12 | |
| **Locoregional Recurrence** | | | | | |
| **Yes** | 0 (0) | 3 (75) | 1 (25) | 4 | **0.12** |
| **No** | 20 (20) | 74 (76) | 4 (4) | 98 | |
| **Distant recurrence** | | | | | |
| **Yes** | 0 | 3 (100) | 0 | 3 | **0.605** |
| **No** | 20 (20) | 74 (75) | 5 (5) | 99 | |

Table 2. Demographic data.

| Age | **ILC** | **IDC** | **IMC** | **Total** | ***p*-value** |
|---|---|---|---|---|---|
| <30 | 0 | 3 (0.7) | 0 | 3 | **0.006** |
| 31-40 | 2 (2) | 14 (3.4) | 1 (1.5) | 17 | |
| 41-50 | 12 (11.8) | 67 (16.2) | 10 (15.2) | 89 | |
| 51-60 | 21 (20.6) | 140 (33.8) | 12 (18.2) | 173 | |
| 61-70 | 39 (38.2) | 132 (31.9) | 31 (47) | 202 | |
| 71-80 | 28 (27.5) | 58 (14) | 12 (18.2) | 98 | |
| Total | 102 | 414 | 66 | 582 | |
| **T stage, n (%)** | | | | | **<0.0001** |
| T1 | 51 (50) | 303 (73) | 48 (73) | 402 | |
| T2 | 43 (42) | 109 (26) | 18 (27) | 170 | |
| T3 | 8 (8) | 2 (1) | 0 (0) | 10 | |
| **Tumor Grade, n (%)** | | | | | **<0.0001** |
| 1 | 14 (14) | 84 (20) | 9 (14) | 107 | |
| 2 | 85 (83) | 236 (57) | 50 (76) | 371 | |
| 3 | 3 (3) | 94 (23) | 7 (10) | 104 | |
| **ER, mean (SD)** | 93 (8) | 91 (15) | 93 (7) | | **0.883** |
| **PR, mean (SD)** | 59 (36) | 67 (37) | 62 (38) | | **0.451** |
| **Oncotype risk categories, n (%)** | | | | | |
| Low risk (<11) | 20 (20) | 95 (23) | 13 (20) | 128 | **<0.0001** |
| Intermediate risk (11-25) | 77 (75) | 230 (56) | 46 (70) | 353 | |
| High risk (>25) | 5 (5) | 89 (21) | 7 (11) | 101 | |
| **Locoregional recurrence** | | | | | **0.266** |
| Yes | 4 (4) | 16 (4) | 0 (0) | 20 | |
| No | 98 (96) | 398 (96) | 66 (100) | 562 | |
| **Distant Recurrence** | | | | | **0.927** |
| Yes | 3 (3) | 10 (2) | 2 (3) | 15 | |
| No | 99 (97) | 404 (98) | 64 (97) | 567 | |
| **Predictors of High-risk ODX-RS , *p*-value** | | | | | |
| Tumor grade | NS | <0.0001 | 0.045 | | |
| Nuclear pleomorphism | 0.006 | 0.004 | NS | | |
| Mitotic count | 0.003 | NS | NS | | |
| ER H score | 0.047 | NS | NS | | |
| PR H score | <0.0001 | 0.014 | NS | | |
| Modified Magee score (MME) | 0.019 | NS | NS | | |
| MME based on TAILORx cutoffs | NS | 0.024 | NS | | |

**Publication Number:** PS9-12

Vitamin and supplement use and documentation in a breast cancer survivorship clinic

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**Introduction:** Breast cancer survivors take vitamins and supplements to bolster their general health and to try to decrease the risk of cancer recurrence. Healthcare professionals are frequently unaware of the specific type and dose of vitamins and dietary supplements taken by their patients. This information is often poorly documented in the electronic medical record (EMR). The aim of this study was to document accurately patients' dietary supplements and vitamins in the EMR and to inform patients' medical teams of this important information.**Methods:** All patients seen between May 5th and June 24th, 2020, with a history of nonmetastatic breast cancer (mean years since diagnosis=13.9) were invited to participate in the study prior to their routine visits at the Weill Cornell Breast Cancer Survivorship Clinic. 50/51 women consented (ages 46 to 87, mean age=70). The nurse practitioner called each patient the day before their visit to obtain informed consent and to document their use of supplements and vitamins. The labels for each vitamin and supplement were reviewed and patients were asked the reason why they were taking each supplement. Study data were collected and managed using REDCap electronic data capture tools hosted at Weill Cornell Medicine. Due to COVID-19, 48/50 patient visits were conducted through telemedicine.**Results:** Of the 50 patients enrolled in the study, 72% were taking two or more vitamins and/or supplements (mean=2.4, range= 0-9). 82% were taking a Vitamin D supplement, 42% were taking a calcium supplement, and 24% were taking a vitamin C supplement. 16% were taking a daily multivitamin and 8% were taking no supplements or vitamins. Some of the rare supplements patients were taking included ginseng root tea, shiitake extract, and kamwo tea (one patient each). Patients reported a variety of reasons for their vitamin and supplement use. Some patients stated the supplement was recommended by their physician or a friend, some did not know why they were taking a specific supplement, some reported that they had "always taken it", and many stated that the supplement was a preventative measure against bone loss or catching a cold. Five patients mentioned immunity or prevention of COVID-19. We compared the patient reported list with the medication list in the EMR. The majority of the participants had multiple providers who entered medications in the EMR. Of the 50 participants in our study, none had an accurate list of the vitamins and supplements in the EMR. **Conclusion:** 46 of the 50 breast cancer survivors in our study were taking vitamins and/or supplements. No study participant had a complete list of their vitamins and supplements in the EMR. Accurate vitamin and supplement documentation is important for optimal patient care. For example, vitamins and supplements may interfere with prescription medications taken by patients with a history of breast cancer. The inaccurate EMR documentation also precludes the investigation of vitamin and supplement use in future retrospective analyses. As a result of this study, we strongly recommend more attention to accurate vitamin and supplement recording by providers and the development of a more tailored and convenient method for documentation of vitamins and supplements in the EMR.

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# Efficacy of the tyrosine kinase inhibitor lapatinib in the treatment of patients with HER2-negative metastatic breast cancer and HER2-positive circulating tumor cells - results from the randomized phase III DETECT III trial

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**Background:** It is well-known that tumor biology may change during the course of the disease due to clonal evolution, and such changes might have important implications for response to targeted treatments. Circulating tumor cells (CTCs) could serve as a real-time liquid biopsy to detect changes in tumor biology. It has been demonstrated that patients with HER2-negative metastatic breast cancer (MBC) may have discordant, HER2-positive CTCs in the peripheral blood. However, up to now there is no randomized clinical trial investigating whether treatment decisions based on CTC phenotype provide benefits in terms of improved outcome. The aim of the DETECT III study is to investigate whether patients with initially HER2-negative MBC and HER2-positive CTCs benefit from HER2-targeted therapy with the tyrosine kinase inhibitor lapatinib. In addition, the significance of CTCs as an early predictive marker for response to therapy will be analyzed. **Methods:** The randomized phase III DETECT III trial (NCT01619111) compares lapatinib in combination with standard therapy versus standard therapy alone in patients with initially HER2-negative MBC and HER2-positive CTCs. Efficacy of lapatinib treatment is evaluated by CTC clearance rate, progression-free survival (PFS) and overall survival (OS). In addition, we investigate the association between CTC results and both PFS and OS to assess the utility of CTCs as an early predictive marker for treatment response. CTC enumeration and phenotyping was performed using the CellSearch® technology (Menarini Silicon Biosystems; Bologna, Italy). Survival data are analyzed using log rank tests, univariable and adjusted multivariable cox regressions. **Results:** First results on CTC clearance rates, PFS and OS of 105 prospectively randomized patients will be presented. **Conclusion:** This first randomized clinical trial in breast cancer patients with treatment decisions being based on the phenotype of CTCs will show whether patients with HER2 negative MBC and HER2 positive CTCs benefit from additional HER2-targeted therapy with lapatinib. This finding might be increasingly important as novel HER2-targeted drugs become available.

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# Concordance and use patterns of tissue and cell-free based genomic testing in metastatic breast cancer

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Genomic testing has transformed clinical care in metastatic breast cancer. Cell-free DNA (cfDNA) has made sequential testing feasible, however, concordance between tissue and cfDNA, sensitivity of cfDNA, and optimal sampling frequency have not been examined on large data sets with clinical annotation. Of the 648 genes in the tissue NGS Tempus xT assay, 105 genes are also included in the Tempus xF cfDNA plasma-based test. Both platforms are run on Illumina and detect SNVs, indels, CNVs, and rearrangements/fusions with high sensitivity and specificity (>90%). This study used the Tempus Labs LENS™ tool to identify the most recent ~3,300 metastatic breast cancer patients who underwent clinical testing and had either tissue-based testing, cfDNA testing or both. Of the 212 patients with xF and xT testing, 87 had xT before xF, 135 had xF before xT, and 7 had the testing performed at the same time. The most common pathogenic germline versus somatic alterations on tissue-based testing and their concordance will also be reported. In summary, this data suggests a variable amount of concordance between tissue-based and plasma-based assays. Timing of assay performance and inclusion of germline DNA might play an important role in contributing to these differences which need further exploration.

**Table: Count of Reported Variants and xT/xF Concordance by Gene**

| Somatic Genes | xF frequency (n) | xT frequency(n) | Concordance Between xF and xT |
|---|---|---|---|
| *TP53* | 139 | 110 | 43% |
| *PIK3CA* | 84 | 80 | 58% |
| *ESR1* | 58 | 41 | 41% |
| *BRCA2* | 38 | 21 | 7% |
| *ERBB2* | 37 | 26 | 29% |
| *NF1* | 32 | 21 | 13% |
| *RB1* | 27 | 24 | 16% |
| *ATM* | 30 | 16 | 5% |
| *GATA3* | 21 | 34 | 41% |
| *FGFR1* | 3 | 35 | 3% |
| *PTEN* | 19 | 30 | 36% |
| *ARID1A* | 25 | 18 | 23% |

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Prognostic significance of age, histologic subtype, tumor size and nodal status on breast cancer specific survival of “clinical low risk” grade 1 ER+/HER2- breast carcinoma patients - SEER analysis 2010-2012

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**Introduction**: TAILORx and MINDACT clinical trials on ER+/HER2-/lymph node (LN) 0 or LN 1-3 positive breast carcinoma (BC) patients (pts) revealed that breast-cancer-specific-survival (BCSS) of pts with low Oncotype DX or MammaPrint genomic assay scores did not improve with addition of adjuvant chemotherapy (CTH) to endocrine therapy. Furthermore, pts from MINDACT trial with “clinical low risk” (CLow) BC had no benefit from the use of CTH regardless of the MammaPrint score (low or high), underscoring the importance of identifying these CLow patients who might not obtain value from genomic testing. CLow is defined as the 10-year probability of BCSS >88% without CTH among women with ER+ tumors. MINDACT trial algorithm based on grade, tumor size and lymph node status is used to classify patients into CLow vs. “clinical high-risk” group. We investigated the significance of age, histologic subtype, tumor size, nodal and PR status on BCSS in a subgroup of CLow pts with grade 1 tumors ≤30 mm in size and N0-1 LN, utilizing Surveillance Epidemiology and End Results (SEER) database.
**Methods**: “Incidence, SEER research, 18 registries, Nov 2019 sub (2000-2017)” database was used to select female BC pts with ER(+)/HER2(-) BC diagnosed between 2010-2012 to allow for at least a 5-year follow-up (2010-2017). A subgroup of clinical low-risk pts was selected based on MINDACT trial algorithm: grade 1/N0/≤30 mm tumor size, or grade 1/N1/≤20 mm tumor size. Five invasive BC histologic types were selected: ductal (IDC), lobular (ILC), cribriform (ICC), tubular (ITC) and mucinous (IMC). Frequency statistics and a multivariate Cox regression were used for analyses of patient’s characteristics and BCSS using SPSS Version 25 (Armonk, NY: IBM Corp).
**Results**: From 132,822 female pts diagnosed with BC from 2010-2012, 20,677 pts (age range 19-85+) fulfilled above selection criteria. Age, tumor size, nodal status and ILC were significant (p<0.05) predictors for BC death in a multivariate Cox regression analysis: pts ≥50, tumor size 21-30 mm, 1-3 LN positive, and ILC histologic type were respectively 2.9 (95% CI=1.8-4.7), 2.6 (95% CI=1.8-3.6), 2.7 (95% CI=2.1-3.6) and 1.4 (95% CI=1.1-1.9) times more likely to die from BC than pts <50, tumor size 1-20 mm and negative LN (Table). IDC and IMC histologic types and PR status did not significantly influence BCSS, although PR status was borderline significant (0.05) in ILC histologic type. Cox regression analysis did not include ICC and ITC pts due to low number of BC caused death. A 5-year BCSS was the best for ITC and the worst for ILC pts, with 3/608 (0.5%) and 52/2047 (2.5%) pts dying from BC, respectively (Table), confirming ITC as an indolent, “good prognosis carcinoma”.
**Conclusions**: Our results show that 5-year breast cancer specific survival is significantly influenced by patient’s age, ILC histologic type, tumor size and nodal status even in the lowest risk of “clinical low risk” ER(+)/HER2(-), grade 1 BC pts. Since addition of CTH to endocrine therapy is not beneficial in these patients, further studies/clinical trials are needed to evaluate different endocrine therapy regimens for this subgroup of “clinical low-risk” patients in order to improve their BCSS.
**Table:**

| **Clinicopathologic characteristics of a grade 1 subgroup of "clinical low-risk" ER+/HER2(-) patients** | | | | | | |
|---|---|---|---|---|---|---|
| **Histologic subtypes** | N=20,677 (100%) | **IDC** | **ILC** | **ICC** | **ITC** | **IMC** |
| **Variables** | N=20,677 (100%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| | N=20,677; Mean +/- SE = 62 +/- 0.016; Median = 62 | | | | | |
| **Age (years)** | <50 | 2568 (15.3) | 274 (13.1) | 17 (19.1) | 132 (21.6) | 118 (11.3) |
| | >50 | 14,265 (84.7) | 1825 (86.9) | 72 (80.9) | 479 (78.4) | 927 (88.7) |
| | N=20,677; Mean +/- SE = 11.27 +/- 0.041; Median = 10 | | | | | |
| **Tumor size (mm)** | 1-20 | 15,893 (94.4) | 1768 (84.2) | 83 (93.3) | 603 (98.7) | 864 (82.7) |
| | 21-30 | 940 (5.6) | 331 (15.8) | 6 (6.7) | 8 (1.3) | 181 (17.3) |
| **Grade** | Grade 1 | 16,833 (100) | 2099 (100) | 89 (100) | 611 (100) | 1045 (100) |
| **Lymph nodes** | Negative | 14,915 (88.6) | 1881 (89.6) | 81 (91) | 594 (97.2) | 1022 (97.8) |
| | 1-3 Positive | 1918 (11.4) | 218 (10.4) | 8 (9.0) | 17 (2.8) | 23 (2.2) |
| **PR** | Positive | 15,553 (92.4) | 1800 (85.8) | 86 (96.6) | 542 (88.7) | 986 (94.4) |
| | Negative | 1280 (7.6) | 299 (14.2) | 3 (3.4) | 69 (11.3) | 59 (5.6) |
| **BCSS** | Alive | 16,584 (98.5) | 2047 (97.5) | 88 (98.9) | 608 (99.5) | 1028 (98.4) |
| | Dead from BC | 249 (1.5) | 52 (2.5) | 1 (1.1) | 3 (0.5) | 17 (1.6) |

| **Prognostic significance of age, tumor size, histologic subtype, lymph node and PR status on BCSS in a multivariate Cox regression analysis** | | | | |
|---|---|---|---|---|
| **Variable** | ***p value*** | **Adjusted Odds Ratio** | **95% CI Lower** | **95% CI Upper** |
| **Age >=50** | ***<0.001**** | 2.943 | 1.827 | 4.741 |
| **Tumor size 21-30 mm** | ***<0.001**** | 2.599 | 1.884 | 3.587 |
| **IDC** | Referent | | | |
| **ILC** | ***0.019**** | 1.443 | 1.062 | 1.96 |
| **IMC** | *0.811* | 1.063 | 0.646 | 1.748 |
| **Lymph nodes 1-3 positive** | ***<0.001**** | 2.759 | 2.097 | 3.631 |
| **PR negative** | *0.1* | 1.336 | 0.945 | 1.887 |
| **Legend** | N = Total number; % = percentage; IDC = Invasive ductal carcinoma; ILC = Invasive lobular carcinoma; ICC = Invasive cribriform carcinoma; ITC = Invasive tubular carcinoma; IMC = Invasive mucinous carcinoma; PR = Progesterone receptor; BCSS = Breast cancer specific survival; BC = Breast carcinoma; *= Significant | | | |

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# Genomic analysis from the talazoparib beyond BRCA clinical trial: Homologous recombination (HR) deficiency scores, loss-of-heterozygosity and mutations in non-BRCA1/2 mutant tumors with other HR mutations

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Background: Talazoparib, a PARP1 inhibitor, is active in germline BRCA1/2 mutant advanced HER2-negative breast cancer, but its activity beyond BRCA1/2 less well understood. The Talazoparib Beyond BRCA clinical trial treated 20 patients with germline (g) or somatic (s) mutations in HR pathways genes other than BRCA1/2, which included PALB2, CHEK2, ATM, BRIP1, RAD50, ATR, PTEN, and FANCA. Talazoparib treatment was associated with a 31% overall response rate in patients with breast cancer, including tumor regression from baseline as best response in 6 out of 6 patients treated g*PALB2* mutations. We now present the results of additional genomic studies to further characterize treatment responses and resistance mechanisms. Methods: Primary and metastatic tumor biopsies were assessed using the commercially-available next-generation sequencing HRD assay (Myriad). Panel gene sequencing of tumors was performed for 108 genes associated with genomic instability. Loss-of-heterozygosity (LOH) was assessed in tumors. Tumor/normal exome sequencing identified pre-treatment somatic variants. Circulating-tumor DNA at baseline and disease progression was assessed by targeted panel sequencing and plasma whole exome sequencing. Results: Of the 18 HRD assays performed, 3 failed and were thus excluded. Seven patients had HRD analysis performed on both primary and metastatic tumors. For these patients the HRD score was significantly higher in the metastasis versus the primary (means 46.2 versus 36.5, p = 0.018 by paired t-test). By panel sequencing of tumors (n=18) the most common alterations detected included mutations in PIK3CA (n=8), PALB2 (n=6), ATM (n=5), KRAS (n=4), PTEN (n=5) and TP53 (n=4). In all cases except one, the HR-associated mutation used as entry criteria were detected. LOH analysis showed that of tumors with g*PALB2* mutations, 3 of the 6 had LOH for *PALB2*, and an additional two tumors had 2 independent *PALB2* mutations suggesting bi-allelic inactivation. The one remaining tumor had an uncertain LOH result due to test failure. Thus, it is likely that most, if not all, of the tumors in our cohort with g*PALB2* mutations had complete inactivation of *PALB2* gene function. Other detected mutations that were associated with LOH included all s*TP53* mutations (n=4), all g*CHEK2* mutations (n=3), g*FANCA* (n=1), all s*RB1* mutations (n=3) and *NF1* (n=1). Of the three g*ATM* mutations one had LOH, while the others had two independent mutations, suggestive of bi-allelic inactivation. s*ATM* mutations were associated with LOH in a breast cancer and with 2 independent (possibly bi-allelic) mutations in a non-breast cancer. Additional results from ctDNA targeted sequencing and plasma whole exome sequencing of baseline and progression samples will be presented. Conclusions: In this proof-of-concept phase II study, talazoparib demonstrated activity in HER2-negative advanced breast cancer patients with a HR pathway mutation beyond BRCA1/2, especially in patients with g*PALB2* mutations and high HRD scores. These additional genomic analyses provide evidence that HRD scores may be significantly higher in metastatic samples compared to primary tumors. Also, we detected either LOH or bi-allelic inactivation for most HR-associated mutations used to determine eligibility. These findings may inform selection of patients for PARP inhibitor monotherapy beyond BRCA1/2.

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# Comparative analysis of differential gene expression by ancestry using primary breast cancers from Nigeria and the cancer genome atlas (TCGA)

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**Introduction:** Breast cancers differ between genomic and transcriptomic features by ancestry within the TCGA, but current understanding of how gene expression differs across global ancestral populations is extremely limited. We hypothesized that differential expression performed by ancestry and geography may provide insight into population-specific, clinically relevant expression patterns.
**Objective:** To compare differentially expressed protein-coding genes and pathways among primary breast tumors of Nigerian origin versus African- and European-American ancestry in TCGA
**Methods:** We analyzed an integrated dataset of RNA-seq from 93 women in Nigeria, 31 African-ancestry women (TCGA AA), and 39 European-ancestry women from TCGA (TCGA EA) with whole-genome data. Ancestry within TCGA was classified by principal component analysis, with African ancestry as >50% contribution and European ancestry as >90% contribution. RNA was obtained from tumors in Nigeria using Qiagen PAXgene kits. A *STAR*/*HTSeq* pipeline generated read counts. To optimize assay-associated batch effects, we performed differential expression within each PAM50 subtype using *limma-voom* with quantile normalization. Significance was defined as a $\geq$ 1.5-fold change in gene expression (log2 scale) with a false-discovery-rate-adjusted p-value of 0.05. Pathway analysis was performed via Gene Ontology and the Web-Based Gene Set Analysis Toolkit. We also compared gene expression, claudin-low (30 genes) and VEGF (13 genes) signatures to an additional set of 189 primary breast cancers from Nigeria assayed on the NanoString nCounter System using a custom Nano110 probe set (PAM50 + claudin-low & VEGF genes). RNA for these cancers was isolated from paraffin-embedded tumor using the Roche High Pure paraffin kit.
**Results:** Differential expression was performed pairwise across ancestry groups within PAM50 subtypes (see Table). Fewer genes were differentially expressed, and fold change smaller across shared genes, when comparing Nigerian vs. TCGA AA versus Nigerian vs. TCGA EA comparisons, supporting quantile normalization. The strongest gene ontology pathway associations, seen for all subtypes, were intracellular protein targeting and viral gene expression. The epigenetic regulation pathway was significantly associated with comparisons in Basal-like tumors ($p_{adj}$=1.54e-7 for TCGA EA, $p_{adj}$=0.001 for TCGA AA). The PI3K-Akt pathway was significantly associated with Nigerian vs. TCGA-EA within Luminal A ($p_{adj}$=0.006). The Nanostring cohort shared a similar distribution of PAM50 subtypes (see Table, $X^2$ p=0.21). We found concordance in both Nigerian cohorts of relative claudin-low and VEGF expression signature patterns across subtypes. Of 17 genes with significant differential expression by ancestry in the Nanostring dataset, 9 (*ADM, ACTB, BIRC5, CDC6, CENPF, MKI67, MPP1, RAD17,* and *VEGFA*) showed significant differential expression by ancestry in the PAXgene dataset.
**Discussion:** This is one of the first analyses of differential gene expression across tumors from a global population. We identified differential pathways in breast tumors between African and European ancestry populations to target for future work. We also validated several ancestry-specific genes across platforms with potential clinical relevance. Understanding how molecular features differ across global populations will improve precision oncology for all patients.

| PAM50Classification | Nigerian: PAXgene (n=93) | TCGA AA (n=31) | TCGA EA (n=39) | Nigerian: Nanostring (n=189) | Nigerian (PAXgene) vs. TCGA EA Comparison | Nigerian (PAXgene) vs. TCGA AAComparison |
|---|---|---|---|---|---|---|
| **Basal-like** | 41 (42.8%) | 23 (74.1%) | 17 (43.6%) | 78 (41.3%) | 4893 genes | 4687 genes |
| **Her2-enriched** | 27 (28.1%) | 0 | 5 (12.8%) | 31 (16.4%) | 961 genes | N/A |
| **Luminal A** | 14 (14.5%) | 4 (12.9%) | 8 (20.5%) | 39 (20.6%) | 2596 genes | 480 genes |
| **Luminal B** | 11 (11.4%) | 4 (12.9%) | 9 (23.1%) | 25 (13.2%) | 2112 genes | 222 genes |

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**Publication Number:** PS16-12

Double heterozygous pathogenic variants prevalence in a cohort of hereditary breast cancer patients

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Significant progress has been made in the identification of inherited genetic factors underlying hereditary cancers. Inherited pathogenic variants in cancer predisposition genes that confer moderate to high risk of breast cancer (BC) are found in 10% of BC cases. Pathogenic variants in BRCA1 and BRCA2 genes are the underlying alterations in hereditary BC. Women with a pathogenic variant in BRCA1 or BRCA2 are at substantially higher risk of developing breast, ovarian and pancreatic cancers and represent 25-28% of hereditary BC cases. The gold standard for molecular diagnosis of a hereditary cancer syndrome is aNext Generation Sequencing (NGS) panel that includes all genes known to confer moderate to high-risk for BC (TP53, PTEN, CHEK2, ATM, PALB2 STK11, RAD51C and BRIP1). Identifying who is eligible to perform genetic testing remains a challenge but presently age at the time of tumor diagnosis, family history and disease stage are still the best predictors. The identification of a germline pathogenic variant enables appropriate genetic counseling, risk-reducing interventions. The detection of variants in BRCA1, BRCA2 and PALB2 may also determine treatment options in patients with advanced or metastatic disease. The known non-BRCA1/2-associated hereditary BC comprise a heterogeneous group of tumors, for most of which the prevalence of histologic and immunohistochemical (IHQ) phenotypes are yet to be identified while triple-negative BC is the most prevalent in BRCA1 carriers. The co-occurence of more than one germline pathogenic variant in BC genes is a rare event and it may affect cancer risk and penetrance is still unknown. Only a few reports on cases and series of double mutation carriers have been described in BRCA1, BRCA2, PALB2, CHEK2, BLM or NBN. In this series case we report patients with double heterozygous (DH) mutation in BC, their age at diagnosis, presence of second neoplasia and cancer phenotype in moderate and high penetrance genes on germline panels. Considering this scenario, we performed an active search among the 2651 women from the Hereditary Cancer Registry at Hospital Sirio-Libanes, São Paulo, Brazil, between January 2013 and June 2020. We have included 229 patients with a histopathological confirmation of a BC who have tested positive for pathogenic/likely pathogenic variant. Of these, 4,3% (10/229) women were identified with DH mutation in high and moderate penetrance genes in BC (table 1). All patients carried a germline pathogenic variant in at least one high-penetrance gene. A total of 7 cases (7/10) carried at least one BRCA1/2 pathogenic variant. Two women (2/10) included had developed bilateral BC. The occurrence of a second primary cancer was described in three patients (3/10). The median age at first BC diagnosis was 36,7 years old. Two BC were found to be triple negative, five cases were of Luminal subtype and one was HER2+. The age at diagnosis is similar to most hereditary BC related to those developed by BRCA1 and TP53 germline variant carriers. In this case series there is no evidence of additive effect on the risk of tumor development. Larger series of DH mutation carriers are needed to estimate the risk in double heterozygous populations and to determine whether the presence of DH have a synergistic interaction or additive effect on cancer risk.

Table1 - Breast Cancer double variants

Breast Cancer double Variants

| **Gene** | **Variant** | **Age of Breast Cancer onset** | **IHQ status** | **Bilateral BC** | **Other prymary neoplasia (age)** |
|---|---|---|---|---|---|
| BRCA1TP53 | c.5266dupCc.1010G>A | 36 yo | ER- PR- HER2 + | Yes | Pancreas (40), Lung (53) |
| BRCA1PALB2 | c.4165.4166delAGc.1240C>T | 32yo | N/A | No | Breast (37), Skin (50) |
| BRCA1ATM | c.5266dupCc.6729_6730delAA | 33yo | ER - RP- HER2 - | No | No |
| BRCA1RECQL4 | c.3748G>Tc.1568_1573delinsCCCCC | 33yo | ER- PR -HER2- | No | No |
| BRCA2PMS2 | c.2516dupAc.2182_2184delinsG | 49yo | ER+ PR+ HER2 - | No | No |
| BRCA2ATM | c.8960delc.901+1G>A | 32yo | ER+ PR+ HER2- | No | No |
| BRCA1NBNMUTYH | c.1687C>Tc.1142delC c.536A>G | 38yo | ER+ PR + Her2- | No | Breast Cancer (58) |
| TP53MUTYH | c.1010G>Ac.1187G>A | 35yo | N/A | No | No |
| ATMTP53 | c.4906C>Tc.1010G>A | 42yo | ER+PR+HER2- | No | No |
| PALB2CHEK2 | c.2711G>Ac.319+2T>A | 37yo | ER+PR+HER2- | yes | No |
| BRCA2 | c.8960del | 32yo | ER+ PR+ HER2- | No | No |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS11-12

Statin use significantly improves outcome in luminal B relative to luminal A breast cancers

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Cholesterol and statins may have a role in breast cancer progression where statins have been found to associate with reduced breast cancer recurrence risk in early breast cancer patients. Links between breast cancer progression and intra-tumoural cholesterol metabolism have been described, indicating possible underlying cancer biology. Here we set out to explore whether statin use correlated with differences in baseline tumour characteristics including biological tumour sub-type and whether outcomes were impacted by statin use, both overall and within sub-types. Two cohorts of invasive breast cancer patients from a single institution in Western Australia were studied; one comprised of cases across all sub-types (n=417) and one of hormone receptor positive cases only (n=1766), with available data on tumour biology, statin use, and relapse. Statin prescription data was available on 2183 patients, of whom 454 were taking a statin at some point from diagnosis through the end of the follow-up period. Of the patients where statin type was known, 38% were taking a hydrophilic and 62% a lipophilic statin. Although tumour stage did not vary by statin usage, those on a statin had less frequent high grade tumours (12.7 v 18.7%, p=0.025), and were more frequently estrogen receptor positive (96.1 v 93.1, p=0.022) although other receptor expressions did not differ. Finally, luminal A tumours were more common in statin users, at the expense of luminal B and HER2-enriched cancers (81.4 v 74.0, p=0.018) (Table 1).

Overall breast cancer events were more common in statin non-users compared to users (16.7 v 9.3%, HR 1.80, p<0.0001). Due to the influence of the larger hormone receptor positive cohort, the majority of patients had luminal tumours. Looking to the influence of statins on events within sub-types, users compared to non-users experienced substantially less breast cancer events in luminal B cancers (8.8% v 22.3%, p=0.012 ) and modestly reduced events in luminal A cancers (8.3 v 12.6%, p=0.0326). Considering HER2 positive luminal B cancers relative to those afforded luminal B status by virtue of being high grade, the former group showed significantly less events in statin users v non-users (0 v 19.9%, p=0.0047) whereas no significant protection was observed in the latter (18.2 v 24.6%, p=0.294). Low numbers of HER2 positive hormone receptor negative cases precluded analyzing whether protection extended to all HER2 positive tumours, although none of these patients relapsed. No significant differential effect was found by statin type.

In conclusion, statin usage after early breast cancer afforded substantial protection to HER2 positive hormone receptor positive patients, an effect that may extend to all HER2 positive cases. Further validation is warranted. Such patients could be considered for trials exploring statins as agents protecting against relapse.

Table 1: Breast tumour demographics comparing statin users to non-users.

| Statin Use | Cases | Cases | Median size | LN positive | LN positive | Invasive Grade | Invasive grade | Invasive Grade | ER +ive | ER +ive | PR -ive | PR -ive | HER2 +ive | HER2 +ive | Sub-type | Sub-type | Sub-type |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | mm | n | % | | n | % | n | % | n | % | n | % | | n | % |
| | | | | | | | | | | | | | | | lum A | 1117 | (74.0) |
| | | | | | | Grade 1 | 448 | 27.6 | | | | | | | Lum B | 336 | (22.3) |
| NO | 1729 | (79.0) | 18 | 607/1787 | (34.0) | Grade 2 | 867 | 53.5 | 1601/1719 | (93.1) | 1348/1565 | (86.1) | 144/1498 | (9.6) | HER2 enrich | 7 | (0.5) |
| | | | | | | Grade 3 | 307 | 18.9 | | | | | | | TNBC | 50 | (3.3) |
| . | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | lum A | 337 | (81.4) |
| | | | | | | Grade 1 | 131 | 30.2 | | | | | | | lum B | 68 | (16.4) |
| YES | 454 | (21.0) | 17 | 151/475 | (31.8) | Grade 2 | 247 | 57.0 | 440/458 | (96.1) | 363/428 | (84.8) | 32/421 | (7.6) | HER2 enrich | 1 | (0.2) |
| | | | | | | Grade 3 | 55 | 12.7 | | | | | | | TNBC | 8 | (1.9) |
| . | | | | | | | | | | | | | | | | | |
| p (Fishers) | | | NS | | 0.382 | | | 0.025 | | 0.022 | | 0.482 | | 0.251 | | | 0.018 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS8-12

# Interim analysis of a phase I dose escalation study of topical bexarotene in women at high risk for breast cancer

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**Background:** Breast cancer prevention with anti-estrogens, including tamoxifen, raloxifene, and exemestane, has been shown to reduce the incidence of hormone receptor-positive breast cancer. However, agents that can reduce the incidence of hormone receptor negative breast cancer are currently lacking. Rexinoids such as bexarotene are vitamin A analogues that have been shown to be involved in cell differentiation, growth, and apoptosis. In preclinical mouse models that develop ER-negative breast cancers, bexarotene showed a significant reduction in mammary tumor development. Oral bexarotene has been evaluated in BRCA mutation carriers and significant decreases in cyclin D1 were noted in breast cells suggesting biological activity of bexarotene on breast tissue. Systemic side effects of hyperlipidemia and hypothyroidism were also found. Data from chemoprevention studies with topical 4-hydroxytamoxifen support the concept of topical agents penetrating into the breast tissue and exhibiting biological activity. We hypothesize that topical bexarotene can be applied to the breast as a prevention agent with penetration into the breast tissue and without subsequent systemic side effects as seen with oral bexarotene. **Methods:** Women at high risk for breast cancer were recruited and assigned to escalating doses of 1% topical bexarotene: 10mg (1ml) every other day, 10mg (1ml) daily and 20mg (2ml) daily for 4 weeks. Cohorts of 3-4 participants were enrolled and fully evaluated through 4 weeks prior to enrolling the next cohort. Each dose level enrolled a maximum of 10 participants. The primary endpoint of the study was to determine the recommended phase II dose of topical bexarotene 1% gel for evaluation in healthy at-risk women. Dose Limiting Toxicity (DLT) was defined as a grade 2 skin adverse event that persists for at least 6 days or any grade 3 or greater adverse event related to the study drug. A grade 2 skin adverse event that recurs and persists for at least 3 days is also a DLT. The Maximum Tolerated Dose (MTD) was defined as the highest dose level at which no more than 2 participants experience a DLT among 10 participants treated. Once the MTD was determined, interim biomarker analysis will be completed to assess bexarotene levels in serum and tissue samples. An expansion cohort of an additional 10 patients will be recruited at the MTD to further evaluate safety and toxicity. Secondary endpoints include serum bexarotene level, tissue bexarotene levels, and changes in thyroid function tests, lipid profile, and calcium. **Results:** Ten women were enrolled at the dose level of 10mg every other day and 9/10 participants experienced Grade 1 skin related events at the application site. Two participants reported Grade 2 skin related events at the application site but did not last long enough to be considered DLTs. Four women were enrolled at the second dose level of 10mg daily and 3/4 experience Grade 2 skin related events including 2 DLTs which stopped accrual to the study. Therefore, the MTD was determined to be 10mg every other day. No laboratory abnormalities were noted across either dose level and no grade 3 or 4 adverse events were reported. **Conclusion:** Maculopapular rash at treatment site was the most common adverse event related to study drug and resolved with discontinuation. Analysis is ongoing to assess bexarotene drug levels in serum and breast tissue samples.

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**Publication Number:** PS12-12

# Efficacy and safety of AB928 plus pegylated liposomal doxorubicin (PLD) with or without IPI-549 in participants with metastatic ovarian and triple negative breast cancer

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**Background:** Adenosine, derived from ATP released by dying cancer cells in response to chemotherapy, activates the $A_{2a}$ and $A_{2b}$ receptors (R) on immune cells, resulting in an ineffective anti-tumor immune response. Adenosine receptor blockade may improve the efficacy of chemotherapy, notably anthracycline regimens, by enhancing immunogenicity within the tumor microenvironment. AB928, the first clinical-stage small molecule dual $A_{2a}R/A_{2b}R$ antagonist, is highly potent and well tolerated in combination with chemo/immunotherapy. Novel combinations of AB928 with PLD +/- IPI-549, a PI3Kgamma inhibitor believed to shift tumor associated macrophages toward an anti-tumor phenotype, may offer potential clinical benefit for tumors previously considered immunotherapy-resistant. **Methods:** ARC-2 (NCT03719326) is an ongoing Phase (Ph) 1/1b, open-label study in patients (pts) with metastatic or locally advanced, unresectable ovarian or triple negative breast (TNBC) cancer. Eligible pts must have ECOG performance status 0-1 and at least one measurable lesion. In dose escalation, AB928 (75 or 150 mg) administered orally once daily was given with standard PLD in a 3+3 design. Once a tolerable doublet regimen was established, escalating doses of oral IPI-549 (30 or 40 mg once daily) were added. Two expansion cohorts, the doublet of AB928 150 mg + standard PLD and the triplet (+ IPI549 40 mg), are ongoing in pts with TNBC. **Results:** As of 19Jun2020, 29 pts received AB928 as part of the doublet or triplet regimen (Table 1). The number of prior therapies for escalation and expansion range from 0-11 (median=2) and 0-5 (median=1), respectively. Across both regimens, most treatment emergent AEs (TEAEs) were Grade (Gr) 1 or 2. The most common TEAEs (>6 pts) were fatigue, anemia, constipation, stomatitis, cough, and nausea. Four pts reported 6 Gr ≥3 SAEs; none were related to AB928 or IPI-549 and one event (pleural effusion) was at least possibly related to PLD. One pt discontinued study treatment for an AE (Gr 3 peripheral neuropathy) related to the triplet regimen; this pt had a complete response (CR) at the time of discontinuation. Of those pts treated with AB928 + PLD, 16 pts had at least one on-study disease evaluation, 2 pts (1 TNBC, 1 ovarian) achieved a partial response (PR), 8 stable disease (SD) and 6 progressive disease (PD) as best response. The addition of IPI-549 (n=11) resulted in 1 complete response (CR; ovarian), 3 PR (2 ovarian, 1 TNBC), 4 SD, and 3 PD. Nine pts received prior immunotherapy as part of an anticancer regimen; 2/9 achieved a PR on study treatment (1 confirmed, 1 pending). Thirteen pts had prior anthracycline; 6/13 achieved SD as best overall response, including 1 pt who received doublet therapy >1 year. **Conclusions:** AB928 and PLD +/- IPI-549 is tolerable in pts with advanced ovarian cancer and TNBC. Doublet and triplet combination treatment were associated with clinical benefit, including responses in those with progression after prior immunotherapy. The promising observation that late-line pts, including those previously treated with an anthracycline and/or immunotherapy, can experience clinical benefit with AB928 combination therapy warrants further investigation.

**Table 1. ARC-2 Cohort Enrollment and AB928 +/- IPI-549 Dose Received**

| **Study Part:** | **Phase 1** | | | | **Phase 1b** | |
|---|---|---|---|---|---|---|
| **Regimen:** | **Doublet** | | **Triplet** | | **Doublet** | **Triplet** |
| **AB928 dose:** | **75 mg** | **150 mg** | **150 mg** | | **150 mg** | **150 mg** |
| **IPI-549 dose:** | **--** | **--** | **30 mg** | **40 mg** | **--** | **40 mg** |
| *Enrolled, n* | | | | | | |
| Ovarian | 3 | 4 | 3 | 1 | -- | -- |
| TNBC | 0 | 2 | 0 | 2 | 8 | 6 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS19-12

# The study of jag1-notch in the extravasation of triple negative breast cancer cells in metastasis

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In breast cancer, the primary tumor is usually not lethal, while metastatic spread to other organs is a frequent cause of death. Up to 20% of breast cancer diagnoses are triple negative breast cancer (TNBC) makes and late stage metastatic TNBC can have a 5-year survival as low as 11%. TNBC is unresponsive to hormonal and targeted therapies of other types of breast cancer. Surgery and adjuvant chemotherapy are effective treatment options for early stage disease, but there are very few therapeutic options for advanced metastatic TNBC spread. For metastasis to occur, circulating tumor cells (CTCs) must cross the endothelial barrier twice: first to migrate away from the primary tumor and enter systemic circulation (intravasation), and then to exit circulation to colonize other tissues (extravasation).

We are currently exploring the role of Jagged-1 (Jag1), a Serrate class Notch ligand, in the metastatic process. Jag1 is expressed in many human TNBC cell lines and its expression is associated with a worse prognosis in the clinic. Our data suggest that Jag1 presented on tumor cells promotes extravasation behavior, particularly TNBC binding to endothelium and subsequent transendothelial migration (TEM).

Our preliminary studies have blocked Jag1 function with the Notch decoy $N1_{10-24}$, which utilizes EGF-like repeats of the Notch1 receptor that unproductively bind Jag1. Treatment with $N1_{10-24}$ reduces the ability of D3H2LN cells, a $Jag1^{high}$ derivative of the MDA-MB-231, to attach endothelial cells *in vitro.* Treatment with $N1_{10-24}$ also impedes the ability of these highly metastatic human TNBC cells to migrate across a monolayer of human primary endothelial cells. We therefore conclude that Jag1-Notch signaling inhibition via $N1_{10-24}$ suppresses activities required for TEM of TNBC cells. However, the mechanistic role of Jag1, however, is not understood in TEM. Both TNBC and endothelial cells express Jag1, and the aforementioned secreted decoys may target Jag1 signaling either within TNBC cells, within endothelial cells, or between cell types. We hypothesize that tumor expression of Jag1 is critical for metastasis. In order to explore the effects of tumor-derived Jag1 on tumor-intrinsic signaling, we have knocked out Jag1 in D3H2LN cells and generated multiple $Jag1^{KO}$ clonal lines, which have been interrogated for downstream transcriptional changes related to TEM. To explore the effects of tumor-derived Jag1 on neighboring endothelium, we are studying the extravasation capabilities of $Jag1^{KO}$ clonal lines using dynamic systems that will track TNBC adhesion, rolling, and TEM under dynamic flow *in vitro* as well as characterizing their metastatic potential *in vivo*. Our studies are elucidating a mechanism of Jag1-mediated metastasis via endothelial interactions.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS13-12

# Apatinib combined with taxanes and platinum neoadjuvant chemotherapy for patients with triple-negative and HER2-positive breast cancer: A multicenter, randomized, open-label, phase II trial

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**Background:** Apatinib, a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor 2 (VEGFR2), has demonstrated a promising efficacy in patients with metastatic breast cancer. For triple-negative and HER2-positive subtypes, increasing the pathological complete response (pCR) of neoadjuvant therapy may benefit their clinical outcomes. Here, we assessed whether the combination of Apatinib with neoadjuvant chemotherapy elevate the pCR rate in locally advanced breast cancer. **Method:** In this multicenter, open-label trial, we randomized 53 patients into TP neoadjuvant chemotherapy (docetaxel 75 mg/m2 or nab-paclitaxel 260 mg/m$^2$ or paclitaxel liposome 175 mg/m$^2$ day 1, and carboplatin AUC=6 or cisplatin 75 mg/m$^2$ or lobaplatin 30 mg/m$^2$ day 1), or combined with apatinib (500mg day 1-21) . Trastuzumab was added to neoadjuvant therapy in HER2-positive subtype. Six cycles were repeated every 3 weeks. **Results:** In total patients with stage IIb-IIIc triple-negative and HER2-positive breast cancer, the addition of apatinib to TP neoadjuvant chemotherapy (Apa+TP) significantly increased the pCR rate (70.8%, 17/24), compared with TP along (41.4%, 12/29), *P*=0.032. When separating patients into triple-negative (Apa+TP 66.7% (8/12) vs. TP 42.9% (3/7)) and HER2-positve (Apa+TP 75% (9/12) vs. TP 40.9% (9/22)) subtypes, the effect of apatinib on pCR was also improved though no significant differences were found *(P*=0.377; *P*=0.080 separately) compared with control group. The most common Grade 3-4 adverse events (AE) included hypertension (Apa+TP 12.5% vs. TP 0%, *P*=0.173), hand-foot syndrome (Apa+TP 8.3% vs. TP 0%, *P*=0.389) and erythra (Apa+TP 4.2% vs. TP 0%, *P*=0.924). No significant differences of toxic effects were found between Apa+TP and control group. **Conclusion:** Apatinib combined with TP neoadjuvant chemotherapy significantly increased the pCR rate in patients with locally advanced triple-negative and HER2-positive breast cancer, indicating an applicable strategy in the future.

**EfficacyTriple-negative breast cancer efficacyHer2-positive breast cancer efficacySafety**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS15-12

# Initial outcomes of adjuvant proton pencil beam scanning radiation for patients with breast cancer requiring comprehensive nodal irradiation within a single institution

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**Background**:Following lumpectomy or mastectomy, locally advanced breast cancer (LABC)requires adjuvant radiation (RT) to the chest wall (CW) and comprehensiveregional nodal basins (CNI). Proton therapy (PBT) has demonstrated dosimetricadvantages in heart, lung, and esophageal exposures compared to photon RT, butlittle is published regarding oncologic outcomes of PBT for LABC. **Methods**:Consecutive patients treated from 2016-2019 wereretrospectively reviewed. Men and women over the age of 18 requiring adjuvantRT with CNI were included; all patients had at least 6 months of follow up fromRT completion. Initial treatment volumes, excluding boosts to scars or grossdisease, (CTV_init) included CW-CNI per the RADCOMP atlas. CTV_init coveragewas prescribed as 95% CTV_init at 100% Rx dose. All patients were treated with proton pencil-beam scanning RT (PBS-PBT),typically with a two-field anterior SFO technique. Patient, tumor, and dosimetric characteristics wereanalyzed. Tumoral control and survival rates were estimated by the Kaplan Meiermethod. Toxicities were recorded prospectively by treating physicians andreviewed retrospectively. Local recurrence was defined as in-breast, or skin/chestwall; regional recurrence was defined as a nodal failure. **Results**:One hundred patients were included with a median follow upof 15.4 months (6-42). Ninety-eight percent were female, and 61% were white.Median age was 52 years, and 94% of patients had an ECOG PS ≤1.AJCC 8$^{th}$ edition anatomic staging was predominantly stage II (49%)or III (48%).Sixty-five percent of patients were treated for left-sideddisease; 7% of patient received bilateral RT; 87% received cytotoxicchemotherapy (63% neoadjuvant, 37% adjuvant). Twenty six patients receivedconcurrent systemic therapy with trastuzumab (H)/pertuzumab (P)(38% ),capecitabine (29%), H-emtansine (21%), or H (12%). The median initial RT dosewas 50.4 (45-50.4) while median total RT dose was 50.4Gy (45-70.2). Forty-twopercent of patient underwent an RT boost to nodal areas and/or the scar. Allpatients were treated in 1.8 or 2.0Gy fractions. Eighty-seven percent oflesions were invasive ductal carcinomas; 52% were ER+/Her2-, 17% weretriple-negative (TNBC), and 31% were Her2+.Nine (9%) of patients experienced a ≥G3 acute toxicity, all in theform of radiation dermatitis. There was one acute G4 incidence of skinnecrosis. There were no ≥G3 late toxicities or documented major cardiac events atthe time of last follow up. Median doses to critical organs at risk (OARs) were asfollows: mean heart 0.9Gy (<0.1 - 3.9), V25 heart 0.9% (0 - 6.6) ipsilaterallung V20 15% (4.6 - 29.2) ipsilateral lung V5 41.1% (17.5 - 62.2), volume ofthe esophagus receiving 70% Rx dose 0.1cc (0 - 5.3). For bilateral plans, themedian total lung V20 was 15.6% (6.6 - 23.5) and V5 was 41.5% (18.5 - 45.0). Overall, there were 3 local, 3 regional, and 8 distantfailures. All local failures were TNBC; regional and distant failures wereequally distributed between histologies. All distant failures occurred in patientswith at least AJCC 8$^{th}$ Edition anatomic stage IIIA. Actuarial ratesof 2-year local, regional, locoregional, and distant failures were 4% (±3),2% (±2),6% (±3%),and 11% (±4).Two-year actuarial survival was 94% (±3).**Conclusions**:We present a large series of patients with high-risk or LABCtreated with adjuvant PBS-PBT and CNI. Our series includes significant percentagesof TNBC, non-white patients, and patients requiring dose-escalated RT boosts overalldemonstrating promising initial oncologic outcomes and very favorable acutetoxicity and dosimetric profiles. Continued follow up is warranted to confirmlong-term oncologic outcomes.

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**Publication Number:** PS14-12

Trends in breast and axillary surgery for T1-T2 male breast cancer: A study from the national cancer database

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**Introduction:** Due to the low incidence of male breast cancer, large scale prospective trials to guide therapy are lacking. Historically males with breast cancer present at more advanced stages than females and have been surgically treated with modified radical mastectomy. Recent studies suggest that breast-conserving therapy for early-stage male breast cancer yields similar outcomes as for female patients, and that sentinel lymph node biopsy (SLNB) can be used in place of axillary lymph node dissection (ALND) for appropriate clinically node-negative patients. Our study investigates trends in breast and axillary surgery for male breast cancer patients, focusing specifically on the treatment of early-stage disease. **Methods:** The National Cancer Database (NCDB) was utilized to identify male and female patients diagnosed with clinical T1-2 breast cancer from 2004-2016. Patient, tumor, facility, and surgical treatment factors were examined. Patients were stratified by surgery type: partial, unilateral, and bilateral mastectomy; simple versus modified radical mastectomy; SLNB (removal of ≤ 5 lymph nodes) and ALND (>5 lymph nodes). Trends in surgery type were compared between male and female patients and over the study period for each gender. **Results:** 9,782 males and 1,078,105 females with T1-2 breast cancer were identified. Men were significantly older at diagnosis than women (31.4% vs. 23.6% age >70, p<0.0001), were more often insured by Medicare (44.5% vs. 35.3%, p<0.0001), and had greater co-morbidity (21.9% vs. 15.6% Charlson Deyo Score >0). ER/PR+ disease (94.2% vs. 84.1%, p<.0001), moderate/high grade histology (85.4% vs. 77.8%, p<.0001) and lymphovascular invasion (24% vs. 15.3%, p<.0001) were also more common in males vs. females. The majority of all patients were clinically node negative (80.4% of males, 85% of females) and had AJCC clinical stage I or II disease (92.3% men, 95.2% women). Unilateral mastectomy was performed most commonly for men (67.1% men vs. 24.1% women, p<0.001), while women more frequently underwent partial mastectomy (64.7% women vs. 26.4% men, p<0.001). The rates of each surgery type remained disparate by gender and stable over the study period: male unilateral mastectomy rate 59.8% in 2004 and 66.1% in 2016; female partial mastectomy rate 65.9% in 2004, 68.4% in 2016. Modified radical mastectomy rates decreased in favor of simple mastectomy for both genders, 61.8% to 24.1% in males and 58.7% to 20.2% in females, 2004 to 2016. There was a similar overall increase in SLNB vs. ALND for all patients, though SLNB was not adopted as the more common procedure in male patients until 2009. In 2016, 78.2% of females and 65.3% of males underwent SLNB vs. 51.1% and 39.8% in 2004, respectively. **Conclusions**: Although breast-conserving therapy is the treatment of choice for female patients with early-stage breast cancer and could be similarly used to treat men with T1-T2 disease, the majority of male breast cancer patients continue to undergo unilateral mastectomy for early-stage disease. In more recent years, SLNB has surpassed ALND for men, mirroring the trend for women, though in a more delayed and gradual fashion. Partial mastectomy and SLNB warrant consideration for men with T1 and T2 breast cancer, in particular since male breast cancer patients present at older ages and with more co-morbidity than their female counterparts, and may benefit from de-escalation of surgical treatment.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS1-13

The impact of corona virus disease-2019 on breast services at university hospitals of North Midlands, United Kingdom

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**Introduction**: The COVID-19 pandemic has disrupted routine cancer care and training globally. Breast units adopted modified national guidelines in the UK, and significant changes were implemented to ensure the safety of patients and staff. The national breast screening services were temporarily suspended from March 2020. Patients underwent surgery in COVID-19 free zones. Complex oncoplastic procedures and immediate reconstructions were not offered. Adjuvant treatments were modified to reduce the risk of complications and hospital readmission. The objective of our study is to assess the impact of COVID-19 on breast cancer management and surgical training. **Methods**: The resource reallocation was implemented for 100 days, commencing from the 16th of March,2020. Patients diagnosed with breast cancer during this period were identified from the cancer database, and a comparison was made with patients diagnosed last year within the same time frame. We assessed the time taken from the decision to treatment and modifications made to cancer management due to the pandemic. The impact on resident training was evaluated by comparing the number of cases performed or assisted during this period. **Results**: During the pandemic period, out of 1064 patients seen in the Breast one-stop clinic, 64 patients (6.0%) were diagnosed with breast cancer. During the same time frame in 2019, out of 1881 new symptomatic patients, 90 (4.8%) were diagnosed with cancer. In 2019, sixty-three patients were treated for screen-detected cancer, whereas only 23 patients entered the screening pathway before the services were suspended. Majority of patients underwent surgery in 2019 as compared to 2020 (80% versus 36%). Fifty-six percent of patients received endocrine treatment as primary or bridging therapy; whereas, in 2019, only 12% received primary endocrine therapy. In 2020, time from decision to surgical treatment has decreased by half as compared to 2019 (8.6 versus 19.1 days). One patient who underwent surgery developed COVID-19 infection after two weeks, and no postoperative mortality was reported. On average, each trainee was involved in 35 procedures during 2020; whereas in 2019, 54 procedures were assisted or performed by a trainee. **Conclusion**: Our study shows that COVID-19 has made a significant impact on patients' management and surgical training. Majority of the patients were commenced on neoadjuvant endocrine therapy instead of surgery. The conversion rate to cancers in one-stop clinic improved possibly due to a smaller number of benign referrals during the pandemic. The impact on surgical training is due to the reduction in the number of patients operated during this period, and constraints of performing complex oncoplastic procedures and breast reconstruction.

| | **2019 (16.03.2019 to 22.06.2019)** | **2020COVID period (16.03.2020 to 22.06.2020)** |
|---|---|---|
| **Impact on Clinic:** Total number of patients seen in OPD | 1881 | 1064 |
| **Impact on Breast cancer Diagnosis** | | |
| 1.Total | 153 | 86 |
| 2.Screening | 63(41.17%) | 22(34.37%) (who were already in pathway) |
| 3.Symptomatic | 90(58.83%) | 64(65.63%) |
| **Impact on Breast cancer Treatment: 1st treatment** | | |
| 1.Started on Neo-adjuvant chemotherapy | 13(8.49%) | 7(8.13%) |
| 2.Started on endocrine therapy (Both primary and neo-adjuvant) | 18(11.76%) | 48(55.81%) |
| 3.Surgery | 122(79.73%) | 31(36.04%) |
| **Mean days from decision to initiation of treatment** | | |
| 1.Neo-adjuvant chemotherapy | 13.3 | 21.7 |
| 2.Endocrine therapy | 0.4 | 0.1 |
| 3.Surgery | 19.1 | 8.6 |
| Total number of surgeries performed Including those diagnosed before the pandemic. | 160 | 102 |
| Breast surgical training Number of surgeries performed/ assisted by a trainee | 54 | 35 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS4-12

Potential value of FOXA1 expression as genomic predictor of response to docetaxel and carboplatin neoadjuvant (NA) chemotherapy in patients with triple negative breast cancer (TNBC)

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**Background:** TNBC is a particularly aggressive subtype with high recurrence rates and poor long-term survival. Anthracycline-free regimens based on docetaxel plus carboplatin (TCb) achieve around 50-55% pathologic complete responses (pCR) which correlates with better survival outcomes. Identification of genomic predictors of response is key to individualize therapies for this heterogeneous breast cancer (BC) subgroup. FOXA1 is a pioneer factor for androgen (AR) and estrogen receptors (ER). Its under-expression has been linked to cancer stemness in TNBC and better prognosis in ER-positive BC. The differential expression of AR, FOXA1 and BRCA1 is associated with sensitivity to chemotherapy in TNBC patients. Data support the plasticity role of FOXA1 driving basal to luminal BC cells by inducing luminal genes but also by repressing the basal phenotype and thus, tumor aggressiveness, although its role as a biomarker in TNBC is still controversial. We have analyzed RNAseq data of FOXA1 and AR in a series of TNBC tumors homogenously treated with neoadjuvant TCb to study their correlation with survival and response. **Methodology:** 300 TNBC patients have been included in a multicenter, prospective, non-randomized trial aimed to identify predictors of response to TCb in the neoadjuvant setting (NCT01560663). 278/300 patients were evaluable. PAM50 subtypes (NanoString nCounter) and RNAseq (HiSeq2500) were analyzed for those patients with both available samples and evaluable pathological response (n=208). Correlations were studied by the Kendall method. Linear or logistic regressions were adjusted for univariant analysis depending on numerical or categorical response variables, respectively. **Results:** FOXA1 and AR were differentially expressed between basal and non-basal tumor subtypes (PAM50), being overexpressed in non-basal ($p<0.001$ for both FOXA1 and AR). FOXA1 and AR were significantly overexpressed in non-basal subtypes from the Vanderbilt TNBC-type classification (36/208) as well. Both genes expression showed a significant correlation with several luminal marker genes. AR was significantly associated with ANXA9 (p=0,008), GATA3 (p=0,00002) and XBP1 ($p<0.001$), while FOXA1 expression was positively associated with ANXA9 (p=0,03), ESR1 ($p<0.001$),GATA3 ($p<0.001$) and XBP1 ($p<0.001$). In terms of response, significant differences in FOXA1 expression levels were found between responders and non-responders by Residual Disease Burden (RCB) classification taking response as binary variable of PCR vs RCB-I/II/III (p=0.003) as well as pCR/RCB-I vs RCB-II/III (p=0.008) with responders showing a lower FOXA1 expression level. The same analysis for AR expression did not show statistically significant differences. Within the PAM50 basal subgroup, neither AR nor FOXA1 individual gene expression (172/208) showed association with response. For survival, with a median follow-up of 36 months, neither FOXA1 nor AR showed significant impact on EFS or OS per univariate Cox regression analysis (EFS: $HR_{FOXA1}$ 1.076; p=0.307; $HR_{AR}$ 1.156, p=0.084 and OS: $HR_{FOXA1}$1.120, p=0.140; $HR_{AR}$ 1.152, p=0.121). **Conclusions:** Within our cohort, FOXA1 expression is a better predictor of response to NA chemotherapy than AR. FOXA1 is overexpressed in TNBC tumors who do not achieve pCR with neoadjuvant TCb chemotherapy, correlating with non-basal tumor subtypes. This suggests that measuring FOXA1 expression levels in patients with TNBC could be useful to predict response to TCb regimen enabling physicians to select more effective alternative NA schemes in this population.

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# Floor and ceiling effects in the EORTC QLQ-C30 physical functioning subscale among patients with breast cancer enrolled in commercial clinical trials vs. a community trial

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**Background:** The EORTC QLQ-C30 Physical Functioning (PF) subscale is a widely used patient-reported outcome (PRO) measure that quantifies cancer patients' physical function. Responsiveness, the degree to which a scale can assess clinical deterioration and improvement, is an important measurement characteristic that can be assessed by looking at floor and ceiling effects. A floor effect is defined as a high proportion of study participants reporting the lowest possible score in the variable of interest, while a ceiling effect is the opposite. We characterized floor and ceiling effects of the PF subscale in patients with breast cancer enrolled in commercial clinical trials vs. a community-based trial.**Objectives:** (1) Determine floor/ceiling effects of the QLQ-C30 PF items and subscale among patients receiving treatment for breast cancer (2) Compare floor/ceiling effects among patients enrolled in randomized clinical trials vs. those treated in a community care trial.**Methods:** PF data from 5 breast cancer commercial clinical trials submitted to the FDA for review were pooled (Clinical Trial or CT Cohort). A subgroup of breast cancer patients from the Alliance PRO-TECT trial was also analyzed (Community Cohort). Descriptive statistics were used to assess floor/ceiling effects, distributions of PF items, and the summed PF score at baseline and follow-up, for both cohorts. **Results:** The CT Cohort and Community Cohort consisted of 5,975 and 178 patients, respectively. Most patients in both cohorts were female, over the age of 50, and White. They were from varied treatment settings (adjuvant, 1$^{st}$ line, and 2$^{nd}$ line). 78% of CT patients had a baseline ECOG score of 0 (fully active), vs. only 44% in the Community Cohort. Baseline and follow-up floor effects (i.e. % of patients with the lowest response option - "not at all") are presented in Table 1. Floor effects were more pronounced in the CT Cohort, with 43 to 94% of CT patients responding "not at all" to items in the PF subscale at baseline vs. 24 to 89% in the Community Cohort. Additionally, smaller proportions of CT patients responded "not at all" at Cycle 3 follow up compared to baseline. Meanwhile, floor effects in the Community Cohort were similar at baseline and month 3 follow up.Ceiling effects (i.e. % of patients with the highest domain response) were also observed in both cohorts. Over 54% of CT patients scored ≥93/100 on the 100-point PF subscale, at baseline. This proportion decreased to 30% at Cycle 3 follow up. On the other hand, 26% of community patients scored ≥93/100 on the PF subscale, at baseline. This proportion increased to 30% at Month 3.
Table 1: Baseline and Follow Up Floor Effects - % of patients responding "not at all"

| | | **Clinical Trial Cohort** | | **Community Cohort** | |
|---|---|---|---|---|---|
| | | **Baseline** | **Cycle 3** | **Baseline** | **Month 3** |
| **Item** | **Question** | **% (n)** | **% (n)** | **% (n)** | **% (n)** |
| 1 | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 43% (2,540) | 27% (573) | 24% (42) | 27% (43) |
| 2 | Do you have any trouble taking a long walk? | 60% (3,554) | 28% (585) | 24% (42) | 30% (47) |
| 3 | Do you have any trouble taking a short walk outside of the house? | 88% (5,256) | 68% (1,395) | 58% (104) | 64% (101) |
| 4 | Do you need to stay in bed or a chair during the day? | 73% (4,364) | 57% (1,181) | 46% (82) | 51% (81) |
| 5 | Do you need help with eating? | 94% (5,599) | 93% (1,904) | 89% (159) | 91% (145) |

**Conclusion:** We observed high floor/ceiling effects in the PF domain of the QLQ-C30 among patients in commercial clinical trials, more so than in the community. Inclusion of patient advocacy groups in the item selection process may increase the relevancy and sensitivity of the PF domain to the population being studied. Stakeholders in clinical trial and clinical practice settings may consider adding additional high functioning items from the EORTC's item library, to more accurately determine the impact of anti-cancer treatment on patients' physical functioning.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS3-12

# Prediction of pathological complete response to neoadjuvant chemotherapy in early triple negative breast cancer patients by serial breast ultrasound examination

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**Background**. Pathological complete response (pCR) following neoadjuvant chemotherapy is associated with a good prognosis and long-term survival in patients with triple negative breast cancer (TNBC). Imaging offers significant information in monitoring response to neoadjuvant chemotherapy as a complement to conventional tumor assessment by physical examination. **Methods.** This is a single institution, retrospective cohort study. The primary objective was to determine whether volumetric measurement by ultrasound examination, of the pre-treatment breast tumor size, post-cycle two, post-cycle four and at completion of neoadjuvant chemotherapy predicted pCR. Tri-dimensional measurements were used to calculate the volume index. The percentage change between pre-treatment and cycle 2, pre-treatment and cycle 4, and pre-treatment and completion of treatment was calculated. Patients were treated with taxane, anthracycline, and alkylating agents based neoadjuvant chemotherapy. A pCR was defined as the complete disappearance of the invasive cancer in the breast and absence of tumor in the axillary lymph nodes. A radiological complete response (rCR) was defined as no malignant legions detected by ultrasound (0mm). Receiving operating characteristics (ROC) analysis was used to determine the association between pCR and percentage of tumor shrinkage. Specificity was defined as the proportion of patients with a non-pCR that were correctly classified as non-responders by ultrasound measurement. Sensitivity was defined as the proportion of patients with a pCR that were correctly classified as complete responders by ultrasound assessment. Statistical analysis was performed using NCSS version 11 and statistical tests used the significance level of 0.05. **Results**. Seventy-eight TNBC patients with a median age of 48 years (range 27-85 years). The population's tumor sizes were classified as T1 = 18 (23%), T2 = 54 (69%), T3 = 6 (8%). Positive glands in 33 (43%) patients and negative glands in 45 (57%) patients. Stage I = 11 (23%) patients, Stage IIA = 40 (51%) patients, stage IIB = 22 (28%) patients and stage III = 5 (6%) patients. The median volume pre-treatment was 18624mm$^3$ (SD = 41284mm$^3$). A pCR rate of 57% was documented. A 80% shrinkage of tumor, following the second cycle of chemotherapy, was associated with a pCR in 74% of responders (specificity 71%, sensitivity 70%). A 93% shrinkage following four cycles of chemotherapy was associated with a pCR in 73% of responders (specificity 62%, sensitivity 81%). A 97% shrinkage upon completion of chemotherapy was associated with a pCR in 70% of responders (specificity 45%, sensitivity 93%). A shrinkage of more than 90% was associated with a pCR in 93% pts (specificity 79%, sensitivity 66%). Radiological CR was associated with a pCR in 84% pts (specificity 70%, sensitivity 68%). Patients attaining a pCR had a mean volume of 877mm compared to patient not attaining a pCR with a mean volume of 833mm ($p < 0,97088$). **Conclusion.** The breast ultrasound is a useful, non-expensive, non-invasive test to monitor TNBC pts undergoing neoadjuvant chemotherapy. Measurement of the tumor by serial ultrasound is a useful predictor of pCR in these patients. Percentage shrinkage of more than 90% of the tumor at the completion of treatment, is more accurate in predicting pCR compared to radiological CR.

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Palmitate exacerbates breast tumorigenesis in vitro via induction of a senescent-like phenotype in fibroblasts

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**Background:** Obesity is associated with a worse breast cancer prognosis, conferring an increased risk of recurrence and mortality. At the same time, recent evidence suggests that obesity is also correlated with development of cellular senescence, an inflammatory state associated with exacerbation of breast tumorigenesis in preclinical models. As obese individuals present greater levels of inflammation at baseline, research efforts are warranted to examine the means by which obesity promotes the development of a senescent phenotype, which may further exacerbate inflammation. Additionally, studies have yet to determine whether obesity-induced senescence modulates the tumorigenic process in the context of breast cancer specifically. **Methods:** To this end, we exposed fibroblasts to the obesity-associated circulating factor palmitate and used qPCR and western immunoblotting to assess the expression of genes and proteins involved in the senescent state, including interleukin (IL)-1a, IL-6, IL-8, senescence-associated beta-galactosidase (SA-beta-gal), and matrixmetalloproteinase (MMP)-9. As a mechanistic investigation, we next assessed the impact of palmitate on activation of NF-kB signaling using western immunoblotting, immunofluorescence, and NF-kB luciferase reporter assays. Finally, we utilized cell counting, MTT, wound healing, and colony formation assays to examine the impact of these palmitate-exposed fibroblasts on breast cancer cell proliferation, viability, motility, and survival, respectively. **Results:** We found that palmitate induced fibroblast gene expression of IL-1a, IL-6, and IL-8, major components of the senescent secretome, as well as expression of the senescent markers SA-beta-gal and MMP-9. The mechanism at least partially involved activation of NF-kB, responsible for production of about 75% of senescent secretome components. More importantly, these palmitate-exposed fibroblasts were of pathological impact, exacerbating in vitro measures of breast cancer cell aggressiveness. **Conclusions:** These findings contribute to our understanding of the impact of obesity-associated factors on breast tumorigenesis, demonstrating a mechanistic link between palmitate and the pro-tumorigenic effects of senescent cells. Our studies will ultimately aid in the identification of a therapeutic target that can be used to improve the comparably worse outcomes of the obese breast cancer patient.

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# Balixafortide (a CXCR4 antagonist) plus eribulin in HER2 negative metastatic breast cancer: Final analysis from the Phase 1 single arm trial

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**Background:** Balixafortide (B) is a potent, selective antagonist of the chemokine receptor CXCR4. High CXCR4 levels correlate with aggressive metastatic phenotypes and poor prognosis in metastatic breast cancer (MBC). Efficacy and safety data were published recently from the Phase 1 trial investigating B + eribulin (E) in patients with HER2 negative MBC[1]. We report the final safety and efficacy analyses from this trial, including an assessment of dose-response and adverse events of particular interest (AEPIs) (e.g. neutropenia, peripheral neuropathy).
**Methods:** In this single-arm, dose escalation trial, patients (pts) received E + increasing doses of B using a 3+3 design in 3 parts: *Part I* cohorts received low B doses (0.5−1mg/kg) + increasing E doses (1.1−1.4mg/m$^2$); *Part II* dose-escalation cohort for B (1−5.5mg/kg) + 1.4mg/m$^2$ E; *Expanded Cohort* (EC) to confirm safety and efficacy of B 5.5mg/kg + 1.4mg/m$^2$ E. Most cohorts received E on days 2 and 9, and B on days 1−3 and 8−10 of 21-day cycles.
**Results:** At entry, all 56 women (age range 33−82 years) were HER2 negative, CXCR4 positive. Most pts were Caucasian and heavily pretreated in the metastatic setting (line of chemotherapy on study: 29% 2$^{nd}$ line, 50% 3$^{rd}$ line, 21% 4$^{th}$ line). 75% were hormone receptor positive and 23% had triple negative breast cancer.
A linear dose-exposure was observed over the entire dose range tested for B. $C_{max}$ and AUC for E were within published ranges.
Safety findings (including AEPIs) remained similar to those reported previously[1].
No dose-limiting toxicities were confirmed; therefore, the maximum tolerated dose of B was not reached. The highest B dose evaluated was 5.5mg/kg; pharmacokinetic evaluation showed that further protocolled dose increments of B would not have provided a sufficient increase in plasma levels. In addition, the objective response rate in Part II was 3-fold greater than published for eribulin alone which suggested
that the anti-tumor activity of B was worthy of further exploration at 5.5mg/kg in the EC.
Efficacy data for the trial are shown in the table.

| | **Part II(N=21)** | **Expanded Cohort(N=24)** | **Overall Efficacy Population(N=54)** |
|---|---|---|---|
| **Objective Response Rate (95% CI)** | 33% (15−57) | 38% (19−59) | 30% (18−44) |
| **median duration in months (IQR)** | 2.8 (1.4−3.3) | 4.4 (3.1−5.3) | 3.2 (2.2−4.5) |
| **Clinical Benefit Rate (95% CI)** | 43% (22−66) | 63% (41−81) | 44% (31−59) |
| **median duration in months (IQR)** | 5.4 (4.2−6.7) | 8.1 (6.3−10.8) | 6.9 (5.4−10.3) |
| **median PFS in months (95% CI)** | 4.2 (3−5.4) | 6.2 (2.9−8.1) | 4.6 (3.2–5.7) |
| **median OS in months (95% CI)** | 10.4 (7.7−18.4) | 18 (12.2–27.2) | 16.8 (10.6–18.4) |
| **Landmark OS estimate** | | | |
| **12 months (95% CI)** | 40% (19−60) | 75% (53−88) | 60% (45−72) |
| **18 months (95% CI)** | 30% (12−50) | 50% (29−68) | 42% (29−55) |
| **24 months (95% CI)** | 20% (6−39) | 33% (16−52) | 25% (14−37) |

CI: confidence interval; IQR: interquartile range; OS: overall survival; PFS: progression free survival
These data suggest a potential dose-response relationship for B across all efficacy endpoints, with efficacy being numerically greatest in the EC. While PFS and OS should be interpreted with caution in single arm trials, these data suggest potential benefit for this combination. Further analyses will be presented.
Responses were observed regardless of line of chemotherapy on study or extent of CXCR4 expression and were numerically higher in hormone receptor positive patients.
**Conclusions:** A consistent dose response effect for B + E was suggested across all efficacy endpoints for heavily pretreated pts with HER2 negative MBC. When these results are compared with published data for E monotherapy in similar populations, the EC consistently shows numerically greater benefit for all efficacy endpoints[2, 3].
The safety and tolerability of B + E appear comparable to published data on E or B alone, particularly for neutropenia and peripheral neuropathy[1].
These results suggest that B + E could potentially provide a new treatment option in heavily pretreated patients with HER2 negative MBC. A Phase 3 trial exploring efficacy and safety of B 5.5mg/kg + E is ongoing.
1. Pernas S et al. Lancet Oncol. 2018; 19: 812−242. Cortes J et al. Lancet. 2011; 377: 914−9233. Kaufman PA et al. J Clin Oncol. 2015; 33: 594−601

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# National comprehensive cancer network (NCCN) recommendations for drugs without US food and drug administration (FDA) approval in metastatic breast cancer: A cross-sectional study

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**Background**: NCCN guidelines include recommendations not approved by the FDA. We aimed to compare the NCCN recommendations for metastatic breast cancer (MBC) with the FDA approved indications and to identify characteristics that are associated with NCCN recommendations for off-label treatment. **Methods**: All NCCN recommendations for MBC and their supporting data were identified. Drug labels were reviewed to determine whether recommendations are FDA approved indications. Odds ratio (OR) and 95% confidence interval (CI) were calculated to compare between FDA approved and off-label recommendations for pre-specified categories including drug type, tumor subtype, level of recommendation and line of therapy. **Results**: Of 124 recommendations identified, 68 (55%) were off-label. Chemotherapy and human epidermal growth factor receptor 2 (HER2) targeted drugs were associated with less frequent approved indications (OR=0.28, 95% CI 0.12-0.62, p=0.001 and OR=0.29, 95% CI 0.12-0.70, p=0.005, respectively). Recommendations for endocrine therapy (OR=3.44, 95% CI 1.32-9.09, p=0.009) and non-HER2 targeted treatment (OR=10.0, 95% CI 3.03-33.33, p<0.001) were associated with FDA approved indications. Compared to combination therapies, monotherapies were more likely to be FDA approved (OR=3.45, 95% CI 1.64-7.23, p=0.001). Category 1 (OR=7.63, 95% CI 2.19-26.55, p=0.001) and preferred NCCN recommendations (OR=5.49, 95% CI 2.36-12.77, p<0.001) were more likely to be FDA-approved indications. Compared to off-label recommendations, NCCN recommendations of approved drugs were based on significantly higher sample size (mean 477 vs. 342 patients, p=0.017) and were non-significantly associated with availability of randomized data (OR=1.92, 95% CI 0.87-4.24, p=0.10).**Conclusion**: More than half of all NCCN recommendations for MBC are off-label, mostly involving chemotherapy containing regimes for HER2 negative disease and combinations which include HER2 targeting drugs. The clarity of the NCCN guidelines can be improved by underlining the strength of the evidence supporting various recommendations for MBC and the hierarchy between various treatment options.

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**Publication Number:** PS1-14

# Impact of axillary dissection and patterns of care in patients with ypN1 triple negative breast cancer receiving regional nodal irradiation

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**Background**: The benefit of axillary lymph node dissection (ALND) in patients with pN1 disease on sentinel lymph node biopsy (SLNB) following neoadjuvant chemotherapy for invasive breast cancer in patients receiving regional nodal irradiation (RNI) is unclear, even in patients with high risk histologic features such as triple negative disease. We sought to determine any association of ALND with improved survival, as well as patterns of care in this cohort using the National Cancer Database (NCDB).
**Methods**: The NCDB was queried for women ages 18-75 with cT1-3N1 and ypT0-T3N1M0 breast cancer that underwent definitive surgical resection with axillary staging followed by adjuvant regional nodal irradiation, with triple negative receptor status. Only patients who were treated from 2012 - 2015 were included for appropriate coding of the extent of axillary surgery. Overall survival was estimated using the Kaplan-Meier method and Cox proportional hazards models. An analysis of the number of lymph nodes removed, rate of RNI utilization, and rate of ALND was performed using the Wilcoxon rank-sum test, proportions of RNI utilization compared using the Chi-squared test, and correlation of these to year of diagnosis was evaluated with the Pearson correlation coefficient.
**Results**: A total of 572 women were identified that met inclusion criteria. The median age was 53 (range 24-75) years. 67 (11.7%) of women had SLNB alone and 505 (88.3%) had ALND with or without SLNB. Four year OS was 66.7% in patients undergoing ALND compared to 70.6% in those that had SLNB alone (p = 0.47). Charlson-Deyo comorbidity index (CDCC) (p = 0.01) and clinical T3 stage (p = 0.03) were significantly associated with survival. After adjusting for age, histology, clinical and pathologic T-stage, and CDCC, there was no significant relationship between receipt of ALND and overall survival (OS), however CDCC (p = 0.01) and cT3 or pT3 (p = 0.02 and p =0.01) remained significantly associated with OS. The mean number of lymph nodes sampled from 2012 to 2015 increased from 11.68 to 13.46 (p = 0.07). The rate of RNI increased from 55.6% in 2012 of patients to 58.4% in 2015 (p = 0.6). The rate of ALND increased from 83.9% in 2012 to 90.8% in 2015 (p = 0.2). Pearson correlation coefficients between mean number of lymph nodes sampled, rate of RNI, and rate of ALND were 0.83. 0.13, and 0.95 respectively.
**Conclusions**: There was no difference in overall survival between patients with cT1-3N1M0 and ypT0-3N1M0 triple negative breast cancer receiving SLNB compared to ALND with adjuvant RNI, even when adjusting for tumor size and comorbidities, which remained significant risk factors. There was a trend towards an increase in the mean number of lymph nodes sampled and increased utilization of ALND, though these failed to reach statistical significance. We await the results of the Alliance 011202 randomized trial to provide prospective guidance of the utility of ALND in this high risk subgroup.

**Table 1. Baseline Characteristics For Triple-Negative Patients**

| | **SLNB (n=67)** | **ALND (n=505)** |
|---|---|---|
| **Median Age (Years)** | 53 | 53 |
| **Histology (n, %)** | | |
| Ductal | 61 (91%) | 452 (90%) |
| Lobular | 2 (3%) | 15 (3%) |
| Other | 4 (6%) | 38 (7%) |
| **T-Stage (n,%)** | | |
| cT1 | 11 (16%) | 73 (15%) |
| cT2 | 34 (51%) | 290 (57%) |
| cT3 | 22 (33%) | 142 (28%) |
| **CDCC (n,%)** | | |
| 0 | 54 (81%) | 441 (87%) |
| 1 | 9 (13%) | 51 (10%) |
| 2 | 4 (6%) | 8 (2%) |
| 3 | 0 (0%) | 5 (1%) |
| **Mean CDCC** | 0.25 | 0.16 |
| **Facility Type (n,%)** | | |
| Community | 5 (7%) | 36 (7%) |
| Comprehensive Community | 27 (40%) | 171 (34%) |
| Academic/Research | 13 (19%) | 160 (32%) |
| Integrated Network | 13 (19%) | 72 (14%) |
| Other/Unknown | 9 (14%) | 66 (13%) |
| **Lymphovascular Invasion (%)** | 32.84% | 32.48% |
| **Median Tumor Size (cm)** | 3.6 | 3.3 |
| **Median Nodes Examined** | 4 | 12 |
| **Median Nodes Positive** | 1 | 2 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS11-13

# Multidimensional molecular profiling of repeated metastatic TNBC biopsies in the intensive trial of omics <ITOMIC> safely guides treatment decisions

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**Background** Metastatic triple negative breast cancer (mTNBC) is an inherently diverse disease and while molecular classification of mTNBC has assisted in treatment decisions, if based on only an initial biopsy, it does not take into account the evolution of metastatic cancer. Characterization of emerging metastases is needed to reveal both new resistance or sensitivity to available therapeutics. The goal of “Intensive Trial of OMics in Cancer (ITOMIC) - Intensive Longitudinal Monitoring in Subjects With Triple-Negative Breast Cancer” (NCT01957514) - was to determine the feasibility of longitudinal collection of patient biopsies that would be subjected to molecular analysis to provide actionable, relevant and timely information to guide treatment decisions.**Methods** Multiple biopsies were collected longitudinally, including pre- and post-treatment, from 29 mTNBC patients enrolled in the ITOMIC study and subjected to multi-dimensional molecular profiling including WES, WGS, cancer gene panel sequencing, RNA-seq, and proteomics and/or IHC for tumor biomarkers. This information was used to guide iterative, patient- and tumor- individualized treatment recommendations made by a multi-institutional ITOMIC Tumor Board (ITB) and conveyed to each subject’s oncologist.**Results** Longitudinal biopsy collection was found to be safe. Molecular profiling revealed that 2 of an original 31 enrolled subjects likely had lung cancer rather than mTNBC, supporting the merit of repeated tissue analysis. While the other 29 subjects had all been given a diagnosis of mTNBC before entering the trial, estrogen receptor, progesterone receptor, and/or HER2 were found to be over-expressed in at least one sample for 12 subjects; appearance of receptor positivity suggests targeted therapy may be effective. Tumor evolution in response to the first on-study treatment for most subjects (cisplatin) was revealed by copy number alterations, changes in single nucleotide variants, and insertions/deletions in pre-/post-treatment biopsies. Over the course of the study, the ITB convened 54 times and 39 of 182 recommended treatments were evaluated and accessed through either an existing clinical trial, a single patient IND, approved off label or label indication. While not all ITB treatment recommendations were followed, 24 subjects did receive at least one ITB-recommended drug, frequently as part of a clinical trial. Currently, for 27 subjects (2 withdrew) median survival is ~31 months. There are 4 surviving patients in treatment with a remarkable median survival of >51 months.**Conclusion** Collection and molecular analysis of multiple biopsies during the course of patient’s disease, shown here to be safe and feasible, provides information vital to appropriate treatment choice and reveals new targets for and resistance to therapy in metastatic TNBC.

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Non-invasive screening for breast cancer risk based on circulating ensembles of tumor associated cells

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Background: Common modalities for breast cancer screening include self-breast examination (SBE) for detection of palpable lumps as well as Mammography scans for detection of suspicious nodules or masses. While both approaches have low specificity, SBE has lower sensitivity for early stage cancers while mammography is associated with radiation exposure risks. A blood-based non-invasive approach for determination of breast cancer risk in asymptomatic individuals can facilitate early detection and improve prognosis and survival. Circulating Ensembles of Tumor Associated Cells (C-ETACs) are heterotypic clusters of malignant cells which originate in a tumor and are ubiquitously detected in peripheral blood of individuals with solid organ cancers. We present findings from two large-cohort prospective observational studies showing the suitability of C-ETACs for non-invasive, non-radiological screening for breast cancer. Methods: 15 ml of peripheral blood was collected from 14,962 female volunteers among whom 832 were suspected cases of breast cancer and 14,962 were asymptomatic individuals with age-associated risk of breast cancer. The 832 suspected cases underwent a foundational (first diagnostic) biopsy following collection of blood while the 14,962 asymptomatic individuals underwent a mammography scan following collection of blood. Peripheral blood mononuclear cells (PBMCs) were isolated from all blood samples and treated with an epigenetically activating treatment medium which exerts selective cytotoxicity towards non-malignant hematolymphoid cells and allows survival of apoptosis resistant malignant cells and their clusters (C-ETACs). C-ETACs were defined as clusters of 3 or more cells which were EpCAM+, PanCK+ and CD45+/-. Results: Among the 832 suspected cases, 779 were eventually diagnosed with breast cancer and 53 with benign breast conditions. C-ETACs were detected in 701 / 779 cases of breast cancer (90.0% sensitivity) with comparable detection rates in metastatic (365/408 = 89.5%) as well as non-metastatic (336/371 = 90.6%). C-ETACs were also detected in 1 / 53 (1.9%) cases of benign breast tumor. Among the asymptomatic cohort of 14,130, C-ETACs were detected in 657 cases (4.7%), which included 509 / 10,859 (4.7%) individuals with BIRADS 1 and in 148 / 3,271 (4.5%) of individuals with BIRADS ≥2. These individuals have been advised clinical follow-up. Conclusions: We show that C-ETACs are ubiquitous in breast cancers and rare in individuals with benign conditions as well as asymptomatic individuals. Being derived from the tumor mass, C-ETACs are specific for cancer and thus provide direct visual evidence of malignancy in cancer cases and risk of malignancy in asymptomatic cases. The non-invasive nature of the approach is well suited for screening of large asymptomatic populations for breast cancer.

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# Safe margins for delineation of left anterior descending artery (LAD) using cardiac-gated CT-scan (CG-CT) in left side breast cancer patients

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***Background:*** Cardiac toxicity after breast cancer (BC) radiotherapy (RT) is partly due to the large radiation doses to coronary arteries. The left anterior descending artery (LAD) is particularly exposed. A first step in achieving robustly proven dose constraints to the LAD during treatment planning is homogeneous delineation based on guidelines. LAD delineation can be problematic due to heart movements.***Purpose/Objective(s):*** The aim of the study was to establish a safety margin for delineation of the LAD in BC patients.***Materials/Methods***: We studied 45 left-sided BC patients who had an indication for adjuvant radiotherapy between 2015 and 2018. They all underwent cardiac-gated computed tomography scan (CG-CT), as well as planning CT scans (P-CT) with or without contrast agents, to assess LAD diameter and movements. CG-CT was performed while monitoring the cardiac cycle. Acquisition was launched immediately after contrast injection (arterial sequence), with deep inspiration breath hold and use of a beta-receptor blocking agent. By manually reviewing each scan, the LAD positions and diameter were defined at 20 different phases of the cardiac cycle at 5 different sites: ostium, circumflex (Cx) bifurcation (bfc), first diagonal (D1) bfc, second diagonal (D2) bfc and apex (right coronary anastomosis). Next step is to introduce it in softwear of automatic delineation to improve the atlas of cardiac structures.***Results:*** Movement of the LAD is maximal at the ostium, then constant overall even when far from its origin. The diameter decreases with the distance from ostium: 4.9 mm (OS), 3.9 mm (Cx), 3.5 mm (D2) and 3.1 mm (D2).***Conclusion:*** We suggest using a safety delineation margin consisting of a cylinder with a diameter of 10 mm surrounding the LAD. These findings must be validated in independent series of patients treated for BC.

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Population-based tool to estimate residual risks of breast cancer specific mortality (BCSM) and non-BCSM

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**Background:** The risk of breast cancer death persists for at least 20 years from diagnosis. Most reports describing this risk have been based on selected patients (pts) enrolled into clinical trials. These studies report absolute risks at fixed timepoints (i.e. 10 or 20 years) and do not consider the dynamic changes in risks over time. The aim of this study was to develop a tool to calculate residual risks of BCSM and non-BCSM based on individual pt and tumor characteristics, at any given time after breast cancer diagnosis. **Methods:** Using data from the Surveillance, Epidemiology, and End Results (SEER) program, we identified women diagnosed with non-metastatic invasive breast cancer between 1990-2005, with one primary cancer in their lifetime, and known hormone receptor (HR) status. We estimated the effect of baseline clinical and pathologic variables known to be prognostic, including pt age, HR status, tumor size (T), nodal status (N), and tumor grade, on residual cumulative risks of BCSM and non-BCSM over time. The tool generates the residual death risk (RDR), which is a nonparametric estimate of the cumulative risk of BCSM and non-BCSM by year 20 after any given time from initial diagnosis, among patients defined by baseline clinical and pathologic variables using the method of Gray (1988) implemented in the cmprsk package in R. **Results:** We included 235,015 pts (median follow-up = 14 years). Among all breast cancer deaths, the proportion occurring after 5 years was 60% for HR+ vs 24% for HR- ($p<0.001$). The table shows risks of BCSM and non-BCSM by HR and N status. The cumulative risk of BCSM in year 5-20 ranged from 4.2% in HR+ T1a N0 to 50.1% in HR+ N3. Using the RDR tool, a 54 year-old pt, diagnosed 7 years prior with a HR+, T1c, N1, grade 2 breast cancer, has a 16.6% residual cumulative risk of BCSM over the following 13 years, and a residual cumulative risk of non-BCSM over the same period of 4.0%. For a 66 year-old pt, diagnosed 10 years prior with a HR+, T1c, N0, grade 1 breast cancer, her residual cumulative risk of BCSM over the following 10 years is 2.9%, and her residual cumulative risk of non-BCSM over the same period is 10.0%. For a 45 year-old pt, diagnosed 8 years prior with a HR-, T2, N1, grade 3 breast cancer, her residual cumulative risks of BCSM and non-BCSM over the following 12 years are 4.4% and 4.9%, respectively. **Conclusions:** For HR+ breast cancer, risks of BCSM remain high beyond 5 years from diagnosis. For HR- breast cancer, the risk of BCSM is highest within 5 years from diagnosis; however, risks beyond 5 years are still considerable. The RDR tool provides population-based long-term estimates of cumulative risk of BCSM and non-BCSM over time, based on individual pt and tumor characteristics.

| | | **BCSM** | | | | **non-BCSM** | **All-cause mortality** |
|---|---|---|---|---|---|---|---|
| | | **% Event-Free** | | **Cumulative risk (%)** | | **Cumulative risk (%)** | **Cumulative risk (%)** |
| | | **at 5 y** | **at 10 y** | **y 5-20** | **y 0-20** | **y 0-20** | **y 0-20** |
| **Nodal status by HR status (any T)** | | | | | | | |
| HR+ | N0 | 97.2 | 93.9 | 8.6 | 10.6 | 33.2 | 43.8 |
| | N1 | 92.1 | 83.9 | 20.0 | 25.2 | 25.5 | 50.8 |
| | N2 | 81.5 | 66.2 | 36.1 | 45.6 | 21.2 | 66.8 |
| | N3 | 67.7 | 49.1 | 50.1 | 63.1 | 16.1 | 79.2 |
| HR- | N0 | 89.2 | 85.4 | 7.3 | 17.0 | 22.7 | 39.7 |
| | N1 | 74.2 | 68.3 | 12.2 | 34.3 | 17.0 | 51.3 |
| | N2 | 57.0 | 49.3 | 20.0 | 53.5 | 14.5 | 68.0 |
| | N3 | 40.7 | 33.5 | 26.2 | 68.7 | 9.3 | 78.0 |
| **Tumor size among N0 only** | | | | | | | |
| HR+ | T1a | 99.0 | 97.6 | 4.2 | 5.0 | 30.4 | 35.4 |
| | T1b | 98.9 | 97.2 | 5.1 | 5.9 | 34.4 | 40.2 |
| | T1c | 97.6 | 94.3 | 8.7 | 10.5 | 32.9 | 43.3 |
| HR- | T1a | 97.3 | 94.7 | 4.9 | 7.3 | 23.0 | 30.3 |
| | T1b | 95.1 | 91.9 | 6.2 | 10.5 | 27.1 | 37.7 |
| | T1c | 91.7 | 87.9 | 7.5 | 14.8 | 23.0 | 37.8 |

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# Impact of trastuzumab on Ipsilateral breast tumor recurrence after breast conserving surgery

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**Background:** Trastuzumab is well known to be effective to control locoregional recurrence and distant metastasis of human epidermal growth factor receptor 2 (HER2)-overexpressing breast tumor. However, few studies have reported the effect of ipsilateral breast tumor recurrence (IBTR) in spite of higher incidence of IBTR for HER2 overexpressing subtype than other subtypes. The purpose of this study is to investigate the difference in the incidence of IBTR of HER2-overexpressing breast tumor according to adjuvant trastuzumab.
**Methods**: We retrospectively reviewed 996 patients who had done surgery for HER2-overexpressing breast cancer between January 2000 and December 2017 in our institution. Patients with tumors smaller than 0.5cm without axillar node metastasis were excluded. As regarding IBTR as recurrence “in” the ipsilateral breast, only patients who had done breast conserving surgery were included.
**Results:** There were 735 patients who had finished adjuvant trastuzumab as first planned and 555 patients with hormone receptor positive. Median follow-up period for all patients was 70.7 months (range 12.7-239.6 months). The 10-year IBTR-free survival rate showed a significant benefit for the group treatment with trastuzumab than the group without trastuzumab (97.0% versus 91.9%; p=0.007). In a multivariate analysis, presence of lymphovascular invasion (Hazard ratio [HR], 2.53; 95% Confidence interval [CI], 1.19 - 5.41), closed or involved resection margin (HR, 2.62; 95% CI, 1.20 - 5.74), positive hormone receptor (HR, 3.70; 95% CI, 1.69 - 8.08), positive axillar lymph node (HR, 5.21; 95% CI, 1.75 - 15.57), and omitted or uncompleted adjuvant trastuzumab (HR, 2.72; 95% CI, 1.11 - 6.67) were independent predictors of IBTR. However, subgroup analysis of the patients with hormone receptor negative tumor showed no benefit of adjuvant trastuzumab (98.1% versus 96.6%, p=0.669) while it controlled IBTR for hormone receptor positive tumor (95.7% versus 86.2%; p=0.002). When additionally analzyed, trastuzumab showed benefit for 10-year locoregional recurrence-free survival (95.5% versus 89.7%, p=0.012) and distant metastasis-free survival (93.5% versus 77.8%, p<0.001).
**Conclusions:** Trastuzumab has a clinical benefit in not only locoregional recurrence but also IBTR among HER2-overexpression breast cancer, especially with negative hormone receptor.

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# Irreversible inhibition of HER2 activating mutations with neratinib enhances the pre-clinical efficacy of trastuzumab emtansine and trastuzumab deruxtecan

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**Background:** HER2 activating mutations occur in 2-5% of metastatic breast cancer (MBC) patients, and three phase II or basket clinical trials have shown that the irreversible pan-HER tyrosine kinase inhibitor, neratinib, has good single agent efficacy for HER2 mutated MBC patients. Current trials are combining neratinib with other targeted therapies to increase response rate and progression free survival for these patients. **Methods:** We established patient derived xenografts (PDX) and organoids from two patients with HER2 mutated, non-amplified MBC and used them to test neratinib with the antibody drug conjugates (ADC's), trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), both in 3D culture and in vivo. Real time, in vivo uptake of these ADC's was visualized with a near infrared fluorophore. **Results:** PDX lines WHIM51 and WHIM64 were established from ER+, HER2 non-amplified MBC patients that had HER2 activating mutations. WHIM51 has HER2 exon 20 insertion mutation at amino acid 776 (ERBB2 A775_G776insYVMA) and WHIM64 has a HER2 L869R missense mutation, both of which are located in the HER2 tyrosine kinase domain. Both of these HER2 mutations have been previously characterized and are known activating mutations. Organoids were established from both PDX's and were grown in 3D culture. Drug combination testing of neratinib with T-DM1 in 3D culture showed strong synergy and the mechanism was explored. We demonstrate that neratinib and other irreversible HER2 inhibitors increase the endocytic uptake of T-DM1, but this effect does not occur with the reversible HER2 inhibitors, tucatinib and lapatinib. Real time, in vivo uptake of T-DM1 was measured by labeling the ADC with a near infrared fluorophore and we observed statistically significant increase in T-DM1 uptake with neratinib pre-treatment. Combining neratinib with T-DM1 increased apoptosis at day 3 post-treatment and enhanced tumor shrinkage. With the FDA approval of T-DXd at the end of 2019, we hypothesized that this same mechanism may apply to neratinib combined with T-DXd. We have tested both the combinations of neratinib + T-DXd and neratinib + T-DM1 in vivo in both HER2 mutant PDX's and observed statistically significant tumor regression with the neratinib + ADC combinations as compared to either T-DXd or T-DM1 on its own. **Conclusions:** Neratinib increases the endocytosis of trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), thereby increasing tumor cell kill and causing greater tumor regression in HER2 mutated MBC. These data provide preclinical justification for trials of neratinib plus HER2 ADCs including T-DXd or T-DM1 in HER2 mutant or HER2+ MBC. Further, this mechanism of neratinib stimulated HER2 endocytosis may also apply to HER2 low MBC.

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Silicone implant based sustained localized drug delivery of fulvestrant to prevent breast cancer

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Background: Hereditary breast cancer is common. With enhanced awareness and the recent introduction in affordable multi-gene germ line testing, an estimated 0.5-1 million women will learn that they carry a considerable risk to develop breast cancer. Thus, a rapidly increasing number of women, many of them very young, will be in need of effective strategies for breast cancer prevention. Current options to prevent breast cancer in women at high risk include bilateral mastectomies or systemic anti-estrogen therapy. Both options, while effective, may have a detrimental impact on the physical and emotional well-being of the patient. Localized delivery of an established anti-estrogen to breast tissue only may thus offer an attractive alternative for cancer prevention and may replace systemic therapy for ductal carcinoma *in situ* and early stage breast cancer with minimal risk for metastases. Methods: As such, we have sought to develop a silastic-silicone device, which when placed under breast tissue, will deliver the anti-estrogen fulvestrant directly to the target tissue. Sustained slow release of fulvestrant from a silastic-silicone device directly into the mammary tissue will provide the risk reducing benefits of systemic hormonal therapy while minimizing systemic exposure and the resulting poor compliance due to adverse effects. Results: Using a combination of *in vitro* and *in vivo* studies, we show that fulvestrant can be delivered through a silastic-silicone device. Implanted adjacent to mammary tissue, this drug delivery device provides sustained high levels of fulvestrant to inhibit estrogen receptor signaling and breast cancer cell proliferation. In a MCF-7 breast cancer xenograft model we have shown that silastic-silicone delivers fulvestrant selectively to mouse mammary tissue for more than 1 year with anti-tumor effects similar to those achieved with systemic fulvestrant exposure. Using the Sprague-Dawley rat DMBA spontaneous breast cancer induction model, we further demonstrate that fulvestrant delivered by silastic-silicone devices implanted adjacent to mammary tissue significantly delays time to first tumor compared to control animals (n=90, HR = 0.42, 95% CI 0.21-0.83) with minimal systemic exposure (plasma average 1.1 ng/mL, SD $\pm$1.5 ng/mL). Initial large animal safety and toxicity studies in female sheep (ewes, n=2) support the surgical strategy to place the device between breast tissue (*i.e.* udder) and the chest wall (abdominal wall in ewes). Following 1 month of fulvestrant release, gross and histopathological analysis found no adverse effects or implant related toxicity. Bioanalytical analysis of mammary tissues suggested that drug was found highest near the implant (max 341 ng/g, udder average 58.4 ng/g, SD $\pm$17.1 ng/g), with diminishing levels distal from the implant. Systemic exposure was low, with plasma levels 1.2 ng/mL, SD $\pm$0.22 ng/mL, comparing favorably to clinical plasma levels achieved by intramuscular fulvestrant of 500 mg: 28.0 ng/mL, SD $\pm$27.9 ng/mL (FDA package insert). Subsequent large animal studies will focus on the safety and pharmacokinetics of device delivered fulvestrant in longer studies (*e.g.* 3 to 6 months). Conclusions: The greater awareness and genetic identification of individuals at risk for breast cancer brings about an increased need for novel approaches to breast cancer prevention. The development of a silastic-silicone based device for sustained and localized drug delivery with an approved and effective anti-estrogen should allow rapid transition into clinical testing. This strategy will provide an alternative option to mastectomies and allow breast conservation for women identified to have a more than 40% lifetime chance of developing breast cancer, as well as provide an alternative to systemic hormonal therapy in women with ductal carcinoma *in situ* or stage I breast cancer.

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Associations between frailty and cancer-specific mortality among older women with breast cancer

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**PURPOSE** Frailty is assessed when making treatment decisions among older women with breast cancer (BC), which in turn impacts survival. We evaluated associations between frailty and risks of BC-specific and all-cause mortality in older women.
**METHODS** We conducted a retrospective cohort study of Medicare beneficiaries ages ≥65 years with stage I-III BC using the Surveillance, Epidemiology and End Results Medicare Health Outcome Survey Data Resource. Frailty was measured using the deficit-accumulation frailty index, categorized as robust, pre-frail or frail, at baseline and during follow-up. Fine and Gray competing risk and Cox proportional hazards models were used to estimate sub-distribution hazard ratios (SHR) and hazard ratios (HR) with 95% confidence intervals (CI) for BC-specific and all-cause mortality, respectively.
**RESULTS** Among 2,411 women with a median age of 75 years at BC diagnosis, 50% were categorized as robust, 29% were pre-frail and 21% were frail. Compared to robust women, fewer frail women received breast-conserving surgery (52% vs. 63%) and radiation (44% vs. 52%). In multivariable analyses, frail women had higher risks of all-cause mortality compared to robust women (HR 2.16, 95% CI 1.80-2.60).
**CONCLUSION** Frail women in our study had a higher cumulative hazard of BC-specific death, but this observed higher risk was not significant after accounting for differences in treatment and competing risks of other-cause death. Measuring frailty may help determine overall life expectancy but not BC-specific death.

**Table. Risk of Breast Cancer-Specific and All-cause Mortality, using time-varying DAFI measure**

| | **Events** | **Crude SHR** | **Robust 95%CI** | **P-value** | **Minimally Adjusted SHR[a]** | **Robust 95%CI** | **P-value** | **Fully Adjusted SHR[b]** | **Robust 95%CI** | **P-value** |
|---|---|---|---|---|---|---|---|---|---|---|
| **Breast Cancer-Specific Mortality** | | | | | | | | | | |
| **DAFI Categories** | | | | | | | | | | |
| Robust | 89 | 1.00 | | | 1.00 | | | 1.00 | | |
| Pre-frail | 69 | 1.25 | 0.91 – 1.70 | 0.16 | 1.15 | 0.84 – 1.59 | 0.38 | 1.06 | 0.77 – 1.48 | 0.72 |
| Frail | 62 | 1.53 | 1.11 – 2.11 | 0.01 | 1.37 | 1.00 – 1.90 | 0.05 | 1.19 | 0.85 – 1.66 | 0.31 |
| **All-Cause Mortality** | | | | | | | | | | |
| **DAFI Categories** | | | | | | | | | | |
| Robust | 272 | 1.00 | | | 1.00 | | | 1.00 | | |
| Pre-frail | 224 | 1.55 | 1.30 – 1.84 | <0.0001 | 1.41 | 1.19 – 1.68 | <0.0001 | 1.37 | 1.15 – 1.63 | <0.0001 |
| Frail | 236 | 2.3 | 2.12 – 3.02 | <0.0001 | 2.33 | 1.96 – 2.78 | <0.0001 | 2.16 | 1.80 – 2.60 | <0.0001 |

DAFI = deficit-accumulation frailty index; HR = hazard ratio; SHR = subdistribution hazard ratios; CI = confidence intervals[a] adjusted for age categories and breast cancer staging [b] adjusted for age categories, breast cancer staging, surgery type, radiation, Estrogen/Progestin Receptor, race/ethnicity, marital status, and education

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# The value of shear-wave elastography for prediction of treatment response to neoadjuvant chemotherapy in patients with breast cancer

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**Introduction** Recently, Shear-wave elastography (SWE) has been known to be useful for the diagnosis of breast cancer and lymph node metastasis. However, little is known about whether SWE can predict the response to neoadjuvant chemotherapy in patients with breast cancer. This study aimed to investigate the relationship between treatment response and elasticity values. **Method** Pre-treatment shear-wave elastography was performed in 394 patients who underwent neoadjuvant chemotherapy followed by surgery at Gangnam Severance Hospital from January 2012 to May 2020. We evaluated the pathologic complete response (pCR, defined as ypTis/T0, No) according to elasticity values such as ‘Mean stiffness’, ‘Minimum stiffness’, ‘Maximum stiffness’, and ‘Ratio’. **Results** A total of 394 patients, 147 (37.3%) achieved pCR. All elasticity values were significantly lower in patients with pCR after neoadjuvant chemotherapy than those with the residual invasive tumor. In the multivariable analysis, the mean stiffness (OR 0.995; 95% CIs, 0.989-1.000; P=0.039) and the maximum stiffness (OR 0.995; 95% CIs, 0.990-0.999; P=0.024) were independent predictive factors for pCR after adjusting clinic-pathologic factors. Besides, the tumor-infiltrating lymphocytes (TILs) evaluated in biopsy samples were inversely correlated with pre-treatment mean stiffness (CC -0.053, P=0.044), and elasticity ratio (CC-0.288, P=0.033). **Conclusion** In this study, pre-treatment elasticity values measured by SWE were significantly associated with pCR in breast cancer. Our results suggest that SWE can be a useful diagnostic tool for predicting treatment response in patients with breast cancer who will receive neoadjuvant chemotherapy.

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# Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy - ATNEC (ClinicalTrials.gov NCT04109079)

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**Background:** Neoadjuvant chemotherapy (NACT) results in eradication of cancer in the axillary lymph nodes in 40% to 70% of patients. This has raised questions about the benefit of further axillary treatment in these patients with no evidence of residual disease in the lymph nodes. **Trial design:** A multi-centre phase III randomised controlled trial with embedded economic evaluation in which participants will be randomised in a 1:1 ratio. **Study participants:** T1-3N1M0 breast cancer patients aged 18 years or older, with needle biopsy proven nodal metastases, who after NACT have no residual cancer in the lymph nodes on dual tracer sentinel node biopsy and removal of at least 3 lymph nodes (sentinel nodes and marked involved node). **Intervention:** Participants in the experimental group will not receive further axillary treatment (axillary lymph node dissection [ALND] or axillary radiotherapy [ART]), after NACT and surgery. Participants in the control group will receive further axillary treatment (ALND or ART) after NACT and surgery, as per local guidelines. **Stratification:** Institution, type of breast surgery (breast conserving surgery (BCS) vs mastectomy), receptor status (triple negative vs HER2 positive vs ER status positive and/or PR status positive and HER2 negative) **Eligible participants will be/should have**:•Age ≥ 18•Male or female •T1-3N1M0 breast cancer at diagnosis (prior to NACT) •FNA or core biopsy confirmed axillary nodal metastases at presentation •Oestrogen receptor and HER2 status evaluated on primary tumour •Received standard NACT as per local guidelines (Patients undergoing neoadjuvant endocrine therapy as part of another clinical trial are eligible) •Ultrasound of the axilla at completion of NACT •Undergo dual tracer sentinel node biopsy after NACT and at least 3 nodes removed (sentinel nodes and marked node). If axillary node sampling is performed following failed localisation of sentinel nodes, patient will be eligible if at least 3 nodes removed (including the marked node) •No evidence of nodal metastases post NACT (isolated tumour cells, micro or macro metastasis) **Participants will be excluded if they have any one of the following:**•Bilateral invasive breast cancer•Sentinel node biopsy prior to NACT•Marked node not removed *except* where at least one node removed showsoevidence of down-staging with complete pathological response e.g. fibrosis or scarring and at least 3 nodes removed•Previous axillary surgery on the same body side as the scheduled targeted sampling•Any previous cancer within last 5 years or concomitant malignancy *except* basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix oin situ or stage 1 melanoma, contra- or ipsilateral in situ breast cancer **Specific aims:** To assess whether, omitting further axillary treatment (ALND and ART) for patients with early stage breast cancer and axillary nodal metastases on needle biopsy, who after NACT have no residual cancer in the lymph nodes on sentinel node biopsy, is non-inferior to axillary treatment in terms of disease free survival (DFS), and reduces the risk of lymphoedema at 5 years.Statistical methods: All analyses will be carried out on an intention-to-treat basis to preserve randomisation, avoid bias from exclusions and preserve statistical power.
**Target accrual:** 1900, Number of sites: ~100 **ClinicalTrials.gov:** NCT04109079 **Contact information:** atnec@warwick.ac.uk **Disclaimer:** This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (Reference - HTA NIHR128311). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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# The prognostic role of tumor-infiltrating lymphocytes after treatment with neo-adjuvant chemotherapy in inflammatory breast cancer patients

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**Introduction:** Inflammatory breast cancer (IBC) is a rare, but aggressive form of breast cancer. Increasing evidence indicates that immune cells in the tumor micro-environment play an important role in IBC progression: infiltration with stromal Tumor Infiltrating Lymphocytes (sTIL) is associated with a better response to neo-adjuvant chemotherapy (NACT) and longer overall survival in IBC patients. However, the prognostic role of sTIL in patients without a complete pathological response (pCR) after NACT remains unclear. In this study we evaluated the effect of NACT on sTIL in IBC and locally advanced non-inflammatory breast cancer (LABC) and the prognostic impact of sTIL in IBC.
**Methodology:** In this retrospective case-control study we evaluated sTIL in patients with IBC (n=60) and LABC (n= 134) that received anthracyclin-taxane based NACT. Tumor tissue was sampled as part of the routine work-up, before (diagnostic biopsy) and after (resection specimen) NACT. sTIL scoring was performed on Haematoxylin & Eosin stained 5-µm sections of formalin-fixed paraffin-embedded tumor tissue by two different researchers according to the recommendations by the International TILs Working Group. In case of discrepancy, the sample was scored by a third observer in order to obtain a consensus score. sTIL difference between pre-treatment and post-treatment specimen was called δsTIL. Cellularity of the residual cancer after NACT was evaluated according to the MD Anderson Residual Cancer Burden (RCB) method.
**Results:** Most of the IBC patients presented with a hormone receptor (HR) positive carcinoma (n=35/60, 58.3%) and 25 patients had pCR after NACT (42%); the latter patients had less than 1% sTIL in the tumor bed area. Besides having histologically more poorly differentiated tumors ($P$= 0.033), no significant clinicopathological differences between the IBC and LABC cohort were observed. There was no significant difference in the pre-treatment median sTIL score between IBC (12.5%, range: 1% - 80%) and LABC (10%, range: 1% - 85%). Furthermore, both in the IBC (median δsTIL: -4.5%, $P$= 0.01) and in the LABC (median δsTIL: -1%, $P$= 0.06) cohort the number of sTIL was lower after NACT. This decrease was significantly greater in the IBC cohort ($P$= 0.04). In a multivariate model - including HR and HER2 status, histological differentiation grade, nodal status and IBC/LABC phenotype - IBC disease correlated with a stronger decrease of sTILs after NACT (OR: 0.31, 95% CI 0.10 - 0.89, $P$= 0.04).
As we previously demonstrated, higher sTIL score before NACT was associated with better overall survival (OS) ($P$= 0.006) in IBC. IBC patients without pCR, but with a stronger decrease (> 4.5 %) of the number of sTIL after NACT had a better OS ($P$= 0.04) and disease-free survival (DFS) ($P$= 0.04). There was a significant correlation between δsTIL and both higher sTIL score before NACT ($P$< .001) and lower residual cancer cellularity ($P$= 0.02). However, in a multivariate model - including sTIL before NACT, δsTIL and residual cancer cellularity - both a strong decrease of sTIL (HR: 0.32; 95% CI 0.10 - 1.00; $P$= 0.05) and a low residual cancer cellularity (HR: 0.22; 95% CI 0.07 - 0.68; $P$= 0.009) were independent predictors of a better DFS.
**Conclusion:** Both the IBC and LABC cohort had the same number of sTIL before NACT. However, the IBC phenotype was associated with a stronger decrease of sTIL after NACT independent of molecular subtype and nodal stage. Furthermore, a strong decrease in sTIL was an independent predictor of better prognosis in IBC.

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# Men1611 is a pi3k α/β selective and δ sparing inhibitor with long-lasting antitumor activity in different genetic backgrounds of pik3ca mutant breast cancer models

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Dysregulation of the PI3K/AKT/mTOR pathway has the potential to trigger the activation of class I phosphoinositide 3-kinases (PI3Ks) and eventually lead to cancer. Class I PI3Ks are heterodimers composed of the regulatory subunit p85 and the catalytic subunit p110. There are four isoforms of p110, alpha and beta, important in solid tumors, and delta and gamma, preferentially expressed in leukocytes, and drivers in hematological malignancies. While activation of PI3K p110alpha is the most frequent oncogenic event in solid tumors, p110beta plays an important role in PTEN deficient cancers and in mediating resistance to p110alpha selective PI3K inhibitors.MEN1611 is a PI3K inhibitor active on p110alpha (both mutants and wt), beta and gamma (8.6- and 2.2- fold less potent compared to the alpha, respectively), while sparing the delta isoform (36-fold less potent compared to the alpha). Thus, MEN1611 differs from other selective PI3K inhibitors such as alpelisib (p110alpha selective) and taselisib (p110beta sparing). MEN1611 is currently in clinical development for patients with HER2 positive advanced or metastatic breast cancer in combination with trastuzumab with/without fulvestrant (B-PRECISE-01).
Patient-derived xenograft (PDX) models and breast cancer cell lines with different genetic background were used to assess the antitumor activity of MEN1611 in p110 alpha- and beta- dependent tumors. Healthy-donors derived CD69+ B-cells, which are primarily dependent on p110 delta for proliferation and survival were used to test the activity of the compound against the p110delta.
According to the biochemical selectivity, MEN1611 demonstrated a lower cytotoxic potential in a p110delta-driven cellular model (CD19+ B-cells), when compared to taselisib (>150-fold) and an improved cytotoxic activity in the p110beta-driven cellular model (PTEN-null breast cancer cells) when compared to alpelisib. Moreover, MEN1611 selectively decreases the p110alpha protein levels in PIK3CA mutated breast cancer cells in a concentration-dependent manner, with a corresponding reduction in pAKT. *In vivo*, MEN1611 monotherapy showed significant and long-lasting anti-tumor activity, reflected in tumor-stasis or tumor regression in several trastuzumab-resistant PIK3CA-mutant HER2 positive PDXs with different concomitant genomic aberrations. The combination of trastuzumab and MEN1611 significantly improved the efficacy compared to single agent treatment. Interestingly, MEN1611 monotherapy showed a significant tumor volume inhibition in a PTEN-null breast cancer PDX model.
Overall, our data provide evidence that MEN1611 is active against HER2 positive and PTEN-null breast tumors. Moreover, its delta-sparing profile may have potential implications on MEN1611 tolerability and ability to overcome resistance to p110alpha selective inhibitors.

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# Decision making process and contralateral prophylactic mastectomy

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BACKGROUND The relatively high rate of contralateral prophylactic mastectomy (CPM) among women with early stage unilateral breast cancer has raised concerns particularly with the lack of evidence for a survival benefit related to the CPM and with the low risk of developing contralateral breast cancer among women with early stage breast cancer. Women might be choosing this procedure to ease their fear of recurrence, and by believing that CPM may improve their quality of life; others might be influenced by their partner, physician or media. The purpose of this study was to assess the influence of the partner, physician, or media on the decision making process of women with unilateral breast cancer who decided to undergo CPM.
METHODS This is a retrospective study, conducted under MD Anderson Institutional Review Board. Women were identified from an existing cohort of breast cancer patients, age 20-60 years old, who were diagnosed with unilateral breast cancer stage 0 to III, who had no clinical or radiographic evidence of contralateral breast cancer, and who underwent CPM between January of 2010 and December of 2017 at MD Anderson Cancer Center; participants received a link to the quantitative cross-sectional survey using the Red Cap platform, 1341 patients were eligible to participate in the study, of which 397 completed the survey. The survey consisted of 16 questions that were adopted and modified from the Prophylactic Mastectomy Outcomes Study Survey. The survey design provided a numeric description of the factors that are affecting the women decision to undergo CPM; as well as the influence of the partner, physician, or media on the woman's decision-making process. Exclusion included women who had bilateral breast cancer before undergoing CPM, women who had received any treatment for breast cancer before their initial visit to MD Anderson, women who had bilateral breast cancer before undergoing CPM and patients with incomplete documentation of diagnosis of breast cancer, hormone receptor status or metastatic disease. Incidence of doctor, partner, and media influence were each modeled by logistic regression with adjustment for family history of breast cancer and pathology stage. RESULTS 203/343 (59%) patients reported some doctor influence on the CPM decision. The logistic regression model of the incidence of doctor-influence demonstrated significantly higher overall influence on the CPM decision due to doctors compared to self-determination alone (p=.0006), suggesting that 59% of patients' decisions were influenced by doctors. 53/189 (28%) patients with partners reported some partner influence on the CPM decision. The logistic regression model of the incidence of partner-influence demonstrated significantly lower overall influence on the CPM decision due to partners compared with self-determination alone (p<.0001,), suggesting that 28% of patients' decisions were influenced by partners. 36/213 (16%) patients reported some level of media influence on the CPM decision. The logistic regression model of the incidence of media-influence demonstrated significantly lower overall influence on the CPM decision due to media compared with self-determination alone (p<.0001), suggesting that 16% of patients' decisions were influenced by media.
CONCLUSION Partners, physicians, and media all had significant influence ($p < 0.05$) on the decision-making process of women with unilateral breast cancer to undergo CPM. It is important for women with unilateral breast cancer to fully understand the benefits versus the adverse effect of CPM and make an informed decision regarding the irreversible surgical procedure. The findings of this study may inform policy by highlighting the need for educational aids, programs, or tools that help women with unilateral breast cancer make informed decisions that are evidence-based regarding the efficacy of CPM.

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# Holistic artificial intelligence-driven predictor in HER2-positive (HER2+) early breast cancer (BC) treated with neoadjuvant lapatinib and trastuzumab without chemotherapy: A correlative analysis from SOLTI-1114 PAMELA

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**Background:** Positive partial response was observed in patients with primary HER2+ early BC with dual HER2 blockade that were not treated with chemotherapy. In this context and beyond, the low (partial) response rate of chemotherapy-free treatment strategies creates the necessity for patient stratification prior to treatment selection. Here, we tackle the challenging task of evaluating the ability of clinical, gene expression and histopathology data to predict response following dual HER2 blockade without chemotherapy. Our aim is through artificial intelligence to automatically decipher the complementarity of clinical, genomic and histopathology data through an evidence-driven approach towards a low dimensional holistic signature that determines outcomes and could be subsequently used as a clinical biomarker for treatment patient inclusion. **Methods:** PAMELA (Lancet Oncology 2017) was a prospective study in HER2+ BC designed to evaluate the ability of the PAM50 HER2-enriched intrinsic subtype to predict pCR following 18-weeks of neoadjuvant lapatinib and trastuzumab (and hormonal therapy if hormone receptor-positive [HR+]). Clinical-pathological variables (15) were included such as tumor cellularity, tumor-infiltrating lymphocytes (TILs), the expression of BC-related genes/signatures (567) along with histopathological data from pre-treatment samples. Imaging information was obtained from H/E slides, through an unsupervised deep learning approach using an attention network. The semantic segmentation was used to derive at the patch level image and shape characteristics resulted on a pathomics-derived feature vector of (300) variables. An integrative approach that harnessed clinical, genomics and pathomics data into a unified prediction framework was used. Patients were divided into a training set 80% and a testing set 20% with proportions of pCR and non-pCR corresponding to the ones observed. A 100-fold Cross-validation (CV) was performed on the training. Linear and non-linear robust feature selection were used to recover a low dimensional holistic signature along with an ensemble learning approach to select the top 5 machine learning/artificial intelligence methods for prognosis. **Results:** From the high dimensional feature (882) space, a low dimensional holistic signature of 8 predictive variables was automatically retrieved through. The signature consisted of 4 genomics variables (expression levels of ERBB2, ESR1, Luminal A signature and Risk of Relapse score), 2 clinical-pathological variables (histologic grade and ER-status) and 2 imaging variables (mean Short Run Low Gray Level Emphasis of the gray level run length matrix and the mean absolute deviation). To ensure the robustness and generalizability of the results, we present results averaged over 100 splits into training and test. On all cases the same holistic signature was uses and the same prediction methods/principles. The proposed AI-driven prognosis mechanism reached 75% balanced accuracy, 69% precision, 65% sensitivity, 86% specificity and 0.84 AUC demonstrating the relevance of the approach. It was observed a successful classification of 86% for the non-pCR and 65% for the pCR cases. Ablation studies were performed to determine the relevance of the different categories of variables. Genomics variables were the most informative since their removal led to the highest decrease of the metrics (11% in average). **Conclusion**: The proposed method has great potentials for an effective and clinically meaningful implementation of pre-selecting patients that will not achieve a pCR after neoadjuvant dual HER2 blockade. Besides, the generality of the method used here makes it transposable to any type of cancer or therapy.

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Phase II trial of fulvestrant plus enzalutamide in ER+/Her2- advanced breast cancer

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Up to 91% of ER+ breast cancers express androgen receptor (AR), but its function is uncertain. Although AR expression is associated with more indolent tumors, high AR expression relative to ER is associated with endocrine resistance, and in the absence of estradiol or if ER function is blocked, preclinical studies suggest that AR can take over to signal cell survival and proliferation. Following extensive preclinical studies and a brief phase I to demonstrate a lack of significant PK interaction, this phase II trial of fulvestrant plus enzalutamide in ER+/Her2- metastatic breast cancer was conducted. **Methods:** Eligible patients were women with ECOG 0-2, ER+/Her2- measurable or evaluable metastatic breast cancer without CNS disease. Prior fulvestrant was allowed, if clinically indicated as per treating physician. Fulvestrant was administered in standard dosing at 500 mg IM days 1, 15, 29 and every 4 weeks thereafter. Enzalutamide was given at 160 mg po daily on a continual basis. Fresh tumor biopsies were required at study entry and at about 4 weeks on therapy. The primary efficacy endpoint of the trial was clinical benefit rate at 24 weeks (CBR24). Assuming the undesirable rate of 10% and desirable rate of 30%, a sample size of 24 provided 89% power to detect this 25% rate difference using an exact binomial test with a one-sided alpha of 0.085. Due to the exploratory nature of biomarker analysis, the type I error rate was not adjusted for exploring multiple biomarkers. **Results:** A total of 38 patients were consented, of whom 32 were eligible. Median age was 61 years (46-87); PS 1 (0-1); a median of 2 prior chemotherapy and 2 prior hormonal therapies for metastatic disease. Twelve patients had prior fulvestrant, and 90% had visceral disease. TEAEs >20% included fatigue, nausea/vomiting, constipation, headache, anorexia, although most were low grade. There were no G4 or G5 toxicities. Median PFS was 2.0 months (0.5-12). CBR24 was 25% (7/28 evaluable).**Conclusions:** In a heavily pretreated population of women with metastatic ER+/Her2- BC, the combination of fulvestrant plus enzalutamide had manageable side effects, and modest activity. About 25% reached the primary endpoint of clinical benefit of more than 6 months on therapy. Extensive molecular studies of paired fresh biopsies from pretreatment and at 4 weeks are underway. These analyses and correlations with clinical outcome will be described.

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# The AXSANA trial (AXillary Surgery After NeoAdjuvant treatment): An international prospective multicenter cohort study of the EUBREAST study group to evaluate different surgical methods of axillary staging (sentinel lymph node biopsy, targeted axillary dissection, axillary dissection) in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy (NCT04373655)

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**Background**
The optimal surgical staging of the axilla in patients who convert from a clinically positive (cN+) to a clinically negative node status (ycN0) through neoadjuvant chemotherapy is still unclear. Widely diverse techniques such as full Axillary Lymph Node Dissection (ALND), Targeted Axillary Dissection (TAD), Targeted Lymph Node Biopsy (TLNB) and Sentinel Lymph Node Biopsy alone (SLNB) are given preference in different international guidelines. So far, no comparative data on the oncological outcome or the morbidity of the different procedures are available. Further research is needed to safely de-escalate the radicality of axillary surgery in this patient group.
**Trial design**
The EUBREAST study group initiated an international prospective cohort study including cN+ patients converting to ycN0 status and treated with different axillary staging techniques according to the standard at their treating institution. Participants are patients with cT1-3 tumors with axillary lymph node metastasis confirmed by core biopsy or fine needle aspiration and scheduled for neoadjuvant systemic therapy. The trial is funded by the AGO-B Study Group, the Claudia von Schilling Foundation for Breast Cancer Research and the AWOgyn (Working Group for Reconstructive Surgery in Oncology-Gynecology) and supported by the NOGGO (North-Eastern German Society of Gynaecologic Oncology) and the German Breast Group.
**Primary endpoints:** 5-year invasive disease-free survival, 3-year axillary recurrence rate and health-related quality of life (HRQoL). HRQoL will be evaluated using four standardized questionnaires (EORTC QLQ-C 30, EORTC QLQ BR 23, Lymph ICF and SOC-13) at baseline and 1, 3 and 5 years after surgery.
**Secondary endpoints** are the feasibility and performance of different axillary staging techniques (detection rate, number of removed lymph nodes and association with complications, arm morbidity and quality of life, operating time and use of clinical and economic resources); impact of learning curve, and the detailed mapping of surgical and oncological treatment standards in different countries.
**Present accrual** (July 7th 2020): 5. The first study participant has been recruited in June 2020.
**Target accrual:** 3000 patients from EUBREAST member states (20)

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# Gene-expression profiling and response to neoadjuvant endocrine treatment in the phase II LETLOB trial

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**Background:** Hormone receptor positive (HR+)/HER2- breast cancer (BC) is a clinically and biologically heterogeneous disease, encompassing all BC molecular intrinsic subtypes. We here explore the association between gene-expression profiles and response to neoadjuvant endocrine-based treatment in early HR+/HER2- BC.
**Methods:** The LETLOB phase II trial randomized 92 postmenopausal women with clinical stage II-IIIA HR+/HER2- BC to receive neoadjuvant letrozole + lapatinib or letrozole + placebo for 6 months. Objective response was the primary endpoint, as defined by study protocol and previously published (Guarneri, JCO 2014). Gene-expression data (Affymetrix platform) from pre-treatment frozen core-biopsies was available for 66 pts. Intrinsic subtype was assigned using a research-based PAM50 subtype predictor. The PAM50 based chemo-endocrine score (CES) was calculated using published definition (Prat, CCR 2017). Higher values of CES indicate increased endocrine sensitivity, while lower values indicate higher chemosensitivity.
**Results:** Intrinsic subtype distribution was as follows: Luminal A 39% (N=25), Luminal B 36% (N=24), HER2-enriched 8% (N=5), basal-like 18% (N=12). Non-luminal tumors (basal-like and HER2-enriched) were characterized by less differentiated histological grades (Grade 3 65% vs 33%, p=0.037) and higher Ki67 expression at baseline as compared to luminal tumors (median 20% vs 15%, p=0.013). Considering both treatment arms combined, non-luminal tumors showed a significantly lower objective response rate as compared to luminal tumors (47% vs 78%, p=0.031). This difference was statistically significant in the lapatinib arm (43% vs 90%, p=0.021), but not in the placebo arm (50% vs 68%, p=0.449; interaction test p=0.169). After treatment, non-luminal tumors had significantly higher Ki67 levels than luminal ones (post-treatment median 10% and 7%, respectively, p=0.004).
Median CES level at baseline was -0.03 (range: -1.11, +1.12). Each unit increase in CES levels at baseline was numerically associated with higher probability of achieving an objective response (Odds Ratio 1.95, 95% CI 0.74-5.18, p=0.178, both arms combined).
**Conclusions:** In HR+/HER2- early BC patients enrolled in the LET-LOB trial, patients with non-luminal tumor or low CES score showed reduced sensitivity to endocrine-based treatment. The highest response rate (90%) was observed in luminal patients treated with letrozole + lapatinib. Gene-expression profiling could potentially be used to identify patients with low sensitivity to endocrine treatment for which neoadjuvant chemotherapy should be preferred.

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# A randomized, opened, phase II trial assessing the efficacy and safety of ATH-TH(doxorubicin/docetaxel/trastuzumab followed by docetaxel/trastuzumab) versus TCH(docetaxel/carboplatin/trastuzumab) as neoadjuvant treatment in HER2-positive breast cancer

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**Background:** Because Pertuzumab hasn't been approved in China until 2020y, trastuzumab has been standard neoadjuvant treatment for HER2-positive breast cancer. But we don't know which is the optimal chemotherapy with or without anthracyclines in the trastuzumab-based HER2-blockade. We designed this clinical trial to compare efficacy and safety between anthracycline and carboplatin in combination with docetaxel and trastuzumab as neoadjuvant therapy. **Methods:** From Apr, 2013 to Apr, 2019, 124 patients were enrolled. 60 patients were randomly assigned to the ATH-TH group and 64 to the TCH group. The treatment plan is showed as following, 1. TCH group: Trastuzumab(8mg/kg loading dose followed by 6mg/kg maintenance dose on day 1 every 3 weeks) combined with carboplatin(AUC=6 on day1 every 3 weeks) and docetaxel (75mg/m2 d1 every 3 weeks), total 6 cycles ; 2. ATH-TH group: Trastuzumab
combined with doxorubicin( 50mg/m2 on day1 every 3 weeks) and docetaxel (75mg/m2 d1 every 3 weeks) after 4 cycles, followed by Trastuzumab plus docetaxel (75mg/m2 d1 every 3 weeks) 4 cycles. Primary endpoint was pCR(ypT0/is/ypN0). Second endpoints included safety, event-free and overall survial (EFS and OS). This trial is registered with ClinicalTrials.gov, number **NCT 02510781.Results:** Baseline Patients' characteristics were well balanced between ATH-TH group and TCH group: median age 49y/48y, hormone receptor positive 51.7% vs 46.9%, II stage 60.0% VS 64.0%, III stage 33.3% VS 32.8%. The pCR rate was no significant difference(P=0.457) in ATH-TH 56.7%(95% CI:43.8%-69.6% ) and TCH group 50.0% ( 95% CI :37.4%-62.6%) .In hormone positive subgroup, the pCR rate was 36.7% ( 95% CI:18.4%-55.0% )for TCH group, and 51.6% (95% CI:33.0%-70.2%) for ATH-TH group (P=0.24). In hormone negative subgroup, the pCR rate was 61.8% (95% CI:44.6%-79.0% )for TCH group, and 62.1% ( 95% CI:43.3%-80.9%) for ATH-TH group (P=0.98). The most common adverse events were hematologic toxicities. ATH-TH group had higher 3/4 grade leukocyte decrease rates than TCH group ( 86.7% VS 43.8%, p<0.001) and higher 3/4 thrombocytopenia (11.7% VS 1.6%, p<0.016). ATH-TH group had more FN than (43.3% VS 3.1%, p<0.001). LVEF change and cardiac events were similar between two group Four-year EFS estimates were 94.5% for ATH-TH and 91.1% for TCH (p=0.768, HR=0.82, 95% CI: 0.22-3.06). Four-year OS estimates were 97.5% for ATH-TH and97.8%for TCH (p=0.562, HR=2.0, 95% CI: 0.18-22.2). **Conclusions:** This is the first prospective randomised trial compare neoadjuvant
therapy regimen ATH-TH with TCH in HER2-positive breast cancer. We acquired similar pCR rate, four-year EFS and OS but less toxicity in TCH group compared with ATH-TH. Long-term follow-up is required to confirm these results. Clinical trial information: **NCT 02510781. Research Sponsor: None**

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# Advanced precision health resources in the Susan G Komen tissue bank at the IU simon comprehensive cancer center

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**Background:** Understanding how hereditary, lifestyle and demographic risk factors influence the development of breast cancer is critical for its prevention and treatment. For this purpose, the Susan G. Komen Tissue Bank at the IU Simon Comprehensive Cancer Center (KTB) serves as the world's primary repository for normal breast tissue and blood samples from healthy women (~5,500 tissue + blood donors and ~4,500 blood-only donors). In addition, KTB has received mammograms, H&E images and additional longitudinal health and wellness data from its donors via ongoing annual surveys. Whole genome sequencing has also recently been completed on a subset of 500 donors, including ~125 initially healthy donors who later went on to develop breast cancer. To make these disparate, multi-modal data accessible to the larger research community and add advanced precision health analytics capabilities to the KTB database, LifeOmic's Precision Health Cloud (PHC), a secure healthcare-compliant cloud platform, was chosen to host the KTB data moving forward. The PHC provides browsing and querying capabilities across all data including genomic, demographic, histology, donor surveys, and scanned images. Data from donors can be viewed individually as well as analyzed across cohorts of interest. Computation resources, such as informatics workflows and machine learning infrastructure, are available on the same secure environment to leverage the power of cloud computing without having to download large files. This is in addition to visual and custom analytics using Jupyter Notebooks accessible to collaborators.

**Methods:** We loaded all available KTB data from ~10,000 donors into the PHC. Donor-reported data collected at the time of donation and subsequent follow-up questionnaire responses were loaded as FHIR Observations and Medications in the PHC. Additional imaging and genomic data loaded into the PHC include approximately 12,000 mammogram images, 5,000 H&E images, 5,000 ancestry-informative genotypes and 500 VCF and BAM files from whole genome sequencing. A timeline view of each donor shows data collected from each donation and follow-up surveys. All genetic variants were annotated upon ingestion into the PHC with functional effect on genes, population allele frequency, ClinVar clinical significance and in silico predictions for functional impact.

**Results:** To demonstrate the utility of KTB data hosted in the PHC, we will show how the PHC can be used to directly analyze genomic and donor-reported data, specifically focusing on the recent whole genome sequencing data from 500 donors. Whole genome sequencing data will be used to calculate the genetic ancestry of each donor compared to their self-reported ancestry and previously predicted ancestry from a 41-SNP ancestry panel. Additionally, we will calculate genomewide breast cancer polygenic risk scores and compare these with the survey-based Tyrer-Cuzick and Gail score risk measures. We will assess how the polygenic risk score further stratifies the donors that have germline pathogenic variants in a known breast cancer gene. For the ~125 sequenced donors that went on to develop breast cancer we will also investigate correlations between family history of cancer, age of diagnosis, prior gynecological history and lifestyle differences. All generated results will remain in the PHC for access by future KTB collaborators to continue to build the utility and value of the KTB data.

**Conclusions:** We have shown how hosting KTB data in the PHC opens new opportunities for advanced precision health research for breast cancer researchers worldwide. As more specimens and diverse data sets including genomic, longitudinal and imaging information are being tracked and deposited into KTB, this resource will continue to grow to enable diverse research needs.

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Comparison between a breast specific radiosurgery device and intensity modulated proton therapy for accelerated partial breast irradiation

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**Purpose:** A breast specific radiosurgery device **(BSRD)** has recently been FDA cleared for treatment of accelerated partial breast irradiation. Using this device requires a vacuum assisted immobilization system to treat patients in the prone position. Alternatively, APBI delivery using intensity modulated **proton** therapy **(IMPT)** treats patients in the supine position at University of Maryland. This study aimed to compare dose distribution to targets and organs at risk (OARS), using BSRD plans versus IMPT plans for APBI. We hypothesized that despite the physical characteristics of IMPT the BSRD plans would be superior in conformality. **Methods:**An IRB approved retrospective review was performed for 13 patients who previously received a lumpectomy boost using the BSRD in prone position followed by whole breast irradiation in the supine position. APBI plans were created using dose a fractionation of 30Gy in 5 fractions. Previously contoured LPC volumes with a 1cm CTV expansion were created (modified at anatomic boundaries and within 5 mm of skin) followed by a 3 mm PTV expansion for BSRD plans, our standard for all BSRD plans, or CTV with beam specific PTV for IMPT plans. A single physicist created plans for BSRD with a different physicist for IMPT. Physicists were blinded to the results of the comparative plans. Plans were compared with respect to heart max, heart mean, ipsilateral lung V5, V20, normal breast D5, D20, D50 and D80, skin max, CTV coverage, conformality index (CI) and homogeneity index (HI). Paired t-test was used for statistical analysis. **Results:**Six out of thirteen patients had left sided breast cancer. The CTV volumes were comparable, with no difference in coverage of 95% of the CTV receiving the prescription dose (98% vs 97%). BSRD plans had superior CI (0.82 vs 0.63, $p<0.0004$), and HI (0.91 vs 0.65, $p<0.0001$) and improved Ipsilateral Lung V5 (2.3% vs 0.7%, $p<0.055$). IMPT plans had superior max heart dose (1.17Gy vs 4.13Gy, $p<0.001$), heart mean dose (0.05Gy vs 0.8Gy, $p<0.0006$), normal breast D5 (29 vs 31Gy $p<0.003$), D20 (13 vs 18Gy, $p<0.04$), D50 (0.79 vs 6.79, $p<0.0001$), D80 (0.07 vs 2.85, $p<0.0001$). There was no difference in max skin dose or ipsilateral lung V20. **Conclusions**: In conclusion, BSRD plans were associated with better dose conformity to the target and lower ipsilateral lung V5. When comparing dose to the heart and ipsilateral normal breast, both treatments plans delivered low doses below the acceptable limits, however plans were comparatively better with IMPT possibly due to target location. Additional patient evaluation is needed to further assess the impact of the breast immobilization device and target location on doses to OARs and the normal breast tissue. Overall, this comparison supports further evaluation of the BSRD technology

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# The histopathologic profile of pregnancy associated breast cancer by gestational age and lactation: Analysis of the nationwide Dutch Pathology Registry

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**Background:** Pregnancy associated breast cancer (PABC) comprises nearly 4% of all breast cancers. Compared to age-matched non-pregnant breast cancer patients, PABC is generally characterized by a particularly aggressive histopathologic profile. Whether these tumors arise before or during pregnancy, and whether they are stimulated by pregnancy-related hormones and/or epigenetic changes that by itself may affect subsequent hormone concentrations, remains to be elucidated. It is currently even unknown whether the histopathologic profile within PABC patients is affected by gestational age at diagnosis. In addition, some small studies observed a poorer outcome in lactating patients for patients with a postpartum PABC diagnosis. To fill this gap in knowledge, the present study assesses the influence of gestational age and lactation status at diagnosis on the histopathologic profile of PABC in a large population-based cohort.**Methods:**We identified 741 patients with PABC, between 1988 and 2019, in the nationwide Dutch Pathology Registry (PALGA). Histopathologic features (grade, ER-, PR-, and HER2-receptor status) were compared between pregnant- and postpartum PABC patients. Within pregnant PABC patients, histopathologic features were compared between the three gestational trimesters. For PABC patients with a postpartum diagnosis we compared histopathologic features of lactating versus non-lactating women.**Results:**Mean age at diagnosis was 34.2 years and the majority of breast cancers were diagnosed during pregnancy (74.2%); of which nearly half during the third trimester (47.3%). Histopathologic features did not differ between pregnant (n=550) and post-partum (n=191) PABC patients. Within pregnant patients, a significantly higher percentage of tumors were ER-receptor negative in the second (56.8%) and third trimester (57.3%), as compared to the first trimester (41.9%) (p=0.0015). A similar pattern was observed for PR; PR-negative receptor-status within first, second and third trimester: 48.0%, 57.7%, 56.5%, though these differences were not statistically significant (p=0.233). For histologic grade, we observed a higher proportion of grade III tumors with the second (87.4%) and third trimester (79.2%), as compared to the first trimester (73.7%) (p=0.055). For postpartum PABC patients no differences were observed for histologic grade between lactating (n=83) and non-lactating patients (n=94). However, tumors of lactating PABC patients were more often ER-negative (62.7% vs 48.9%, p=0.179), PR-negative (66.3% vs. 57.4%, p=0.258) and HER2-negative (74.7% vs. 61.7%, p=0.100). **Conclusion:**This unique, large population-based study of 741 PABC patients, demonstrates surprising histopathologic differences by gestational age at diagnosis for pregnant PABC-patients, and by lactation status for post-partum PABC-patients, which has not been reported before. Pregnant
patients diagnosed at an advanced gestational age and postpartum PABC-patients who are lactating, seem to have a more aggressive histopathologic profile. This renders interesting clues for further studies, that will be conducted to unravel the molecular and genetic background and to investigate whether this has consequences on outcome.

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# Her2 expression in matched metastatic tumor and circulating tumor cells (ctcs) in breast cancer: Implications for profiling and monitoring of her2 status to help guide anti-her2 therapy

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INTRODUCTION: Despite improvements in early detection, 1 in 8 women in the US (12%) will develop invasive breast cancer over the course of her lifetime. Approximately 20% of breast cancer is HER2 positive. During treatment and at disease progression, HER2 receptor conversion may occur. Once metastatic, it may be difficult to access multiple metastatic sites or perform serial biopsies. Therefore, accuracy of results may be sub-optimal as tissue biopsy is a single time point collection and limited by sampling (inter-tumoral and intra-tumoral heterogeneity). A liquid biopsy is a contemporaneous non-invasive and cost-effective method that allows for collection and analysis of tumor material and includes circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA). We compared prospectively the expression of HER2 in metastatic tumors to HER2 amplification in CTCs. METHODS: We enrolled patients with metastatic breast cancer in the Individualized Molecular Analyses Guide Efforts in Breast Cancer (IMAGE) II Study (NCT02965755). All patients regardless of subtype, had at least one line of therapy (chemotherapy, hormone therapy, or anti-HER2 therapy as appropriate). We analyzed HER2 status on tumor biopsies obtained 0-43 months (mean 7.3 months) prior to enrolling in IMAGE, and CTCs isolated from peripheral blood (PB) drawn ideally before starting a new treatment, 1-2 weeks after starting a new treatment and at the time of first restaging. CTCs were captured by Target Selector TM (Biocept) and analyzed for HER2 amplification by FISH. The biomarker expression profile on the metastatic tumor and CTCs were compared for each patient. Concordance of HER2 expression between CTCs and the metastatic tumor tissue was analyzed using McNemar's test. RESULTS: For 36 evaluable patients, the specificity of HER2 on CTCs to tissue was 92.9% for PB samples collected within 5 weeks of the tumor biopsy and 100% at for PB samples collected between 5-10 weeks post biopsy, with overall concordance of 65% (independent of CTC collection time point), accuracy of 76.5% and specificity of 79.7%. A change in HER2 in amplification between the metastatic tumor and CTCs was noted in 36% (13/36) of patients with 7 patients HER2+ in tissue, HER2- on CTCs and 8 patients HER2- on tissue, HER2+ on CTCs. CONCLUSION: These data demonstrate high accuracy of HER2 amplification on CTCs at baseline and within 10 weeks of treatment and provide a sensitive and specific mechanism to monitor for changes in HER2 status that may be due to either tissue heterogeneity or receptor switch, a well-established phenomenon. This ability to effectively and contemporaneously monitor HER2 status on CTCs has the potential to identify patients who may benefit from the addition of anti-HER2 therapy and those are on anti-HER2 therapy who may not benefit optimally and for whom additional therapeutic options may warrant consideration.

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# Eribulin and paclitaxel differentially affect exosome formation and release from triple negative breast cancer cells

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Extracellular vesicles (EVs) containing proteins, DNA, and RNA facilitate cellular crosstalk within and among tissues and are involved in a variety of physiologic and disease processes. Cancer cells secrete EVs that promote multiple aspects of cancer progression, including epithelial-mesenchymal transition (EMT), angiogenesis, metastasis, and immune suppression. EVs are formed by two different mechanisms, budding from the plasma membrane and through the multivesicular endosome pathway, and these subpopulations of EVs are commonly referred to as microvesicles and exosomes respectively. Notably, exosomes range in size from 50-150 nm, while microvesicles can range from 100-1000 nm. Microtubules are important for the vesicular trafficking involved in exosome formation, cargo loading, and release. Therefore, we hypothesized that microtubule targeting drugs would affect the formation and release of exosomes from triple negative breast cancer (TNBC) cells and alter their cargo. We investigated whether eribulin and paclitaxel differently affect exosome formation and release because they have highly divergent effects on microtubules, in that eribulin causes microtubule loss and paclitaxel increases microtubule density.

Exosome formation was evaluated by immunofluorescence of the multivesicular endosome/exosome marker, CD63, in multiple TNBC cell lines. Eribulin and paclitaxel significantly altered the cellular localization of CD63 after 4 h. High-content imaging analysis revealed a significant intracellular accumulation of CD63, suggesting that eribulin and paclitaxel could impair exosome release. Small EVs/exosomes were then isolated from TNBC cells treated for 8 h with concentrations of eribulin and paclitaxel that maximally disrupted CD63 without causing significant mitotic accumulation or cell death. Small EVs/exosomes isolated from cell-conditioned media were characterized by electron microscopy, immunoblotting and nanoparticle tracking analysis (NTA). The results of NTA show that while paclitaxel did not change the number of EVs released after an 8 h treatment, eribulin caused a modest, but consistent decrease in the number of EVs released by MDA-MB-231 cells. Immunoblot analysis further revealed a significant reduction in CD63 content of EVs from eribulin, but not paclitaxel-treated MDA-MB-231 cells. Additional fluorescent NTA using CD63 antibody labeling showed that CD63+ EVs were substantially reduced by eribulin but unchanged by paclitaxel. Interestingly, the CD63+ EVs that were isolated from eribulin-treated MDA-MB-231 cells were significantly larger than those from control or paclitaxel-treated cells, demonstrating that eribulin inhibits the release of small CD63+ EVs, likely exosomes. Taken with the fact that the total concentration of small EV particles released by eribulin-treated cells was only modestly reduced, our results suggest that eribulin promotes the release of small microvesicles while inhibiting the release of CD63+ exosomes. This shift in the population of EVs released by TNBC cells as a result of eribulin treatment could have implications for other EV cargo that impact cancer progression. Studies to confirm these effects in additional TNBC cell lines and with other microtubule targeting drugs, as well as proteomic analysis of EV content are ongoing. Furthering our understanding of the differential effects of eribulin and paclitaxel on EV formation and cargo has the potential to inform on the more targeted use of these drugs in the future.

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Evaluating the efficacy of immunotherapy in triple negative breast cancer

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The breast cancer microenvironment comprises a complex stroma including tumor-infiltrating lymphocytes (TILs), which can either stimulate tumor progression or promote anti-tumor immunity in response to tumor-derived cues. In general, of all clinical subtypes, triple-negative breast cancer (TNBC) is characterized by the most extensive infiltration of TILs within tumor stroma, which is consistent with the observation that TNBC seems to clinically respond to immunotherapies at the highest rates. Immune checkpoint blockade (ICB), an immunotherapy that promotes prolonged activation of cytotoxic immune cells to mount robust anti-tumorigenic responses, has yielded limited success in treating breast cancer. IMpassion130 was the first clinical trial to indicate that combining anti-PD-L1 with standard-of-care chemotherapy (nab-paclitaxel) to treat TNBC increases progression-free survival in patients exclusively those with PD-L1 positive tumors. Furthermore, the KEYSTONE-522 trial showed that administering anti-PD-1 in addition to various neoadjuvant chemotherapies increased the pathologic complete response in early stage TNBC patients. Despite promising evidence for immunotherapy success, both clinical trials lacked an experimental ICB-only group, and thus cannot address the therapeutic benefit of ICB alone, or which chemotherapy combination would maximize this benefit. Finally, mechanisms of resistance to ICB in breast cancer remain unexplored. We sought to model ICB response *in vivo* to elucidate the mechanisms responsible for immunotherapy efficacy in breast cancer, explore the synergistic effects of ICB with chemotherapies, and model ICB resistance.In this study, we investigated the efficacy of anti-PD-L1 as single-agent or in combination with paclitaxel or doxorubicin in the EMT6 (*Balb/c*) orthotopic mammary tumor model. In this model, single-agent immunotherapy was efficacious in reducing primary tumor growth compared to combination treatment, with a small proportion of complete responses, whereas modest benefit was observed with either chemotherapy alone. Following two rounds of treatment, we analyzed the tumor-immune microenvironment by flow cytometry and gene expression analysis. Anti-PD-L1 alone or in combination with either chemotherapy enhanced infiltration of cytotoxic and effector T cell as well as natural killer cells into the tumor microenvironment. Using gene expression analysis, we observed elevated expression of myeloid recruitment and activation markers in combination-treated tumors, supporting a known role of chemotherapy-induced cell death in myeloid recruitment; however as chemotherapy did not add benefit to tumor response or survival, it is unclear if this effect is detrimental or supportive. Interestingly, completely responsive anti-PD-L1 treated tumors that eventually recurred retained resistance to ICB upon re-implantation in naïve recipient mice, suggesting that tumor-intrinsic factors may contribute to resistance.Herein, we explore an *in vivo* model that corroborates clinical response to combinatorial immunotherapy approaches in breast cancer patients. We report the immunogenic efficacy of single-agent ICB that upregulates tumoricidal immune cell infiltration into the primary tumor, thereby controlling tumor growth, albeit without achieving complete response in all mice. Additionally, post-therapy recurrent tumors retain resistance upon transplantation, indicating tumor-specific adaptive resistance. This study has potentially significant clinical implications for re-evaluating the contributions of chemotherapy in combination with ICB in TNBC patients.

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# Assessment of clip locations on breast MRI during NAC to guide tumor bed biopsy at mid-treatment

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**Background**: The I-SPY 2 TRIAL randomizes patients with breast cancer to neoadjuvant chemotherapy (NAC) with or without experimental agents followed by anthracycline-cyclophosphamide (AC). As part of a de-escalation strategy to avoid overtreatment in good responders, combined information from serial MRI and mid-treatment core biopsy will be used to identify patients who may be candidates to skip AC. Presented are results of a pilot study to assess the location of biopsy clip in relation to tumor enhancement in MRI before and during treatment.
**Methods**: 40 patients enrolled in I-SPY 2 who underwent mid-treatment core biopsy were reviewed. Patients had MRIs at four time points: pre-treatment (T0), early treatment (T1, 3 weeks after the start of first regimen), inter-regimen (T2, 12 weeks after completing the first regimen), and pre-surgery (T3). Clip visibility and location were assessed by a trained researcher on T1 weighted, fat suppressed dynamic contrast enhanced MR images at three time points: T0, T1, and T2. If clip was visible, location was scored 1 (inside), 2 (edge), or 3 (outside) in relation to tumor enhancement seen on a signal enhancement ratio (SER) map. Clips inside (score 1) were fully embedded and surrounded by a clear margin of tumor enhancement. Clips on the edge (score 2) were not fully embedded, with a portion of the clip touching tumor enhancement. Clips outside (score 3) had no portion of clip touching tumor enhancement. For patients with a focal tumor but with multiple clips visible in MRI, the clip most embedded within tumor enhancement was designated as the primary clip for evaluation. In cases of multifocal disease, the clip visualized in the largest area of tumor enhancement was assessed. Clips touching tumor cavity edge and enhancement were scored as 3.
**Results:** Among 40 patients, two patients had no clips visualized in MRI at all three time points. One patient had no clip visualized at T0, but a clip was observed at T1 and T2. In addition, one T1 MRI was rejected due to incomplete exam and one T2 MRI was rejected due to different scanner from baseline. At T0, 51% (19/37) of clips were inside tumor enhancement and no clips were assessed outside tumor enhancement. 59% (22/37) of clips at T1 were on the edge or outside. At T2, 73% (27/37) of clips were on the edge and 19% (7/37) of clips were outside. While no clips were identified outside of tumor at baseline, tumor shrinkage with treatment resulted in clips outside of tumor in approximately 20 percent of cases at inter-regimen, and higher rates of clips identified at tumor edge.
**Conclusions:** Clips were visible and location could be assessed in MRI in a majority of cases. Clip evaluation can be challenging and attention to clip placement is essential for patients with multifocal disease or diffuse tumors. The results of this study may have implications for assisting the mid-treatment core biopsy and selecting candidates for de-escalation of neoadjuvant chemotherapy.

Table 1: Clips observed at three MR time points

| | T0 | T1[2] | T2[3] |
|---|---|---|---|
| 1 (inside) | 19 | 15 | 3 |
| 2 (edge) | 18 | 21 | 27 |
| 3 (outside) | 0[1] | 1 | 7 |

[1] No clips were seen outside tumor enhancement [2] One T1 MR was rejected due to incomplete exam [3] One T2 MR was rejected due to different scanner from baseline

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# Elucidating the biology of high-risk ductal carcinoma in situ (DCIS) through genomics and immunohistochemical profiling of the tumor microenvironment: The DEFENSE study

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**Introduction:** Ductal carcinoma in situ (DCIS) of the breast is a premalignant lesion representing a spectrum of biology and risk. While many patients with DCIS undergo surgical resection with no survival benefit given the indolent nature of their disease, others do possess biologically aggressive DCIS that has the potential to evolve into invasive cancer if left untreated. Yet even among those patients with biologically aggressive DCIS, their risk of dying from metastatic breast cancer is only 3.3% compared to 30-40% among patients with biologically aggressive invasive cancer.[1] The DEFENSE study, supported with funding from the NCI Molecular Characterization of Screen-Detected Lesions (MCL) consortium, was designed to identify molecular, immunological, and stromal-related factors that allow DCIS to develop high-risk features without ever becoming invasive breast cancer.
**Methods:** The overall objective of the DEFENSE study is to compare 100 patients with invasive high-risk breast cancer enrolled on the I-SPY2 trial matched based upon age and tumor molecular profile (Mammaprint) to 100 patients with high-risk DCIS, defined as having at least two of the following characteristics: large (>5cm), high-grade, hormone receptor-negative status and/or HER2-positive status. Tumors obtained from each of these patients are divided into 22 sequential sections with regions of pathologic interest identified prior to undergoing whole exome DNA sequencing, SMART-3SEQ RNA sequencing, multiplex immunofluoresence (mIF) for immune cell infiltrates, and stromal profiling by IHC. Each profiling modality is performed by a different institution included in the MCL consortium (UCSF, UCD, UCSD, Stanford, and UVM). In order to evaluate the logistic and financial feasibility of our multi-institution protocol prior to expanding to our proposed full-scale study, we are conducting a pilot study of 11 high-risk DCIS specimens.
**Results:** The 11 pilot specimens have been successfully sent and received by each institution. H&E images from the sectioned specimens have been uploaded to the NASA Jet Propulsion Lab (JPL) cloud-based platform and shared for pathologic annotation among institutions. mIF of the pilot cohort has been completed, but interpretation of associations between tumor subtype and immune cell infiltrate is limited by the small sample size. Whole exome DNA sequencing, SMART-3SEQ RNA sequencing, and stromal profiling of the pilot cohort are each ongoing. We anticipate being able to provide full results from each profiling modality performed from the pilot cohort, as well as results from an expanded cohort of 40 additional specimens, by December 2020.
**Conclusions:** We have successfully shown that a multi-institution collaboration can effectively share pathologic data and conduct data analyses using a variety of tumor profiling modalities. We anticipate that data from our expanded cohort will allow us to differentiate the underlying biology of high-risk DCIS from invasive breast cancer, identifying mechanistic opportunities for future intervention.

References:[1] Narod SA et al (2015). Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma in Situ. *JAMAOncol.* 1(7): 888-96.

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Feasibility of monitoring symptoms during endocrine therapy with patient reported outcomes collected via smart phone app

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**Background:** Despite known benefits in reducing breast cancer (BC) recurrence and death, up to 50% of patients discontinue endocrine therapy (ET) early. Symptoms are often cited as a reason for early ET discontinuation (DC). The symptom burden during ET captured by patient reported outcomes (PRO) exceeds that captured by clinicians. **Methods:** We initiated a single arm pilot trial evaluating symptom monitoring during ET with PRO collected via smart phone app. Eligible patients are women starting ET for stage 0-III BC. Participants receive text message reminders to complete surveys at baseline (BL), 1, 3, 6 and 12 months (mo). Participants who do not complete 2 sequential surveys may opt out of further surveys. Surveys include PROMIS measures for anxiety, depression, fatigue and the vaginal discomfort domain of sexual function plus PRO-CTCAE measures for concentration, memory, hot flashes, joint pain and vaginal dryness. PROMIS measures are scored by T-score look up tables. PRO-CTCAE responses are reported on a 5 point scale (0-4). Severe or worsening scores trigger email alerts to clinicians as follows: T-scores ≥70 or ≥5 points worse than BL for anxiety, depression, and fatigue; T-score ≥65 or ≥5 points worse than BL for sexual function; scores ≥3 or ≥2 points worse than BL on PRO-CTCAE measures. Recommended management pathways are provided to clinicians upon alert acknowledgement. The primary endpoint is feasibility, with success defined as ≥65% of participants completing the BL survey and ≥65% of participants completing ≥1 follow-up (FU) survey during the first 6 mo of ET. Secondary endpoints include patient-reported symptoms and pathway-concordant symptom management based on chart review. We report here descriptive statistics of the observed data to date and multivariate logistic regression analysis of factors associated with BL survey completion. **Results:** From Feb 2019 to May 2020, 213 of 250 planned participants enrolled. Median FU is 5.7 mo. Mean age is 58.3 years (SD 11.7). 154 (72.3%) participants are white (W) and 32 (15%) are black (B). 189 (88.7%) participants have stage I-II BC. Prior to initiating ET, 82 (39%) had mastectomy, 75 (35.2%) had chemotherapy and 135 (63.4%) had radiation. 138 (64.8%) initiated an aromatase inhibitor and 72 (33.8%) initiated tamoxifen. BL survey completion rate is 73.7% (95% confidence interval (CI) 67.3-79.5%). To date, 69.3% (95% CI 60.5-77.2%) of participants completed ≥1 FU survey during the first 6 mo of ET. 25.2% of participants opted out of participation within 6 mo. On multivariate analysis, race was associated with BL survey completion. By race, BL survey completion rate was: 77.9% (W) and 62.5% (B). Mean scores on PROMIS depression, anxiety, fatigue, and sexual function measures at BL, 1 mo, and 3 mo were +/- 0.5 SD of population means. Compared to BL, mean PRO-CTCAE scores for joint pain severity and hot flash frequency worsened at 1 and 3 mo and mean PRO-CTCAE score for vaginal dryness severity worsened at 3 mo ($p<0.05$). 28% of participants had alerts at BL. Most common BL alerts were joint pain and hot flashes. To date, 79.7% of participants had ≥1 alert on a FU survey. Most common FU alerts were joint pain, hot flashes and fatigue. Median number of alerts per participant per FU survey is 1 (range 0-5). To date, clinicians acknowledged 29.8% of alerts within 7 days and made pathway-concordant management recommendations within 30 days for 39.4% of alerts. **Conclusion:** Monitoring symptoms during ET using PRO collected via smart phone app is feasible. Symptoms are common during ET. Updated data, including factors associated with survey completion, clinician response to alerts and the association between PRO scores and early ET DC, will be reported at the conference. These data will be used to design a randomized trial to evaluate symptom monitoring via smart phone app to reduce early ET DC.

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# Immunological analysis of the combination therapy of nivolumab, paclitaxel and bevacizumab in patients with HER2-negative MBC in NEWBEAT trial (WJOG9917BTR)

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**Background:** Synergistic antitumor effect of combined anti-PD-1 antibody and anti-VEGF agent has been expected, based on previous preclinical data. We have conducted NEWBEAT trial to evaluate efficacy of triple combination regimen of nivolumab + paclitaxel + bevacizumab in patients (pts)with HR+ HER2- MBC or metastatic TNBC, and clinical results were presented in SABCS 2019. A biomarker study (WJOG9917BTR) was conducted to evaluate the VEGF and immune status of these patients. **Methods:** HER2-negative breast cancer patients in the NEWBEAT trial were enrolled. To explore the biomarkers for the triple combination treatment, immune status and its dynamics were evaluated with multicolor flowcytometry, multiplex ELISA in peripheral blood before and after treatment. **Results:** Among the 57 patients who were enrolled to the NEWBEAT trial, 50 patients were registered to the biomarker study. The expression of Ki67 and inducible T-cell co-stimulator (ICOS) on T cells increased after treatment, indicating induction of the T cell proliferation and activation. In responder (defined as patients with progression-free survival longer than 1 year, n = 30), the number of naïve CD4+ T cells at pretreatment were higher and effector memory CD4+ T cells were lower than non-responder. On the other hand, CD86+ myeloid DC at pretreatment were lower in non-responder pts. The median concentration of VEGF-A in serum before treatment was 116.065 pg/ml (range: 0-740.23) and decreased below 37 pg/ml at day 8 after treatment. Although serum VEGF-A level is inversely correlated with clinical outcome of pts with anti-PD-1 antibody in previous reports, in this trial VEGF-A high subgroup had better objective response than VEGF-A low subgroup, suggesting that blockade of VEGF by bevacizumab may overcome immunosuppression via VEGF signaling. Interestingly, in recurrent pts , the number of VEGFR-2+ CD4+ T cells / Monocyte were higher, and PD-L1+ CD4+ T cells / Monocyte / myeloid Dendritic Cell tended to be higher than in de novo stage IV pts. These results suggested that immune status of recurrent pts were more immunosuppressive than de novo stage IV pts, and that it might be more effective by the combination therapy to block the VEGF and PD-1 pathways. Moreover, the changes of immune status and dynamics on CD8+ T cells were not observed, suggesting that the therapeutic strategy of breast cancer might require the re-activation of CD8+ effector T cells through the stimulation of antigen-presenting cells followed by modification of CD4+ helper T cells.**Conclusions:** Our analysis showed the different immune status depending stage, subtype and response in advanced breast cancer pts. The dynamic decrease of serum VEGF-A concentration and high expression of VEGFR-1 or VEGFR-2 in the immune suppressive cells in advanced breast cancer pts suggested that combination treatment with bevacizumab might clinically overcome the immune suppression via inhibition of VEGF-A. (UMIN000029590)

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Does breast cancer subtype impact margin status in patients undergoing partial mastectomy?

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BACKGROUND: It is known that breast cancer subtype (e.g., luminal vs. triple negative (TN)) can affect response to systemic therapy and prognosis; however, it is less well-understood whether these subtypes affect margin status and should therefore alter surgical management. METHODS: Data from two randomized trials evaluating cavity shave margins (CSM) on margin status in patients undergoing partial mastectomy (PM) were used for this analysis. The data were restricted to patients who had invasive carcinoma present in the PM specimen, and in whom data for all three receptors (ER, PR and HER-2) were known. Patients were classified as luminal if they were ER and/or PR+, HER-2 enriched if they were ER and PR negative but HER-2 positive, and TN if they were negative for all three receptors. We evaluated the impact of subtype on the margin status at the time the surgeon had completed their standard PM, prior to randomization to CSM vs. no CSM. Non-parametric statistical analyses were performed using SPSS Version 26. RESULTS: 350 patients were included in this cohort for analysis. The median patient age was 64 (range; 32-94 years) and the median invasive tumor size was 1.2 cm (range; 0.6-8.0 cm). 326 (93.1%) were luminal type, 22 (6.3%) were triple negative, and 2 (0.6%) were HER-2 enriched. Subtype was significantly correlated with race (black patients were more likely to have TN disease than white patients, 22.2% vs. 3.8%, p=0.001), palpability (TN tumors were more likely to be palpable than luminal cancers 54.5% vs. 29.8%, p=0.007) and grade (78.9% of TN cancers were high grade vs. 13.5% of luminal cancers p<0.001). Subtype did not correlate with Hispanic ethnicity, node positivity, nor lymphovascular invasion (p>0.05 for all). While patients with TN and HER-2 enriched tumors were more likely to receive neoadjuvant therapy, this did not reach statistical significance (p=0.117). Surgeons were no more likely to take selective margins on the basis of molecular subtype (p=0.413). In this cohort, the overall positive margin rate was 33.7%. This did not vary based on molecular subtype (positive margin rate: 33.7% for patients with luminal tumors vs. 36.4% for those with TN tumors, p=0.425). On multivariate regression controlling for molecular subtype, race, grade and palpability, the only factor which predicted positive margin status was grade (p=0.005), with high grade tumors being significantly more likely to have a positive margin than low grade tumors, independent of other factors (OR=3.503, 95% CI: 1.638-7.494, p=0.001). CONCLUSION: While molecular subtype correlates with race, tumor grade and palpability, it does not predict margin status. Therefore, molecular subtype should not, independent of other factors, influence surgical decision-making.

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Distinct tumor microenvironments of breast cancer bone metastases in pre- and post-menopausal patients

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Breast cancer (BC) patient prognosis has improved over the past 2 decades with a 99% 5 year survival rate for localized BC, yet metastatic BC continues to cause high mortality with a 5 year survival rate of 27%. Recent advances have been made in the treatment of primary BC, providing an opportunity to apply this positive momentum towards treating metastatic disease. Approximately 70% of BC metastases occur in the bone, with the majority of patients retaining estrogen receptor positive (ER+) disease. The BC tumor microenvironment (TME) in bone exhibits an osteolytic bone pathology of bone destruction and is composed of primarily four cellular groups including the cancer, immune, vascular and bone cells. These cellular constituents are uniquely responsive to estradiol (E2) and exhibit unique TMEs dependent on menopause status, when circulating E2 is lost. Both menopause and BC endocrine therapies induce an E2-deprived post-menopausal state in patients. However, studying the distinctions of pre- and post-menopausal BC patient TMEs is still necessary to understand how natural menopause status impacts non-treatment naïve ER+ BC that is already in a therapy induced menopausal state. In particular the full extent of the unique phenotypes harbored by pre- versus post-menopausal ER+ BC tumor induced bone disease (TIBD) remains unknown, and elucidation of these difference may identify novel mechanisms of TIBD.
We investigated a cohort of demineralized formalin-fixed and paraffin-embedded (FFPE) pre- and post-menopausal lytic bone metastasis biopsies from non-treatment naïve ER+ BC patients. We utilized immunohistochemistry (IHC), NanoString nCounter gene expression panels and GeoMx Digital Spatial Profiling (DSP) to observe distinct TMEs in our archival biopsy cohort. IHC staining of pre- and post-menopausal samples displayed alterations to immune cell infiltration and composition. Differential gene expression analysis revealed enrichment of myeloid function in pre-menopausal patients compared to post-menopausal patients. Alterations to immune signaling pathways and cell profiles were also exhibited in pre-menopausal patients compared to post-menopausal patients. DSP analysis presented changes in both the tumor and microenvironment, and unique immune cell infiltration with checkpoint proteins in both pre-menopausal and post-menopausal ER+ BC bone metastases. The identification of these targetable markers unique to pre- and post-menopausal TIBD could provide new therapeutic strategies for ER+ BC patients with bone lesions. Thus, we propose that bone biopsies could be performed to guide selection for metastatic BC patients into appropriate therapeutic interventions, with pre- and post-menopausal patients receiving tailored treatments based on their distinct protein and RNA expression of available therapies. This personalized approach to treating metastatic disease could enhance patient quality of life and survival.

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# Pathogenic variants in hereditary cancer syndrome genes are prevalent among breast cancer patients not meeting various ex-U.S. genetic testing guidelines

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**Background:**Therapeutic and risk management options have expanded for patients harboring pathogenic variants (PVs) in cancer predisposition genes. Historically, testing costs and clinical implementation challenges led to restrictive testing guidelines in many countries. Increasing evidence demonstrates that narrow criteria will miss patients with potentially actionable PVs and broader testing is a cost-effective way to identify patients (and their family members) with PVs. Here we assess the efficacy of multiple international testing guidelines in identifying breast cancer patients with clinically actionable PVs.
**Methods:**We reanalyzed a prospective cohort of breast cancer (BC) patients referred by their providers for multigene germline genetic testing (PMID: 30526229) 50% of which met U.S. testing criteria, by design. The is a cohort of U.S.-based patients, primarily Caucasian of Northern European ancestry. We applied testing guidelines from Australia, U.K. and 2 Canadian provinces (Ontario, British Columbia) to this cohort to determine their efficacy in selecting patients with PVs. These countries were chosen because of their single-payer healthcare model and their similar ethnic distribution to the U.S. Analysis focused on yield of PVs in high risk (>4x risk compared to general population) breast/ovarian (BC/OV) cancer genes.
**Results**:Table 1 displays the distribution of in criteria (IC) vs. out of criteria (OOC) patients by country/testing criteria. Over 75% of patients in each country/province analyzed were OOC. Rates of PVs were similar between IC and OOC patients across countries. Existing Canadian, Australian and U.K. criteria missed up to 30% of patients with high risk PVs (Table 1). The majority (>80%) of PVs in OOC patients were in genes with published management guidelines.
**Conclusions:**In our cohort, select ex-U.S. testing criteria identified <30% of patients with PVs, while almost half of OOC patients harbored clinically relevant, potentially actionable mutations. These data suggest expanding certain international testing criteria would allow better identification and improved management for many patients diagnosed with breast cancer across the globe, and their families via cascade testing. This study also suggests additional research is needed to evaluate the efficacy of additional provincial and international criteria, including cost-effectiveness analyses, to inform future guideline updates.

| | | **Overall** | | | | | **In criteria** | **Out of criteria** |
|---|---|---|---|---|---|---|---|---|
| Country/providence | Guideline | Total n of cohort | IC (% of total cohort) | OOC (% of total cohort) | Total PV IC (% of IC cohort) | Total PV OOC (% of OOC cohort) | High risk^ PVs (% of total PVs) | High risk^ PVs (% of total PVs) |
| U.S. | NCCN | 953 | 473 (49.6) | 480 (50.4) | 43 (9.1) | 40 (8.3) | 22 (26.5) | 8 (9.6) |
| Ontario | MOHLTC | 953 | 210 (22.0) | 743 (78.0) | 18 (8.6) | 65 (8.7) | 5 (6.0) | 25 (30.1) |
| B.C. | BCHCP | 953 | 203 (21.3) | 750 (78.7) | 24 (11.8) | 59 (7.9) | 9 (10.8) | 19 (22.9) |
| Australia | eviQ | 953 | 180 (18.9) | 773 (81.1) | 19 (10.6) | 64 (8.3) | 12 (14.5) | 18 (21.7) |
| U.K. | NICE* | 826** | 127 (14.7) | 736 (85.3) | 11 (8.7) | 64 (8.7) | 6 (7.2) | 22 (26.5) |

Table 1. Findings in IC vs. OOC patients
US, United States; B.C., British Columbia; UK, United KingdomNCCN, National Comprehensive Cancer Network v. 2017MOHLTC, Ministry of Health and Long Term Care BCHCP, BC Provincial Health Services Authority Hereditary Cancer Program NICE, National Institute for Health Care Excellence *testing eligibility requires >10% BRCA mutation detection rate, typically assessed by BOADICEA model in the UK but for this cohort risk estimates were only available via BRCAPro ** BRCAPro scores were not available for the full cohort ^Includes *BRCA1, BRCA2, PALB2, TP53, RAD51C, RAD51D, MSH6*

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Matrin3 inhibits breast cancer growth by suppressing microtubule nucleation protein MZT2B

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Despite improvement in overall survival, many patients with breast cancers still succumb to this disease. Identification of new biomarkers and safe therapeutic targets are urgently needed to improve the overall clinical outcome of breast cancer patients. Our studies discovered a RNA binding protein, MATRIN3 (MATR3), as a novel tumor suppressor. MATR3 is expressed at a significantly reduced levels in breast tumors. MATR3 inhibited short and long-term viability as well as migration and invasion of breast cancer cells. Further, MATR3 overexpression suppressed tumor growth, while its depletion induced tumor growth in orthotopic mouse tumor models. RNA seq and RNA immunoprecipitation analyses revealed that MATR3 binds and directly regulates the expression of several microtubule-associated proteins. Mechanistic studies identified MZT2B, a mitotic spindle organizing protein as a down stream effector of MATR3. MZT2B knockdown or knockout using CRISPR-CAS9 resulted in significantly decreased short and long term viability as well as reduced migration and invasion of breast cancer cells. Notably, MZT2B overexpression rescued the inhibitory effect of MATR3 overexpression on breast cancer growth. Furthermore, MATR3 overexpression downregulated expression of key microtubule nucleation protein complex including γ-tubulin and γ-tubulin ring complex protein (TUBGCP). Our data suggest that MATR3 inhibits breast cancer growth and progression by inhibiting MZT2B and consequently microtubule nucleation in breast cancers.

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Efficacy and safety of palbociclib (PAL) in patients (pts) with estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) with preexisting conditions: A post hoc analysis of PALOMA-2

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**Background:** In the PALOMA-2 trial, PAL + letrozole (LET) significantly prolonged progression-free survival (PFS) vs placebo (PBO) + LET in pts with ER+/HER2– ABC. This post hoc analysis assessed efficacy and safety of PAL + LET in pts from PALOMA-2 with baseline preexisting conditions grouped by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC). **Methods:** Postmenopausal pts with ER+/HER2– ABC received PAL (125 mg/d, 3/1 schedule) + LET (2.5 mg/d, continuous) or PBO + LET. Pts were grouped by the following MedDRA SOC preexisting conditions: Gastrointestinal, Musculoskeletal, Metabolism, and Vascular/Cardiac. Baseline characteristics, PFS, and safety were assessed. **Results:** At baseline, 41.4% of pts had preexisting gastrointestinal disorders, 58.6% musculoskeletal disorders, 38.9% metabolism disorders, and 57.4% vascular/cardiac disorders. Baseline characteristics were similar between treatment arms within each subgroup and also between subgroups. Within each subgroup, ≥40% of pts also had ≥1 of the other coexisting conditions. Median PFS (mPFS) was significantly longer with PAL + LET vs PBO + LET regardless of preexisting condition (**Table**). In general, adverse events (AEs) were more frequent with PAL + LET in all subgroups; neutropenia was most common. Within each treatment arm, AEs and dose modifications due to AEs were similar regardless of preexisting condition. **Conclusion:** PAL + LET showed prolonged PFS and a consistent safety profile regardless of baseline preexisting condition in pts with ER+/HER2– ABC. **Clinical trial identification:** Pfizer Inc (NCT01740427)

**Table**

| Preexisting Condition | PAL + LET | | PBO + LET | | PAL + LET vs PBO + LET | |
|---|---|---|---|---|---|---|
| | n | mPFS (95% CI) | n | mPFS (95% CI) | HR (95% CI) | *P* Value |
| Gastrointestinal | 176 | 27.6 (17.5-33.1) | 100 | 13.6 (11.0-18.5) | 0.57 (0.42-0.78) | <0.001 |
| Musculoskeletal | 252 | 27.6 (21.4-33.1) | 138 | 16.3 (11.2-19.1) | 0.53 (0.41-0.69) | <0.001 |
| Metabolism | 186 | 27.6 (19.3-30.6) | 73 | 13.8 (8.3-27.4) | 0.62 (0.44-0.87) | 0.003 |
| Vascular/Cardiac | 254 | 30.4 (25.1-36.2) | 128 | 14.5 (11.0-18.5) | 0.51 (0.39-0.66) | <0.001 |

**Publication Number:** PS16-15

The influence of mechanical and chemical insult on the integrity of vascular endothelial cells and associated impact on epithelial protein lost in neoplasm (EPLIN) and potential partner protein network

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Background. Vascular endothelium is the frontline structure in the body facing constant high velocity flow and external harmful agents absorbed within the circulation. It is not fully understood how endothelial cells respond to such external insults. We have previously shown that a cytoskeleton binding protein, Epithelial Protein Lost in Neoplasm (EPLIN) is an essential protein in regulating the migration and adhesiveness of vascular endothelial cells and in doing so, contributing to the normal process of angiogenesis and its responsiveness to complex environments, thereby influencing tumour development (1). The portraited role of EPLIN in the intracellular process has led to the hypothesis that EPLIN has an important role to play during the response of endothelial cells to external hostile factors by providing a stable and coordinated mechanism. The current study explores the influence of EPLIN and its associated protein network in the endothelial cell response to physical injury and extrinsic carcinogenic agents.
Method. Human primary cultured vascular endothelial cells and immortalised endothelial cells were used as cell models. The cells were subject to either physical wounding injuries or exposure to a carcinogenic chemical, namely diethystibestrol (DIET). Gene expression patterns from the endothelial cells were subject to analysis by gene microarray. The cellular response of endothelial cells was explored using proliferation and migration assays. The potential paracrine impact on cancer cells in close proximity to the endothelial cells was tested using endothelial cell conditioned media.
Results. Both mechanical injury and chemical challenge (at non-toxic concentration range) resulted in mild yet statistically insignificant reductions in EPLIN expression in both endothelial models. A number of the proposed EPLIN network partners in immortalised endothelial cells were affected by mechanic injuries, most notably CTNNA1, CTNNAL1, CTNNA3, CTNNB1 and the caveolins. Chemical injury resulted in more drastic reductions of caveolin and its variant2 (CAV2) ($p<0.001$ for both). In the cell model, neither mechanical nor chemical insults caused significant changes in the regulatory elements of the network, namely signal-induced proliferation-associated gene 1 (SIPA1) nor its variants. Likewise, other network members closely linked to the cytoskeleton, including gamma-catenin and paxillin, were also unaffected. A similar response was seen with primary culture endothelial cells. Endothelial cells, following mechanical injury had a stimulatory effect on the growth of breast cancer cells (MDA MB-231 and BT20) due largely to a rapid rise in G2 and S phase of cell cycle and migration of breast cancer cells, in a co-culture assay. However, the effects of endothelial cells treated with DIET elicited more profound effects on the migration of cancer cells.
Discussion. Our results demonstrate that vascular endothelial cells are sensitive to the external mechanical and harmful chemical damages. Such damage appears to influence breast cancer cells in a paracrine fashion. Similarly, such damage resulted in altered expression of a range of cell adhesion molecules but did not significantly influence EPLIN. EPLIN, a central element of this network may be involved in co-ordinating this response though further study is needed.
Reference1 Sanders AJ, Ye L, Mason MD, et al. The impact of EPLINα (Epithelial protein lost in neoplasm) on endothelial cells, angiogenesis and tumorigenesis. Angiogenesis. 2010 Dec;13(4):317-26.

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Pharmacokinetics of H3B-6545 in patients with locally advanced or metastatic estrogen receptor-positive HER2 negative breast cancer (ER+ and HER2- BC)

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**RATIONALE:** Addition of CDK 4/6 inhibitors to endocrine therapy has become standard for patients (pts) with ER+ and HER2- BC with improvements in overall survival. However, acquired resistance to front-line therapy is inevitable, and response to later-line therapy is poor. H3B-6545 is a selective, orally available, small molecule covalent antagonist of the estrogen receptor (ERα). H3B-6545 binds covalently to a cysteine residue at position 530 of both wild-type and the constitutively active mutant ERα proteins. H3B-6545 demonstrated significant antitumor activity in multiple PDX breast cancer models, including those with mutated *ESR1* (the gene encoding ERα). A phase I-II study was conducted to explore the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics, and efficacy of this agent in advanced ER+ and Her2- breast cancer pts (NCT03250676). **METHODS:** PK samples in phase I were obtained at day 1 and day 15 of cycle 1 (Predose, 0.5, 1, 2, 4, 6, 8, 10, and 24 h post dose) and sparse PK samples were collected in the phase II part of the trial. For pts enrolled in the food effect sub-study of phase II, plasma samples were collected during cycle 1 on day 15 and day 22 (Predose, 0.5, 1, 2, 4, 6, 8, 10, and 24 h post dose). Nonlinear mixed effect model (NONMEM) was applied for development of population PK models to fit H3B-6545 plasma concentration data with NONMEM® version 7.4 software. R was used for data management, visualization and statistical summaries. **RESULTS:** This phase I-II trial enrolled 47 pts in phase I part and 83 pts in the phase II part at the recommended phase II dose of 450 mg QD as of May 15, 2020. The 1180 plasma concentrations of H3B-6545 from a total of 103 pts at doses of 100-600 mg available as of January 15, 2020 were included in this analysis, with the following characteristics [n or (median, min-max) unit]: race (n=91/5/1/6 for White/Black/Asian/others), age (62.5, 31-81) yrs, body weight (79.5, 49-140) Kg, BMI (26.9, 17.6-45.6) Kg/m$^2$, albumin (40, 29-52) g/dL, ALP (88.5, 39-917) IU/L, ALT (28, 10-193) IU/L, AST (36.5, 13-259) IU/L, bilirubin (8.6, 1.7-25.7) µM and creatinine clearance (112, 49.5-389) mL/min. The median number of prior therapy in the metastatic setting was 3 (range: 1 - 10). Out of 103 patients, 32 pts received treatment with a single high-fat meal to test food effect on PK over a randomized crossover design. H3B-6545 plasma concentrations were best described with a one compartment disposition PK model, plus a combined first- and zero-order parallel absorption and lag time. The estimated apparent clearance (CL/F) and volume of distribution (V/F) were 31 L/h and 422 L, respectively, with a typical terminal half-life of about 10 hours. H3B-6545 was absorbed fast, with a typical $t_{max}$ of about 4 hours. A moderate to high variability (40-60%) was identified in major PK parameters (CL/F, V/F, bioavailability [F1]). A high-fat meal increased bioavailability by approximately 45% and prolonged $t_{max}$, roughly from 4 hours to 6 hours post dose. No significant effect was identified from other covariates: age, body weight, race, albumin, AST, ALP, ALT, bilirubin and creatinine clearance. **CONCLUSIONS:** H3B-6545 PK profiles in breast cancer patients were well described by a one-compartment disposition model with no significant effect of demographics, liver and renal function. When administered with a high fat meal, H3B-6545 exposure was modestly increased.

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# The HER2 circulating ratio to define HER2 expressing circulating tumor cells in advanced breast cancer

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**Background** Currently, there are no validated data derived from prospective trials that demonstrate a benefit from anti-HER2 targeted therapy in HER2 negative advanced breast cancer (ABC) patients (pts) bearing HER2 expressing (HER2+) circulating tumor cells (CTCs). Although some retrospective studies suggest that a group of these pts could benefit from a target treatment, a substantial proportion of those will never respond. A better characterization of the HER2+ CTCs could improve the pts selection. We hypothesize that a high correlation between different HER2+ CTCs subgroups and the HER2 status on solid biopsy can predict the likelihood of response of the corresponding subgroup. Here we propose a simple algorithm to identify those HER2+ CTCs subgroups that have demonstrated a higher correlation with HER2+ positivity in the solid biopsy. **Methods** The IRB-approved study retrospectively analyzed blood samples at two different timepoints (before treatment and at the first evaluation) from 110 ABC pts treated at Northwestern University (Chicago, IL) between 2016 and 2019. CTCs were enumerated through CellSearch™ (Menarini Silicon Biosystems, Bologna, Italy), and characterized for HER2 expression using the CellSearch CXC Kit. HER2 expression in CTCs was defined and categorized in 4 different categories (0,1+,2+,3+) as previously reported (Riethdorf et al., 2010). Four different scores were assessed in their ability to predict a HER2 positive disease (based on metastases HER2 status). Score 0 (negative CTCs), Score 1 (1+ CTCs), Score 2 (2+ CTCs), Score 3 (3+ CTCs) and Score 4 (cHER2 ratio, defined as the sum of 2+ CTCs and 3+ CTCs divided by the total number of CTCs). The performance of these 4 different biomarkers was explored longitudinally through the Wilcoxon test. **Results**: Out of 110 pts, 49 showed a CTCs count ≥ 5 (stage IV $_{aggressive}$). Among these pts, Score 0 was associated with a HER2 negative disease with an area under the ROC curve (AUC) of 0.14. No correlation was found between Score 1 and HER2 status (AUC 0.45). A marginally significant association was found in Score 2 and Score 3 (AUC respectively 0.67 and 0.64). A direct correlation was observed between Score 4 and Her2 status (AUC 0.73). The analysis performed on stage IV $_{indolent}$ patients showed a non-significant association among all 4 scores. Significant association was not found among the scores and molecular subtypes, only a numerical increase among HER2+ disease and Score 3 and Score 4 (respectively p=0.06 and p=0.1). The patients were observed longitudinally and a dynamic Score evaluation was performed. No significant changes were found among Score 1 and Score 2 at the two different timepoints (p= 0.35 and p=0.11). Both, Score 0 and Score 4 were significantly decreased among pts at the second timepoint (p=0.0019 and 0.006) **Conclusions** The data highlighted a strong performance of cHER2 ratio (score4) identifying a HER2 positive disease on tissue biopsy, comparable with the known ability of score0 (presence of only HER2 negative CTCs) to predict a HER2 negative tissue biopsy. Furthermore, the cHER2 ratio has proven to be dependent on the treatment administration, allowing to be considered as a predictive biomarker in future study, to gain a prospective validation.

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# Analysis of systemic therapies following progression on frontline CDK4/6-inhibitor therapy

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**Background**: Hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (Her2-) breast cancers represent the majority of metastatic breast cancers (mBC) among women and are often treated with sequential courses of endocrine therapy (ET) prior to the eventual need for chemotherapy (CT). Inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6i) block cell cycle progression and decrease proliferation of breast cancer cells. Currently, there are three available CDK4/6i: palbociclib, ribociclib and abemaciclib. Each has been shown to improve progression-free survival (PFS) when given with ET in the frontline setting, compared to ET alone. After progression on CDK4/6i, no standard of care exists for the next line of systemic therapy, and there are no prospective data to help guide clinical practice. Analysis of real-world data may provide insight into optimal second-line treatment for women who have progressed on CDK4/6i therapy. **Methods**: The nationwide Flatiron Health electronic health record-derived de-identified database was utilized for this analysis. We evaluated patient data collected from 2015-2020 for women with HR+/Her2- mBC who received CDK4/6i as frontline therapy and received a documented second-line systemic therapy. The objectives of this study were to describe what therapies were given as second-line treatment and estimate the real-world PFS (rwPFS) of those therapies. rwPFS was defined as time between initiation of second-line therapy until clinician-recorded progression (or death). Patients (pts) who did not progress or die were considered censored at the end of follow-up or end of second-line therapy. **Results**: A total of 1,210 pts with HR+/Her2- mBC received CDK4/6i with ET in the frontline setting, including 29.1% with de novo metastatic disease. Average age at diagnosis of metastatic disease was 64.4 years (range 28-84). A majority of pts received palbociclib in the frontline setting (88.2%), and 68.8% received an aromatase inhibitor (AI) as the frontline ET partner. 839 pts subsequently received second-line therapy (Table 1). CDK4/6i was continued as part of second-line treatment in 308 (36.7%) pts. 249 (29.7%) pts received CT as second-line treatment. The proportion of pts who continued CDK4/6i increased from years 2015-2020 (p=0.035), and the proportion who received CT decreased over time (p<0.001). Of the 308 pts who received a CKD4/6i in the second-line setting, most received the same CDK4/6i in both lines; however, pts treated with abemaciclib or ribociclib in the first-line setting were more likely to receive a different CDK4/6i than those who started with palbociclib (54.2% and 39.1%, respectively, vs. 22.3%). Among 160 pts who received CDK4/6i with fulvestrant in the second-line setting, 81.2% had previously received an AI in the frontline setting. Unadjusted rwPFS appears to favor those pts who continued the CDK4/6i (rwPFS 11.27 months, 95% CI [8.87, 13.31]), compared to CT (rwPFS 4.73 months, 95% CI [3.88, 5.59]), fulvestrant (rwPFS 3.68 months, 95% CI [2.99, 5.22]), or mammalian target of rapamycin (mTOR) inhibitor-based therapy (rwPFS 4.27 months, 95% CI [3.23, 6.14]) (p<0.001). **Conclusion**: The use of CDK4/6i continuation after frontline progression has increased over time, while the use of CT has decreased. Continuation of CDK4/6i in the second-line setting appears to be the strategy with the greatest rwPFS benefit on unadjusted analysis. Adjusted rwPFS and overall survival will be reported in the future.

TABLE 1. Second-Line Therapy Used. F, fulvestrant; T, tamoxifen

| SECOND-LINE THERAPY | Overall (N=839) |
|---|---|
| AI | 23 (2.7%) |
| CDK4/6i | 4 (0.5%) |
| CDK4/6i + AI | 97 (11.6%) |
| CDK4/6i + F | 160 (19.1%) |
| CDK4/6i + F + AI | 35 (4.2%) |
| CDK4/6i + F + T | 3 (0.4%) |
| CDK4/6i + T | 3 (0.4%) |
| CT | 249 (29.7%) |
| F | 70 (8.3%) |
| F + AI | 14 (1.7%) |
| mTOR | 99 (11.7%) |
| PARP | 4 (0.5%) |
| PI3K | 16 (1.9%) |
| T | 11 (1.3%) |
| Clinical Trial | 51 (6.1%) |

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# Utilizing education to strengthen oncologist' understanding of immunotherapy in triple negative breast cancer

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**Background:**Immunotherapy was first introduced into the treatment of triple negative breast cancer with the approval of nab-paclitaxel + atezolizumab in patients with metastatic PD-L1-positive disease. Continued research sheds light on the utility of other immuontherapies in the metastatic setting as well as a potential role for immunotherapy in neoadjuvant disease. Given the factors impacting patient eligibility and the rationale for further exploring immunotherapy in novel settings, education can help ensure that oncologists are well-informed about available clinical trial data and ongoing research to optimize the use of immunotherapy in this subtype of breast cancer. The goal of this study was to determine if participation in an educational activity can improve the knowledge and competency of oncologists on the application of checkpoint inhibitors in the treatment of triple negative breast cancer.**Methods:** An online continuing education (CME) activity consisted of a 30-minute video discussion with synchronized slides between 2 panelists about the rationale and ongoing clinical trials exploring data for immunotherapy in triple negative breast cancer. Educational effect was assessed using a repeated pairs pre-assessment/post-assessment study design and compared of content-based pre- and post-assessment responses. A chi-square test was used to identify statistical differences between pre- and post-assessment responses. *P* values were calculated and those < 0.05 were considered statistically significant. Data from oncologist participants in the educational activity were collected between 3/22/20 through 5/19/20. **Results:**Participation in education resulted in statistically significant improvement and a considerable educational effect for oncologists (n=121; p <0.0001). 61% of oncologists reported practicing in a community setting with 67% treating patients beyond breast cancer alone. Overall, oncologists demonstrated a 20% increase in confidence in identifying the role and stage in triple negative breast cancer therapy for the use of immune checkpoint inhibitors. Improvements in knowledge were observed in: •Understanding the biological rationale for using immune checkpoint inhibitors in patients with triple negative breast cancer (69% vs. 83%; p <0.05) •Knowing the ongoing clinical trials that may impact the use of immune checkpoint inhibitors across the continuum of TNBC (69% vs. 87%; p <0.01) •Emerging clinical trial data on the use of immune checkpoint inhibitors utilizing pathologic complete response as an endpoint of efficacy in neoadjuvant disease (73% vs. 82%) **Conclusions:** This online, interactive, CME-certified educational activity resulted in significant overall gains in oncologist knowledge regarding the existing and emerging evidence for immunotherapy in triple negative breast cancer. These results demonstrate the effectiveness of on-demand education but also highlight the effectiveness in reaching community-based practitioners and also practitioners that do not specialize in breast cancer alone. **Grantors:**
This educational initiative was supported through educational grants from Bristol Myers Squibb and Merck & Co., Inc.

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Targeting the PELP1 axis for treating ESR1 mutant driven breast cancer

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**Background**: Mutations in *ESR1* genes (30-40% frequency) play an important role in acquired endocrine therapy resistance and metastases. The most commonly observed are two *ESR1* LBD mutations, *D538G* and*Y537S*. These mutant ERα (MT) proteins have high constitutive transcriptional activity leading to therapy resistance. Furthermore, the ability of the constitutively active mutants to interact with coregulators is associated with the promotion of tumor growth. Proline, glutamic acid-, and leucine-rich protein 1 (PELP1), an oncogenic coregulator of ERα, plays a critical role in ERα signaling, and its dysregulated expression is a prognostic indicator for poorer breast cancer (BCa) survival. The **objective** of this study was to test the utility of Small Molecule Inhibitor of PELP1 (SMIP34) for treating ESR1 mutant (MT-ER) driven BCa. **Methods:** Four BCa models that express either ESR1 mutation D538G or Y537S and their respective wild-typeERα (WT-ER) controls were used to test the utility of targeting the PELP1 axis using PELP1-specific shRNA orSMIP34. Celltiter Glo, MTT, colony formation, and Boyden chamber invasion assays were used to test the efficacy of SMIP34. Western blot, RNA-Seq, and reporter gene assays were utilized to uncover the mechanistic insights. Pre-clinical evaluation was performed using MT-ER expressing xenograft explant (XDEX) and patient-derived explant (PDEX) assays. **Results:** BCa model cells expressing MT-ER showed increased cell proliferation, whilst PELP1 knock-down significantly reduced their proliferation. Immunoprecipitation results confirmed that PELP1 constitutively associates with MT-ER. PELP1 knock-down or treatment with PELP1 inhibitor SMIP34 significantly reduced proliferation of the four MT-ER models with an IC50 of 3-5μM. PELP1 knock-down or SMIP34 treatment significantly reduced the constitutive ERE reporter activity observed in MT-ER models. RTqPCR assays confirmed the downregulation of MT-ER target genes in PELP1 knock-down and SMIP34 treated cells. Furthermore, PELP1 knock-down or SMIP34 treatment significantly reduced the invasiveness and colony formation of MT-ER BCa models. Mechanistic studies using Western blot revealed that SMIP34 contributes to PELP1 degradation by its direct binding to PELP1. SMIP34 significantly decreased proliferation of MT-ER BCa cells in XDEX andPDEX assays, as measured by Ki67 staining. **Conclusion:** Our results suggest that PELP1 associates with MT-ER and targeting the PELP1 axis with SMIP34will have therapeutic utility in treating MT-ER driven BCa. Supported by CPRIT Predoctoral Fellowship CPRIT RTA; RP170345 (K.A. Altwegg) and VA grant I01BX004545(R.K.V)

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# Real-world clinical-genomic data identifies the ESR1 clonal and subclonal circulating tumor DNA (ctDNA) landscape and provides insight into clinical outcomes

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**Introduction:** *ESR1* mutations are biological indicators of endocrine resistance observed in 20-30% of patients with metastatic breast cancer treated with aromatase inhibitor (AI) therapy. A number of *ESR1* resistance mutations have been characterized, including single nucleotide variants in codons 380, 463, 536, 537, and 538. However, *ESR1* resistance mutations have not been characterized using large-scale, real-world population studies. Here we describe the subclonal landscape of *ESR1* resistance in a real-world dataset of patients with advanced breast cancer treated with anti-estrogen therapy.

**Methods:** The GuardantINFORM™ clinical-genomic database links circulating tumor DNA (ctDNA) results (Guardant360®, Guardant Health) with de-identified aggregated clinical encounters including diagnosis, treatments, and real-world outcomes. GuardantINFORM was queried for adult patients, with a confirmed diagnosis of primary breast cancer, with at least one claim for endocrine therapy (tamoxifen and/or an AI), and at least one Guardant360 test completed following AI treatment. Data was reviewed retrospectively to determine the landscape of *ESR1* alterations identified post AI-treatment.

**Results**: 6,541 patients met inclusion criteria. The patient cohort was predominantly female (99%) with a median age at first anti-estrogen therapy of 59.7 years (range 25 - 91 years). 2,044 patients were positive for at least one *ESR1* mutation (31%) on the post AI treatment Guardant360 test. 1,943 patients (95%) had an *ESR1* mutation identified that is known to confer resistance to AI therapy while the remainder had ESR1 mutations of unknown clinical significance. The majority of patients (65.8%) had multiple *ESR1* mutations one of which was always a canonical *ESR1* resistance mutation (Table 1). Preliminary outcome analysis showed no difference in real-world overall survival in those with a canonical *ESR1* mutation with or without an additional co-occurring subclonal ESR1 mutation. Additional analyses to understand the impact of co-occurring *ESR1* alterations and time to therapy resistance is ongoing.

Table 1: Spectrum of ESR1 variants observed in eligible patients in GuardantINFORM

| *ESR1* mutation | Total prevalence in *ESR1* positive patients | Prevalence as sole *ESR1* variant | Prevalence with additional *ESR1* variant(s) |
|---|---|---|---|
| D538G | 53.8% | 13.0% | 40.8% |
| Y537S | 38.2% | 8.8% | 29.4% |
| Y537N | 18.4% | 1.6% | 16.8% |
| E380Q | 13.0% | 2.6% | 10.4% |
| L536H | 5.0% | 0.4% | 4.6% |
| S463P | 1.4% | 0.3% | 1.1% |
| Other | 29.5% | 25.6% | 3.9% |

**Conclusions**: Uniquely well-characterized clinical-genomic data in a proprietary dataset identified that approximately 30% of patients with advanced breast cancer had somatic *ESR1* mutations following AI therapy, consistent with previously published data. The majority of patients had multiple subclonal *ESR1* resistance mutations following AI treatment, always with a canonical resistance mutation, which did not impact real-world overall survival. Additional work is needed to explore the contribution of these *ESR1* subclones to the time to clinical resistance.

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N-RAS as a marker for DCIS progression

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**Background:** Ductal carcinoma *in situ* (DCIS) is a key premalignant stage. Approximately 50% of the DCIS cases will advance to invasive ductal carcinoma (IDC); however, they are usually universally treated leading to overtreatment. While earlier premalignant breast lesions, such as atypical ductal hyperplasia, are nearly all luminal and positive for estrogen receptor α ($ER^+$), up to 8% DCIS are basal-like, which is more aggressive. We have previously shown that N-Ras, which is highly expressed selectively in the basal-like subtype, can promote the growth and transforming activity of basal-like breast cancer (PMID 26166574). In this study we investigate whether *NRAS* expression at DCIS can promote basal-like properties and the progression to invasiveness.
**Methods:** *NRAS* mRNA levels in normal, DCIS, and IDC patient-derived microarray databases and tissue microarrays (TMAs) were compared using student t-test. Correlation between *NRAS* mRNA levels and basal-like properties was assessed by Pearson Correlation. ER protein levels were assessed by IHC. *NRAS* was expressed in a luminal DCIS cell line model SUM225PE cells and the resulting cells were injected intraductally into mice to assess expression of basal-like markers and invasiveness *in vivo*. Conversely, *NRAS* expression was silenced in a DCIS-like basal-like cell line SUM102 and increased expression of luminal markers was assessed by RNA-seq and western blot.
**Results:** In microarray databases, DCIS samples with higher *NRAS* mRNA levels are enriched with basal-like gene expression signature; furthermore, *NRAS* mRNA levels appear to increase progressively from normal to DICS and from DCIS to IDC. A similar correlation between high *NRAS* levels and invasiveness and high Ki67 levels in TMAs was observed by RNA FISH. High levels of *NRAS* mRNAs also correlated with low ER levels.
**Conclusions:** How to identify the subset of DCIS cases that will become invasive is critical for addressing the current problem of overtreatment. Our data support the hypothesis that high *N-RAS* levels in DCIS mark invasiveness, by presumably inducing basal-like more aggressive tumor activities. On-going studies will further delineate whether N-Ras is also responsible for driving DCIS to the invasive state.

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# Plinabulin and pegfilgrastim (Plin+Peg) versus peg monotherapy (Peg) after TAC: A comparison of efficacy, safety, relative dose intensity (RDI) and bone pain

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**Introduction:**Prevention of Chemotherapy Induced Neutropenia (CIN) through primary or secondary prophylaxis is indicated in breast cancer (BC) chemotherapy (chemo) which is administered with curative intent. Granulocyte colony stimulating factors (G-CSFs), including Peg are standard of care in this context. In typical every three-week chemo regimens with primary G-CSF prophylaxis, absolute neutrophil count (ANC) nadir occur approximately day (D) 7, which reduces but does not eliminate febrile neutropenia risk in the first week. However, plinabulin (Plin), a novel non-G-CSF agent, protects against the nadir and CIN in the 1$^{st}$ week after chemo (Blayney ASCO 2019). These findings provided the rationale to combine Plin with Peg after chemo with a high febrile neutropenia risk. Both Plin and Peg act on the neutrophil precursor. Both agents mobilize bone marrow-derived CD34+ progenitor stem cells (Blayney ASH 2018). Plin has also anti-cancer efficacy in an animal BC model (Bertelsen, Int J Rad Biol 2011). Here we summarize the efficacy and safety data with combining Peg with Plin in potentially curable BC patients treated with TAC.
**Methods**: In the randomized phase 2 portion of Study 106 (NCT0329457), BC patients were treated with TAC (docetaxel 75, doxorubicin 50 and cyclophosphamide 500 mg/m$^2$) and either 6 mg Peg alone (Peg6; n=22), or Peg 6mg+Plin 20 mg/m2 (Plin+Peg; n=16). Grade (Gr) 3/4 neutropenia frequency, duration of Gr 3 and 4 neutropenia (DSMN), and neutrophil nadir was calculated from absolute neutrophil counts obtained on days 0, 1, 3, 6, 7, 8, 9, 10, 11, 12, 13, 15. Bone pain was assessed by a validated questionnaire. Percentage of pts with RDI <85% and adverse event rate (Grades 1-5) was calculated.
**Results:** Gr 3 or 4 neutropenia with Plin/Peg vs Peg was 50% vs 81.1% (p<0.04). Median DSMN with Plin/Peg vs Peg was 0.5 day vs 1 day. ANC nadir [mean (95% CI)] with Plin/Peg vs Peg was 1.15 (0.66;1.65) vs 0.80 (0.37;1.22).

| RDI<85% | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 |
|---|---|---|---|---|
| Peg | 0 % | 13.6 % | 19.1 % | 19.1 % |
| Plin+Peg | 0 % | 6.25 % | 6.25 % | 6.25 % |

In the Plin+Peg vs Peg group, Gr 4 AE frequency was 37.3% vs 54.5%, Gr 3 AE frequency was 18.8% vs 27.3%, Gr 2 AE frequency was 25% vs 9.1% and Gr 1 AE frequency was 18.8% vs 4.5%. No Gr 5 AEs occurred in either group. Bone pain was significantly less (P<0.001) with Plin+Peg vs Peg.
**Conclusion:** Addition of Plin to Peg has superior prevention of CIN, superior safety, superior RDI and superior protection against bone pain compared to standard dose Peg alone in this randomized phase 2 trial. A confirmatory global Phase 3 trial comparing Plin+Peg vs Peg alone is underway.

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# Imaging of the distribution of human breast ducts

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While most of the anatomy of the human body is well delineated and understood, the distribution of adult female breast ducts remains largely understudied despite the fact that breast cancer, is thought to start in the lining of a breast ductal lobular unit. These anatomical features develop from stem cells located behind the nipple under the influence of the hormones of puberty. The exact patterns and number of ducts in the normal female breast has received limited attention since the work of Astley Cooper in 1840 who admitted that he had artfully displayed the ducts in two dimensions for his book. Since then, Going et al has used computerized reconstruction to map one breast and investigators in Australia have used hand-held ultrasound on lactating women to gain some insight into the nipple anatomy. The descriptions of the number of ducts exiting the breast at the nipple can be divided into those who have cannulated ducts at the nipple (6-10) and those who enumerated the number of ducts seen on transection of the nipple. (15-20). Local anesthesia can be used as a nipple block allowing duct cannulation in women. Breast cancer starts in the lining of a milk duct which opens the way for the application of new diagnostic techniques such as liquid biopsy. The limitation of this approach, however, is the absence of an imaging modality to direct sampling.

In collaboration with QT Imaging, images were obtained using non-invasive 3D Transmission Ultrasound (TU) imaging of whole in vivo breasts of three patients, a postmenopausal 64 year old woman, a woman with DCIS and one with an invasive cancer. TU is a novel FDA cleared imaging device utilizing 3D ultrasound data and modelling to yield speckle free sub-mm resolution quantitative estimates of tissue characteristics. The women were lying prone with their breast immersed in a water bath with reconstruction of the projection and reflected ultrasound data resulting in co-registered 3D reflection, speed-of-sound, and attenuation images. Machine learning at a voxel level was used to quantitively differentiate and segment breast tissues types based on reconstructed voxel tissue characteristics. These tissue types were then 3D printed into anatomical models representing a normal postmenopausal breast, one with DCIS and one with invasive cancer.

The images demonstrated the distribution of ductal systems in two concentric groupings unrelated to quadrants. The DCIS and the invasive ductal cancer were limited to a single ductal system each.

This new non-invasive technology enables precise localization of intraductal and invasive lesions. It opens up the potential for precise anatomic intraductal liquid biopsy for diagnosis as well as intraductal therapy. In addition, it has ramifications for better directing surgical removal of intraductal and invasive lesions.

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Significance of PD-L1 expressing tumor cells in the combined positive score with triple negative breast cancer

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**Background:** The Tumor Proportion Score (TPS) and Combined Positive Score (CPS) scoring algorithms are used in conjunction with PD-L1 IHC 22C3 pharmDx for the immunohistochemical evaluation of PD-L1 in certain human cancer tissues; both algorithms include PD-L1 staining tumor cells (TC) and have been correlated with response to pembrolizumab therapy (KEYTRUDA®) at specific expression levels in specific tumor indications. This study aims to evaluate whether PD-L1 expression on TC could be important in the evaluation of TNBC with PD-L1 IHC 22C3 pharmDx and the impact on reaching a diagnostic cut-off, as current PD-L1 testing (SP142) for TNBC relies solely on scoring immune cells (IC). TNBC clinical data from KEYNOTE-119 (ClinicalTrials.gov, NCT02555657) and Agilent's internal TNBC tumor bank data were evaluated by TPS, CPS, and Quantitative Immune Cell Density (QID) to determine the significance of including PD-L1 expressing TC in the scoring algorithms. PD-L1 IHC 22C3 pharmDx is not currently approved for use with TNBC specimens.**Methods:** TNBC specimens from clinical trial KEYNOTE-119 and Agilent's internal tumor bank were stained with PD-L1 IHC 22C3 pharmDx and scored using the TPS, CPS, and QID algorithms. The TPS algorithm is defined as the number of PD-L1 staining tumor cells divided by the total number of viable TC, multiplied by 100. The CPS algorithm includes TC and IC and is defined as the number of PD-L1 staining cells (TC, lymphocytes and macrophages) divided by the total number of viable TC, multiplied by 100. In addition to TPS and CPS, QID was also calculated to quantify the contribution from PD-L1 expressing IC. QID is defined as the CPS minus the TPS (QID = CPS - TPS). The data was analyzed to show the percent of specimens that fell below the diagnostic PD-L1 cut-offs of ≥1 and ≥10 when evaluated using QID as compared to CPS. Both scores measure countable PD-L1 staining cells per 100 viable tumor cells. **Results:** A total of 120 PD-L1 IHC 22C3 pharmDx stained TNBC specimens from Agilent's internal tumor bank were analyzed. When evaluated using CPS, 71 specimens were positive for the PD-L1 ≥1 cut-off and 49 were positive for the PD-L1 ≥10 cut-off. When analyzed with QID, 8.5% of specimens fell below the PD-L1 ≥1 cut-off and 26.5% fell below the PD-L1 ≥10 cut-off (Table 1). A total of 964 PD-L1 IHC 22C3 pharmDx stained TNBC specimens from KEYNOTE-119 were analyzed. When evaluated using CPS, 604 specimens were positive for the PD-L1 ≥1 diagnostic cut-off and 284 were positive for the PD-L1 ≥10 diagnostic cut-off. When analyzed with QID, 9.3% of patients fell below the PD-L1 ≥1 diagnostic cut-off and 33.5% fell below the PD-L1 ≥10 diagnostic cut-off (Table 1). **Conclusion:** PD-L1 IHC 22C3 pharmDx stains both TC and IC in TNBC. Removal of the PD-L1 staining TC from the CPS algorithm (QID score) reduces the number of specimens scored as positive for the PD-L1 ≥1 and PD-L1 ≥10 diagnostic cut-offs. This data highlights that a significant portion of TC express PD-L1 in TNBC and inclusion of TC in the scoring algorithm should be considered when evaluating the diagnostic status of a specimen.

Table 1. Agilent Tumor Bank and KEYNOTE -119: CPS and QID

| Diagnostic Cut-Off | CPS Positive Specimens | QID (CPS – TPS) Positive Specimens | Specimens Flipped at Diagnostic Cut-off | Difference (%) |
|---|---|---|---|---|
| **Agilent Tumor Bank** | | | | |
| PD-L1 ≥ 1 | 71 | 65 | 6 | 8.5 |
| PD-L1 ≥ 10 | 49 | 36 | 13 | 26.5 |
| **KEYNOTE-119** | | | | |
| PD-L1 ≥ 1 | 604 | 548 | 56 | 9.3 |
| PD-L1 ≥ 10 | 284 | 189 | 95 | 33.5 |

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# Ipsilateral breast cancer recurrence: Treatment and long-term oncological results at a high volume center

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**Background** A small proportion of patients with primary breast cancer who receive breast conserving surgery (BCS) will develop an ipsilateral breast cancer recurrence (IBCR). In these patients, mastectomy is still considered the treatment of first choice, even if a second conservative surgical approach is technically feasible. The aims of our study are to analyze the characteristics of patients with IBCR after BCS, evaluate and compare the different treatment modalities (repeat BCS *vs.* mastectomy) in terms of patients and tumor characteristics, disease-free interval (DFI), disease-free survival (DFS), and overall survival (OS).**Methods**Our prospectively maintained institutional database was queried, and 309 patients with IBCR after BCS who underwent either repeat BCS or mastectomy, between January 2008 and December 2018, were identified. Ipsilateral breast cancer recurrence was defined as a local tumor reappearance in the same breast or in the surgical scar. Exclusion criteria were: age <18 years, primary cancer treated with mastectomy, residual disease, controlateral recurrence, recurrent benign disease, only distant or axillary recurrence, IBCR not treated surgically, follow-up <24 months, and DFI <6 months.**Results**The mean age of patients at primary breast cancer was 55.3 years. The majority of primary tumors were ductal (87.4%), luminal A-B (81.2%) breast cancers. After BCS, 222 (71.8%) patients underwent radiotherapy. Out of 309 patients with IBCR after BCS, 143 underwent repeat BCS and 166 underwent mastectomy. At multivariable analysis, young age, <65 years (59.6% *vs.* 37.1% if age ≥65 years, odds ratio (OR)=2.374, 95% confidence interval (95%CI)=0.02-0.24, *p*= 0.018) and short DFI <24 months (15.7% *vs.* 10.5% if DFI ≥24 months, OR=2.705, 95%CI=0.02-0.17, *p*= 0.007) were found to significantly increase the probability to receive mastectomy for IBCR after BCS. After IBCR, DFS rate at 3-, 5-, and 10-years was 79.2%, 68.2%, 36.9%, and 77.2%, 65.9%, 55.3%, in patients receiving repeat BCS or mastectomy, respectively (*p* = 0.842). Overall-survival rate at 3-, 5-, and 10-years was 95.4%, 91.4%, 68.5%, and 87.3%, 69.3%, 57.9%, in patients receiving repeat BCS or mastectomy, respectively (*p* = 0.018).**Conclusions**The best candidates for repeat BCS in the treatment of IBCR are patients ≥65 years with a DFI ≥24 months. Young patients (<65 years) with early onset of recurrence (DFI <24 months) have a high probability to receive mastectomy for the treatment of IBCR. Mastectomy does not improve survival in patients with IBCS after BCS. The information about the risk of poor long-term prognosis after mastectomy should be shared with the patient and a repeat BCS could be proposed.

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Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (SAKK 23/16 / IBCSG 57-18 / ABCSG-53 / GBG 101 - TAXIS): A multicenter randomized phase III trial

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***Background*** Main weaknesses of neoadjuvant chemotherapy (NACT) to avoid axillary dissection (ALND) in patients with clinically node-positive breast cancer are frequent failure of achieving nodal pathologic complete response (pCR) and administration of chemotherapy even though not indicated otherwise in many cases. Tailored axillary surgery (TAS) was designed to selectively remove positive nodes and omit ALND in patients with clinically node-positive breast cancer either in the upfront surgery setting or in case of residual nodal disease after neoadjuvant therapy, which distinguishes this trial from all others ongoing and published. ***Trial design*** In this international, multi-center, phase-III, non-inferiority randomized controlled trial, including 61 study sites from six countries, we plan to randomize 1500 patients to either receive TAS followed by ALND and regional nodal irradiation excluding the dissected axilla, or receive TAS only followed by regional nodal irradiation including the full axilla. TAS consists of selective removal of the sentinel lymph nodes (SLNs) and all palpably suspicious findings, thereby tailoring the extent of axillary surgery to the extent of axillary disease, followed by specimen radiography to document removal of the clip placed in the sampled node. Imaging-guided localization is encouraged to increase the chances of clip removal. All patients undergo adjuvant whole-breast irradiation after breast conserving surgery and chest wall irradiation after mastectomy. Inclusion of internal mammary nodes is recommended irrespective of treatment arm. ClinicalTrials.gov Identifier: NCT03513614. ***Inclusion criteria*** - Clinically node-positive breast cancer (all molecular subtypes allowed) - Node-positivity palpable or detectable only by imaging at time of initial diagnosis - Newly diagnosed or isolated in-breast recurrence or second ipsilateral breast cancer after previous breast conserving surgery and sentinel procedure and at least 3 years disease free and no prior axillary dissection or axillary RT. - In case of prior neoadjuvant treatment: residual disease (including residual ITCs) confirmed by pathology at the time of surgery - Clipping of sampled axillary lymph node ***Exclusion criteria*** - Absence of clip in the specimen radiography - Palpable disease left behind in the axilla after TAS - No SLN identified in the axilla ***Specific aims*** To test the hypothesis that treatment with TAS and axillary radiotherapy is non-inferior to ALND in terms of disease-free survival (DFS) of clinically node-positive breast cancer patients. Secondary objective is to test if quality of life is significantly better with TAS and axillary radiotherapy compared to ALND. ***Statistical methods*** With type I error 5% and power 80%, 385 events will be needed to show non-inferiority of TAS and axillary RT in comparison to ALND with a non-inferiority hazard ratio (HR) of 1.289 (corresponding to a DFS at 5 years of 80% in the ALND arm and 75% in the TAS and axillary RT arm), including one interim analysis for efficacy/futility after 20% of the required events have occurred. The sample size needed is 1500 patients (750 per arm). The HR and one-sided 95% confidence interval will be calculated using a Cox regression model based on the per-protocol set. ***Present accrual and target accrual*** The trial was activated on 31 July 2018 and the first patient was randomized on 07 August 2018. **As of 03 July 2020, 291 patients have been randomized.** Accrual is currently running according to protocol and is planned until end of 2023 with the primary endpoint analysis expected in 2029. ***Contact information*** Prof. Dr. Walter Paul Weber, University Hospital Basel; Tel: +41 61 328 61 49; Walter.Weber@usb.ch

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# Mammaprint risk stratification associated with presence of circulating tumor cells in breast cancer

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**Background:** We previously reported the prognostic and predictive value of circulating tumor cells (CTCs) in early and late-stage breast cancer (BC). While the evaluation of CTCs via liquid biopsy in oncology practice guidelines is still evolving, other biomarkers are more commonly used, including multigene sequencing. The 21-gene Oncotype DX (ODX) assay predicts a risk of disease recurrence in patients with estrogen receptor (ER)-positive disease. The 70-gene MammaPrint (MP) panel, on the other hand, predicts a risk of early metastasis, and was developed using ER- and ER+ samples. We sought to understand whether these genomic assays predicted the presence of CTCs.
**Methods:** A cohort of patients with BC and CTC data (i.e. positive or negative) was identified in this retrospective study using the *National Cancer Database* (NCDB) 2004-2016 registry. Clinicopathologic characteristics, including ODX and MP data, were described using frequencies/proportions. At the univariate level, chi-squared tests were used to evaluate for an association between the results of ODX (low-risk as recurrence score of <11, intermediate-risk as 11-25, and high-risk as >25), or MP (low or high risk), and the presence of CTCs. These variables were then assessed at the multivariate level using multiple logistic regression, controlling for other variables we previously showed predicted CTCs, including: race, receptor status, histology and AJCC clinical disease stage. Analyses were performed using SPSS version 26.0.
**Results:** A total of n=4577 patients were evaluated for CTCs: n=940 (20.5%) of which underwent ODX testing, while n=282 (6.2%) underwent MP. Chi-squared analyses showed no association between ODX risk categories and the presence of CTCs (p=0.204), but a significant association between MP and CTCs (p=0.005). Through multivariate analysis, we found the association between a high-risk designation as per MP and the presence of CTCs remained significant (OR 2.65, 95% CI 1.23-5.70, p=0.013), even after controlling for race, receptor status, histology, and AJCC clinical disease stage. A similar multivariate model including ODX as a predictor of CTCs confirmed non-significance (p=0.664). Of patients with MP and CTC data, the majority were 50-70 years of age (n=164, 58.2%), White (n=244, 88.1%), with ductal carcinoma (n=211, 74.8%) on histological evaluation (Table 1). N=12 (4.6%) were diagnosed at stage 0, n=173 (66.0%) at stage I, n=63 (24.0%) at stage II, n=7 (2.7%) at stage III, and n=7 (2.7%) at stage IV. Most were hormone receptor-positive (HR+) and HER2-negative (HER2-) (n=234, 86.3%); n=11 (4.1%) were HR+/HER2+, n=5 (1.8%) were HR-/HER2, while n=21 (7.7%) were triple-negative breast cancers (TNBC). N=62 (22.0%) were assigned high-risk as per MP, while n=220 (78.0%) were assigned low-risk.
**Conclusion:** High-risk of early metastasis, per MammaPrint, was significantly associated with the presence of CTCs. However, a significant association was not observed between Oncotype DX risk stratification and CTCs. This may suggest clinical utility in combining ODX metrics with liquid biopsy in order to maximize survival prognostication, when ODX is utilized as the biomarker. Further evaluation will be required to understand if the MP assay's clinical value contribution is independent of CTC status.

**Table 1:** Multiple logistic regression model predicting presence of CTCs in patients with breast cancer.

| Variable | Circulating tumor cells | | | | |
|---|---|---|---|---|---|
| | Negative (n=211) | Positive (n=71) | OR* | 95% CI | *p*-value |
| MammaPrint | | | | | |
| Low-risk (ref) | 173 (61.3%) | 47 (16.7%) | 1 | - | - |
| High-risk | 38 (13.5%) | 24 (8.5%) | 2.65 | 1.23-5.70 | **0.013** |
| **Age | | | | | |
| <50 | 45 (16.0%) | 23 (8.2%) | - | - | - |
| 50-70 | 126 (44.7%) | 38 (13.5%) | | | |
| >70 | 40 (14.2%) | 10 (3.5%) | | | |
| Race | | | | | 0.993 |
| White (ref) | 182 (65.7%) | 62 (22.4%) | 1 | - | - |
| Black | 18 (6.5%) | 7 (2.5%) | 0.93 | 0.29-2.99 | 0.903 |
| Asian | 7 (2.5%) | 1 (0.4%) | 0.00 | 0.00-0.00 | 0.999 |
| AJCC clinical staging | | | | | 0.091 |
| 0 (ref) | 10 (3.8%) | 2 (0.8%) | 1 | - | - |
| I | 136 (51.9%) | 37 (14.1%) | 0.60 | 0.10-3.56 | 0.572 |
| II | 49 (18.7%) | 14 (5.3%) | 0.55 | 0.09-3.47 | 0.526 |
| III | 1 (0.4%) | 6 (2.3%) | 10.91 | 0.61-194.79 | 0.104 |
| IV | 3 (1.1%) | 4 (1.5%) | 3.67 | 0.273-49.52 | 0.327 |
| Estrogen receptor status | | | | | |
| Negative (ref) | 21 (7.5%) | 6 (2.1%) | 1 | - | - |
| Positive | 190 (67.6%) | 64 (22.8%) | 2.19 | 0.42-11.27 | 0.350 |
| Progesterone receptor status | | | | | |
| Negative (ref) | 39 (13.9%) | 11 (3.9%) | 1 | - | - |
| Positive | 172 (61.2%) | 59 (21.0%) | 1.55 | 0.49-4.89 | 0.457 |
| HER2 receptor status | | | | | |
| Negative (ref) | 192 (69.6%) | 61 (22.1%) | 1 | - | - |
| Positive | 16 (5.8%) | 7 (2.5%) | 1.58 | 0.53-4.70 | 0.412 |
| Histology | | | | | 0.503 |
| Ductal (ref) | 162 (57.4%) | 49 (17.4%) | 1 | - | - |
| Lobular | 32 (11.3%) | 21 (7.4%) | 1.60 | 0.73-3.53 | 0.241 |
| Other | 17 (6.0%) | 1 (0.4%) | 0.00 | NE-NE | 0.998 |

*OR predicting presence of CTCs. **Age not included in the multivariate model.

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# Real world treatment patterns and healthcare resource utilization among HER2+ metastatic breast cancer patients with and without brain metastases: A retrospective cohort study

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**Background:** Human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (MBC) is associated with increased clinical and economic burden. Patients with brain metastases (BM) have significantly worse outcomes, however, limited data exist evaluating healthcare resource utilization (HCRU) among HER2+ MBC patients with BM. **Objective**: To describe treatment patterns and HCRU among HER2+ MBC patients with or without brain metastases who received HER2-targeted therapy using retrospective claims data. **Methods:** Data obtained from the IBM Watson Health™ MarketScan commercial claims and Medicare Supplemental database from July 2012 to December 2018 were used to evaluate HER2+ MBC patients. We describe demographic and clinical characteristics, treatment patterns by line of therapy (LOT) by the presence or absence of BM, and HCRU. The first metastatic diagnosis date was the study initiation (index) date. HCRU outcomes per patient per year (PPPY) in the follow-up period after metastatic diagnosis were measured overall and by BM vs non-BM. These HCRU outcomes included inpatient (IP) services, total length of stay (LOS), emergency room (ER) services, and outpatient (OP) services. **Results**: A total of 4,509 patients were included. One-hundred and three (2.3%) patients had BM and 4,406 had no evidence of BM at index. However, 590 (13.1%) developed BM after study initiation. The mean age at index was 53.7 years. Median follow-up time was 23.2 months overall (22.1 months for patients with BM at index and 23.2 months for patients without BM at index). Median time on treatment (months) was 7.6, 7.2, and 6.2 for first line (1L), 2L, and 3L, respectively. Trastuzumab-based regimens were most used across all LOTs. Trastuzumab emtansine (T-DM1) use in 1L was 0.9% (2.4% in BM and 0.9% in non-BM patients). T-DM1 use increased in 2L (9.7%) and 3L (13.0%) and differed for BM vs non-BM patients in 2L (22.6% vs 7.7%) and 3L (25% vs 10.1%). Overall, lapatinib use ranged from 1.6% (1L) to 8.3% (3L). BM patients had a higher frequency of lapatinib use compared to non-BM patients (1L: 11.8% vs 1.2%; 2L: 20.5% vs 1.8%; 3L: 21.2% vs 5.1%). The mean number of IP services PPPY was 0.6 and higher for BM patients (1.2 vs 0.5). The mean total LOS PPPY was 2.7 days and BM patients had higher total LOS (8.6 vs 2.6 days) compared to non-BM patients. The average number of ER visits PPPY was 1.2 and BM patients had higher frequency of ER visits (2.5 vs 1.2). The mean number of OP services PPPY was 57.1; however, no obvious difference was observed between BM and non-BM patients (62.1 vs 56.9). **Conclusions**: Among HER2+ MBC patients, there is significantly higher HCRU among BM patients compared to patients without BM. This highlights the need for more effective systemic therapies that improve outcomes and reduce disease and healthcare system burden for HER2+ MBC patients, particularly those with BM.

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# Mixed invasive ductal lobular carcinomas (mDLC) are clinically more similar to invasive lobular carcinoma (ILC) than to invasive ductal carcinoma (IDC)

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Clinicopathologic differences between histological subtypes of invasive breast cancer are increasingly being appreciated. Mixed invasive ductal lobular carcinomas (mDLC) are thought to be composed of both ductal and lobular components, and we sought to determine whether mDLC clinically align more closely with invasive ductal (IDC) or invasive lobular (ILC) carcinoma subtypes or if they display intermediate or unique features dissimilar to either type. Key clinical and histologic parameters were compared between cohorts of patients with mDLC (N = 410), IDC (N = 12,979), and ILC (N = 1,569) identified from cancer registry data of a single large healthcare system.Patients with mDLC were older (59 years (49 - 68)) than those with IDC (57 years (48 - 67), p = 0.014)) and younger than those with ILC (61 years (51 - 70), p = 0.006). Tumor size in mDLC was larger (19mm (12 - 27)) than IDC (16mm (10 - 25), p < 0.001) and smaller than ILC (20mm (12 - 35), p = 0.036). Similar to ILC, mDLC were more likely than IDC to be ER+ (92% vs 78% in IDC, p < 0.001), and less likely to be HER2+ (8% vs 15% in IDC, p = 0.04). mDLC were also similar to ILC with regards to higher likelihood of diagnosis at higher stage (p < 0.001), yet with lower grade (p < 0.001), at diagnosis as compared to IDC. Heatmap visualization, as well as dimension reduction by multidimentional scaling (MDS), demonstrates significant overlap of the mDLC and ILC cohorts. Furthermore, an elastic net regression model based on clinicopathologic parameters predicts mDLC to align more closely with ILC than IDC. For patients for whom oncotype Dx scores were available, there was a trend for enrichment of low risk RS scores with rare high-risk RS tumors in mDLC, similar to ILC. With regards to response to neoadjuvant chemotherapy, a subset of the aforementioned cohorts who had received neoadjuvant chemotherapy, mDLC (N = 17), IDC (N = 180), and ILC (N = 57), were compared. Among patients in whom breast conserving surgery (BCS) was attempted, patients with IDC were more likely to have a successful BCS than those with ILC, with less margin positivity thereby avoiding re-excision and/or completion mastectomy (70% vs 32%, respectively; p = 0.003). Successful BCS was achieved with mDLC 56% of the time, although compared to IDC and ILC statistical significance was not reached. In a limited cohort receiving neoadjuvant endocrine therapy (mDLC (N = 7), IDC (N = 37), and ILC (N = 21)) no differences with regard to rates of successful BCS were identified. Pathologic complete response rates (pCR) were additionally evaluated, although small study numbers precluded our ability to perform statistical analysis.Collectively, the aforementioned findings support a higher concordance between mDLC and ILC as compared to IDC. It is feasible that the lobular component of mDLC tumors is predominant, leading to the observed histopathologic similarities noted between mDC and ILC cohorts. We are planning meta-analyses including data from other institutions, and molecular studies to further understand complexities of mDLC.The authors acknowledge grant support from ASCO Conquer Cancer (to NW and AN).

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# Impact of neoadjuvant chemotherapy on breast reconstruction - systematic review and meta-analysis

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**Background**Impact of neoadjuvant chemotherapy (NACT) on breast reconstruction outcomes remain unclear. We did a systematic review and meta-analysis to assess the effect of NACT on post-operative complications and delay to adjuvant therapy among women undergoing immediate breast reconstruction.
**Methods**In this systematic review and meta-analysis, we searched medical databases from inception of this technique to May 2, 2020 to identify articles that assessed the impact of NACT on separate techniques of immediate breast reconstruction. Studies reporting on at least one of our pre-defined major post-operative complications were included. Study authors were contacted for individual patient-level data which was not available. Study quality and risk of bias are reported through NOS Scores and GRADE table. PROSPERO registration CRD42020183761.
**Findings**Of 477 identified articles, 17 studies (3249 patients) were eligible for inclusion. NACT did not increase the risk of overall complications after immediate breast reconstructions RR: 0.91(95% CI 0.74 to 1.11, $p = 0.34$). There was no large increase in flap losses (total and partial) in patients receiving NACT compared to control group (RR:1.23, 95% CI 0.70 to 2.18, $p = 0.47$; $I^2 = 0\%$). There was however, some evidence of increased risk of implant/expander loss after NACT treatment (RR:1.50, 95% CI 1.03 to 2.20, $p = 0.04$; $I^2 = 34\%$). NACT treatment was not associated with increase in haematomas, seromas or wound complications or significant delay to adjuvant therapy access; RR:1.59, 95% CI 0.66 to 3.87, $p = 0.30$
**Interpretation**Immediate breast reconstruction after treatment with NACT remains a safe procedure. Careful patient selection may play a bigger role when planning implant-based reconstructions after NACT.
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The spectrum of germline susceptibility gene variants in Mexican patients with breast cancer (BC): A Prospective Multicenter study

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**Background:** *BRCA* mutations are responsible for a significant proportion of hereditary breast and ovarian cancers. However, other cancer susceptibility genes are also associated with an increased risk of developing breast cancer (BC). In Mexico, approximately 15% of patients with BC have been identified with *BRCA* mutations. Despite our growing understanding of *BRCA* mutations, the contribution and characterization of non-*BRCA* mutations in Mexican patients with a BC diagnosis remains unknown. We aimed to investigate the spectrum of BC-associated mutations among Mexican patients with BC referred for genetic cancer risk assessment (GCRA) in the multinational Clinical Cancer Genomics Community Research Network (CCGCRN). **Methods:** Mexican patients with a primary BC who were enrolled in the IRB-approved CCGCRN registry protocol and underwent genetic counseling and multigene panel testing (MGPT) were included. Pathogenic and likely pathogenic variants (PV) in genes associated with increased BC risk were used for analyses. Clinical and demographic characteristics of *BRCA* and non-*BRCA* carriers were compared. **Results:** From December 2012 to February 2020, 725 Mexican patients with BC who had MGPT results with a median age (years) of 41 (range 25-76) were included. 142 (19.6%) patients carried a BC-associated PV. Of these, 98 (69.0%) carried *BRCA* PVs: 58 in *BRCA1* (41.5%) and 40 in *BRCA2* (26.7%). PVs in other BC-associated genes (n = 42) accounted for 29.5% of all observed PVs and were distributed as follows: *PALB2* (n = 13), *CHEK2* (n = 11), *RAD51C* (n = 6) , *ATM* (n = 3), *PTEN* (n = 3), *TP53* (n = 3), *BRIP1* (n = 2), and *CDH1*(n = 1). Other actionable genes represented 3.5% of all PVs (*PMS2* [n = 3]; *MSH6* [n = 1]; *MSH2* [n = 1]). Suspected founder mutations in Latinas, *PALB2* c.2167_2168delAT (n = 5) and *CHEK2* c.707T>C (n = 9), represented 33.3% (n = 14/42) of the detected non-*BRCA* PVs. Mean age at first cancer diagnosis (years) for *BRCA* and non-*BRCA* carriers was: 37 (range 26-58) and 42 (range 25-76) ($p<0.05$), respectively. Among carriers, those with *BRCA* PVs had a significantly greater proportion of triple-negative (TN) tumors compared to non-*BRCA* PVs (45.2% vs 9.5%; $p<0.05$). **Conclusion:** A significant proportion of Mexican women carried a BC-associated mutation and a third were non-*BRCA* PVs. Among non-*BRCA* PVs, recurrent *PALB2* and *CHEK2*, which had previously been characterized in *BRCA*-negative US Latinas with BC, were the most common and confirms their presence and clinical impact in Mexico. BRCA carriers were younger and more commonly had the TN molecular subtype.

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# Atlas-based auto-segmentation of a high risk cardiac zone on non-contrast computed tomography (CT) scans for indirect optimization of left anterior descending coronary artery (LADCA) dosimetry for breast radiotherapy

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**Background :** Breast radiotherapy is associated with an increased cardiotoxicity risk which could be decreased by taking into account the left anterior descending coronary artery (LADCA) during treatment planning. However, LADCA manual contouring is time-consuming, complex and poorly reproducible on non-contrast simulation computed tomography (CT) scans where it is often hardly noticeable. Alternatively, auto-segmentation algorithms have been proposed for cardiac substructure contouring but they are usually unreliable for LADCA automatic delineation in daily practice.
**Purpose :** The aim of this study was to implement and to evaluate auto-segmentation of a “high risk cardiac zone” which would be a reproducible LADCA surrogate and which would be reliably delineated by atlas-based algorithms for dosimetric purpose when planning breast radiotherapy on non-contrast CT scans.
**Materials/methods :** 40 breast cancer patients treated with intensity modulated radiation therapy were randomly selected from our institutional database. “High risk cardiac zones” (HRCZ) were defined as segments of the anterior cardiac wall centered around the inter-ventricular groove from top to bottom (where the LADCA anatomically lies), with a constant 1cm-thickness and a symmetrical lateral margin on both sides of the groove. For each patient, eight HRCZ were contoured, differing by their width, ranging between 1 cm and 8 cm, in steps of 1 cm. Each contour was validated by a staff of three radiation oncologists. An atlas was constituted using the HRCZ contours of 20 patients and implemented in the “Workflow Box” (Mirada Medical) atlas-based auto-segmentation (ABAS) software. The ABAS algorithm delineated the HRCZ on the 20 remaining patients and the auto-contouring performances were evaluated by comparison with the manual HRCZ contours (defined as the reference contours), using dice-similarity coefficients (DSC) and Jaccard indexes, as a function of the HRCZ width.
**Results :** Performances of the atlas-based auto-segmentation algorithm for HRCZ delineation are reported in **table 1**, as a function of HRCZ width. Auto-segmentation performance and reproducibility improved with HRCZ width, as evidenced by increased DSC and Jaccard indexes and lower relative standard variations; in particular, for a HRCZ width larger than 4 cm, HRCZ automatic segmentation was constantly satisfactory (DSC > 0.6; relative standard variation < 20%).

Table 1: performance of atlas-based auto-segmentation of high risk cardiac zones (HRCZ)

| HRCZ **width (cm)** | **DSC (mean)** | DSC SD | DSC RSD | **Jaccard Index (mean)** | Jaccard SD | Jaccard RSD |
|---|---|---|---|---|---|---|
| **1** | **0.300** | 0.115 | 63.35% | **0.187** | 0.162 | 54.04% |
| **2** | **0.537** | 0.125 | 33.14% | **0.379** | 0.140 | 26.05% |
| **3** | **0.622** | 0.106 | 23.06% | **0.459** | 0.104 | 16.69% |
| **4** | **0.659** | 0.099 | 19.95% | **0.498** | 0.093 | 14.06% |
| **5** | **0.674** | 0.102 | 19.81% | **0.515** | 0.092 | 13.67% |
| **6** | **0.682** | 0.104 | 19.77% | **0.524** | 0.092 | 13.43% |
| **7** | **0.687** | 0.104 | 19.67% | **0.530** | 0.091 | 13.27% |
| **8** | **0.693** | 0.105 | 19.57% | **0.537** | 0.092 | 13.23% |

*Table 1: performance of atlas-based auto-segmentation of high risk cardiac zones (HRCZ), a LADCA surrogate, as a function of HRCZ width. DSC: Dice Similarity coefficient; sd : standard deviation; rsd : relative standard deviation.*
**Conclusion :** We implemented and evaluated auto-segmentation of high risk cardiac zones (HRCZ) on non-contrast CT scans, defined as segments of the anterior cardiac wall geometrically centered around the inter-ventricular groove from top to bottom (where LADCA anatomically lies) with a constant thickness of 1cm and a total width ranging between 1 cm and 8 cm. For HRCZ width larger than 4cm, auto-segmented HRCZ contours were constantly reliable and may be used as LADCA surrogate for heart dosimetric optimization during breast radiotherapy planning on non-contrast CT scans.

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# Rare patients in routine care: Treatment and outcome in advanced invasive lobular breast cancer in the prospective German research platform OPAL

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**Introduction** Invasive lobular breast cancer (ILC) is with 5-10% the second most common histologic type of invasive breast cancer after invasive ductal breast cancer (IDC). ILC differs from IDC, for example in its metastatic pattern. However, guidelines do not provide special treatment recommendations for this subtype and specific clinical studies are rare. Here we present prospective data on characteristics, treatment and outcome of patients (pts) with advanced ILC in routine care in Germany. **Methods** The Tumor Registry Breast Cancer (TMK) has prospectively documented data of pts with breast cancer by oncologists in Germany since 2007. Since 2017 OPAL continues the TMK work with representation of all specialists (medical and gynecologic oncologists) treating advanced breast cancer (ABC). Both projects are prospective, observational, open, longitudinal multicenter cohort studies (clinical registries). Pts at the start of their treatment can be included after signing informed consent. Together over 7500 pts (4250 with ABC) will be recruited from over 150 sites in Germany. There is no treatment specification. Details on all (sequential) treatments, patient and tumor characteristics, clinical and patient-reported outcomes are documented. Follow-Up is until death or up to 5 years. Here, data as of March, 31st 2020 are presented. **Results** Pts with advanced ILC (n=372) were older at start of first-line treatment (median 68 vs. 63 years) while ECOG performance status (ECOG 0 25% vs 29%) and Charlson Comorbidity Index (CCI 0: 82% vs 84%) were similar compared to pts with IDC (n=1745). The lobular tumor was more often hormone receptor (HR) positive (87% vs 74%) and less often HER2 positive (14% vs 27%). The percentage of primary metastatic disease (M1) was 34% in both groups, while grade at diagnosis was more frequently G1/2 in the ILC group (73% vs 51%). The metastatic pattern was more often non-visceral only for the ILC group (26% vs 19%), and metastases were found more often in bone (52% vs 42%) and peritoneum (9% vs 2%) and less often in liver (20% vs 25%) and lung (7% vs 25%). Overall, pts with ILC were treated more often with endocrine therapy (ET) +/- CDK4/6-inhibitors (CDK4/6i) than pts with IDC (52% vs 33%), yet, ILC is more often HR-positive than IDC. Of pts receiving chemotherapy (CT) 53% of ILC and 56% of IDC tumors were treated with taxanes as first-line treatment. 20% of ILC vs. 24% of IDC tumors received a combination-CT. First-line treatment strategy was analyzed for the HR-positive, HER2-negative subgroup. From 2007-16 pts with ILC received more often ET (ILC (n=162) 54% vs IDC (n=696) 44%), while IDC were more often treated with CT first-line. Since approval of CDK4/6i, distribution of treatment strategies has been quite similar (ILC (n=123): CDK4/6i: 76%, ET: 15%, CT: 10% and IDC (n=311): CDK4/6i: 72%, ET: 12%, CT: 15%). Overall survival (OS) from start of first-line treatment was estimated for all pts recruited by 2016 (follow-up of at least 3 years). Median OS was comparable: ILC (n=224) 30.6 months (68% events, 95%-CI 26.1 - 36.9 months) and IDC (n=1217) 34.1 months (60% events, 95%-CI 30.6 - 38.4 months). For the HR-positive, HER2-negative subgroup, OS was also similar. A multivariate regression analysis on factors affecting OS will be presented. **Conclusion** Registries, like TMK/OPAL, can provide data on rare tumor subtypes. We show that ABC with an invasive lobular histology differs in receptor status (more often HR-positive) and metastatic pattern (e.g. more often non-visceral) from the invasive ductal subtype. Nevertheless, treatment strategies for first-line treatment are similar and median OS is comparable despite ILC pts being markedly older. Future research should focus on identifying pts who could benefit from personalized treatment approaches including tumor subtype as a factor to consider.

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# The complete estrogen receptor antagonist OP-1250 shrinks tumors in xenograft models and has favorable preclinical pharmacokinetic attributes

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Antiestrogens are widely used to treat ER+, HER2- breast cancer however these may produce estrogen-like agonist effects in a cell and gene-specific manner. Furthermore, this partial agonism has been implicated in the development of tumor resistance. In contrast, a complete ER antagonist lacks agonist activity in all tissues. Given the high risk of recurrence in ER+ patients treated with endocrine therapies, we hypothesize that drugs that completely antagonize ER-mediated signaling will have a clinical advantage in treating resistant tumors, particularly in tumors for which the ER has acquired mutations conferring estrogen-independent growth.

We previously identified OP-1250 in our laboratory as a complete antagonist and degrader of wild type and mutant ERalpha in breast and uterus cells. Here we explore the pharmacokinetic properties of orally administered OP-1250 and its ability to shrink breast tumors from xenograft models expressing both wild type and mutant estrogen receptors. Orally administered OP-1250 produced high and stable levels in multiple species, suggesting that once daily dosing may be sufficient to produce excellent drug exposure in patients. OP-1250 shrank ER+ tumors in multiple patient-derived tumor xenografts in mice at daily doses of 3 mg/kg, including in tumors expressing the Y537S allele of ERalpha that confers estrogen-independent growth and tumor resistance. Furthermore, OP-1250 accumulated within tumor specimens, indicating excellent target penetration was achieved with low daily doses.

These preclinical studies indicate that OP-1250 has the potential to be a best-in-class antiestrogen due to its ability to complete antagonize ER, potent efficacy in shrinking tumors, and robust drug exposure. A Phase 1/2 dose escalation and expansion study in patients with ER+, HER2- metastatic or advanced BC previously treated with an endocrine therapy will be initiated this year.

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# Increased cancer mortality after second primary malignancy among breast cancer survivors

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**Background**: Due to advances in early detection and treatment, the number of breast cancer survivors in the US is expected to increase to 5 million by 2030. Although it is well established that breast cancer survivors are at increased risk of second primary malignancy (SPM), there is limited data on the impact of a SPM on overall and cancer-specific mortality compared to women with a first primary cancer. This information could inform prognosis for women with breast cancer as well as screening and treatment recommendations.
**Methods**: A retrospective cohort study was conducted using the Surveillance, Epidemiology, and End Results (SEER) 18 database, which collected cancer incidence and mortality from 18 US cancer registries (represents 28% of US population) between 2000 and 2016. For this analysis, we focused on the top 10 SPM in breast cancer survivors: breast cancer, lung cancer, colorectal cancer, uterine cancer, lymphoma, melanoma, thyroid cancer, pancreatic cancer, ovarian cancer, and leukemia. Propensity scores were used to match SPM with first primary cancer 1:1 on race, primary site, year of diagnosis, age of diagnosis, tumor stage, and treatments (surgery, chemotherapy, and radiotherapy). Hazard ratio (HR) and 95% confidence interval (CI) for cancer-specific death comparing SPM to first primary cancer were estimated from Cox proportional hazard regression, accounting for competing risk of death from conditions other than cancer. Subgroup analyses were conducted by SPM tumor stage, SPM primary site, and time interval between first breast cancer and SPM diagnosis.
**Results**: The study population included 31,712 breast cancer survivors with SPM and 1,471,886 women with first primaries. Women with SPM were older (mean age of 66.6 years) than first primary cancers (mean age of 62.1 years). 52.8% of SPM and 47.5% of first primary cancers were diagnosed at local stage. Women with SPM had higher cancer mortality than women with first primary cancer (HR: 1.27, 95%CI: 1.23-1.30). Mortality difference was larger among local stage SPM (HR: 1.95, 95%CI: 1.82-2.08) and regional stage (HR: 1.40, 95%CI: 1.33-1.47) than for distant stage (HR:1.10, 95%CI:1.06-1.14). Among the top 10 SPM, increased mortality was observed for thyroid cancer (HR: 3.02, 95%CI: 1.96-4.67), breast cancer (HR: 2.26, 95%CI: 2.11-2.42), and melanoma (HR: 1.76, 95%CI: 1.36-2.28). There was no statistically significant difference in mortality for second lung (HR: 1.06, 95%CI: 1.00-1.17) and pancreatic cancer (HR: 0.93, 95%CI: 0.82-1.06). Larger mortality difference comparing SPM to first primary cancer was observed for SPM diagnosed within 5 years (HR: 1.39, 95%CI: 1.35-1.44) than after 5 years (HR: 1.09, 95%CI: 1.04-1.13).
**Conclusion**: Breast cancer survivors with a SPM had higher cancer-specific mortality overall and for several cancers compared to women diagnosed with the same type of cancer for the first time suggesting that prior breast cancer is an important prognostic factor. Our results support the evaluation of improved risk stratification and/or novel screening and treatment approaches to improve outcomes from second cancer in breast cancer survivors.

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# Pilot study of carboplatin, nab-paclitaxel and pembrolizumab for metastatic triple-negative breast cancer

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**Background**. Given the significant clinical activity of the anti-PD1 inhibitor pembrolizumab as either a single agent or in combination with cytotoxic chemotherapy in the treatment of patients with metastatic triple-negative breast cancer (mTNBC), as well as the favorable cytotoxic and immunomodulatory properties of carboplatin and nab-paclitaxel, we identified a strong rationale to treat patients with mTNBC with the combination of carboplatin (C), nab-paclitaxel (N) and pembrolizumab (P) (CNP).
**Material and Methods**. We undertook a prospective, single-arm pilot study of 30 patients with mTNBC treated at two institutions. Inclusion criteria included: radiographically measurable mTNBC, ECOG performance status of 0-1, ≤2 prior therapies for mTNBC, and willingness to undergo a primary pre-treatment biopsy of a metastatic focus for research purposes. A second post-treatment research biopsy was encouraged but not mandated. Eligible patients received 3 cycles of CNP, with each cycle initially consisting of C (AUC 6 on days 1 of a 21-day cycle), N (100 mg/m2 IV on days 1, 8 and 15 of a 21-day cycle), and P (200 mg IV on day 15 of each cycle). Because of significant bone marrow toxicity, C was subsequently reduced to AUC 4.2 and N was reduced to 75 mg/m2. After completing 3 cycles of CNP, patients with either responding or stable disease by RECIST 1.1 criteria were eligible for additional cycles of CNP. The primary objective of this study was to determine overall response rate (ORR) in patients treated with CNP. The true response rate of therapy was estimated based on the number of responses using a binomial distribution and its confidence intervals were estimated using Wilson's method. Secondary objectives included: determine progression-free survival (PFS) and safety/tolerability of CNP. The Kaplan-Meier method was used to estimate PFS and OS. The probability of PFS at 6, 12, and 18 months were 51.8%, 24.7%, and 6.2%, respectively. The median PFS was 6.1 (95% CI: 5.1, 11) months. The probability of OS at 6, 12, and 18 months were 79%, 47%, and 5.9%, respectively. The median OS was 11.5 (95% CI: 8, 14.1) months. Correlative biopsy analyses will be undertaken to identify pathologic and genomic correlates of response to CNP. Factors including pathologic and genomic correlates that predict survival outcomes will be identified by Cox model or extensions of the Cox model.**Results**. Twenty nine patients have completed treatment and 1 remains on single-agent P. ORR was 53% (2 CRs and 14 PRs). Four patients had SD. The most common toxicity was infection (10 patients, grade 3) .The most common immune-related adverse events were pneumonitis (1 patient, grade 3) and hepatitis (1 patient, grade 3). There was only 1 grade 4 toxicity (increased creatinine).
**Conclusions**. CNP demonstrated significant activity in patients with mTNBC. Studies are underway to identify pathologic and genomic correlates of clinical response to CNP.

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# Evaluation of workflow box mirada software for automatic delineation of left anterior descending coronary artery (LADCA) in order reduce cardiac toxicity for radiotherapy breast cancer treatments

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**Purpose/Objective:** In order to preserve the patient's cardiac integrity, a good practice that would be simple and quick to implement would be to optimize dose on the left anterior descending coronary artery (LADCA) during dosimetric planning treatment. However, manual delineation of LADCA remains complicated to perform in clinical routine on non-injected CT-scans. To conclude on the feasibility of such a practice, we investigated the automatic delineation robustness of the Mirada software (Mirada Medical, UK) to generate these volumes. **Materials/methods:** Forty randomly selected CT-scans of breast cancer patients were used. All were delineated by a radiation therapist following international recommendations (Duane et al., 2017). A planning organ at risk volume (PRV) with a 10 mm margin centered on the LADCA was also performed. Among the forty CT-scans, twenty were used to develop the automatic segmentation atlas using “Workflow Box” auto-segmentation algorithm. The remaining twenty other CT-scans were compiled on the software in order to obtain auto-segmented structures. The relevance of the contours was carried out with the Artiview software (Aquilab, Loos-lès-Lille, France) in order to determine both Dice-similarity coefficients (DSC) and Jaccard indexes. Finally, dosimetric planning treatment in volumetric modulated arc therapy conditions was performed using Eclipse treatment planning system (Varian). **Results:** Because of variability, both in terms of shape and spatial localization, the atlas-based auto-segmentation software did not succeed in LADCA delineation. Then, LADCA contours were not available for DSC and Jaccard indexes assessment. On the other hand, the use of margins on the LADCA made it possible to create such an Atlas. The average DSC is 0.36 ± 0.15 and the Jaccard index reaches 0.23 ± 0.11. The results associated with dosimetry planning treatment are presented in Table 1.**Table 1 Dosimetric results from VMAT optimization for breast radiotherapy treatments.**

| | Left breast | | Right breast | |
|---|---|---|---|---|
| | PRV | LADCA | PRV | LADCA |
| Average dose (Gy) | 12.71 ± 6.54 | 13.24 ± 7.48 | 5.86 ± 1.34 | 5.61 ± 1.39 |
| Median Dose (Gy) | 11.75 ± 6.57 | 13.32 ± 8.33 | 5.75 ± 1.32 | 5.59 ± 1.27 |
| Maximum dose (Gy) | 33.29 ± 12.85 | 25.28 ± 11.18 | 10.25 ± 1.96 | 7.99 ± 2.09 |

The use of a PRV instead of the LADCA contour tends to overestimate the maximum doses by around 30%. However, the mean and median doses are of the same order of magnitude. **Conclusion:** Small volume structures do not allow the creation of a robust contouring atlas. However, to overcome this limitation, the use of margins to define a PRV has been quite effective. However, it overestimates the maximum doses by about 30%, so the constraints used to limit doses to the coronary arteries during treatment planning will have to be adjusted in this way.

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B-catenin-ccl2 axis regulates breast cancer stem cells via crosstalk between cancer cells and tumor-associated macrophages

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Breast cancer is most frequently diagnosed cancer among women worldwide. Though advance in diagnosis and treatment strategies have prolonged disease-free survival (DFS) and overall survival (OS) for different molecular types of breast cancer patients, many patients initially benefit from chemotherapy but experience recurrence, metastasis, and ultimately death. Breast cancer stem cells (BCSCs) are tumor initiating cells with self-renewal, low differentiation, and high tumorigenicity and metastasis abilities. The ineffectiveness of conventional chemotherapy to eradicate BCSCs frequently results in therapy failure. Therefore, understanding the molecular pathways sustaining BCSC characteristics and targeting BCSCs will ultimately improve breast cancer treatments. Here, we found that activation of β-Catenin directly regulated CCL2 expression at the transcriptional level, and in turn, promoted tumor-associated macrophage **(**TAM) infiltration and M2 polarization. Moreover, crosstalk between the TAM and breast cancer cells increased secretion of CCL2, which promoted cancer progression by regulating BCSCs characteristics through feedback activation of β-Catenin. The combined inhibition of CCR2 and β-catenin synergistically suppressed breast cancer growth. The results described herein provide novel insights into our understanding how the β-Catenin-CCL2 feedback loop mediates the crosstalk between cancer stem cells and tumor-associated macrophages. They may also facilitate the development of useful therapeutic targets against BCSCs for breast cancer therapy.

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Symptoms of cold discomfort are reduced in breast cancer patients with a composite cytokine pattern associated with increased anti-tumor immunity

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**Background:** In preclinical models of breast cancer (BC), chronic stress enhances tumor growth and metastasis through β-adrenergic signaling as part of the “fight or flight” stress response pathway. These effects involve norepinephrine-mediated sympathetic regulation of cancer-related immunity. In a novel discovery, adrenergic stress in tumor-bearing mouse models of BC was associated with symptoms of intense cold discomfort, reduced CD8+ T cells, and higher immunosuppressive myeloid derived suppressor cells (MDSC) and regulatory T cells. BC survivors often experience heightened sympathetic activation and anecdotally report symptoms of feeling overly cold. Based on preclinical findings, symptoms of cold discomfort reported by BC survivors are hypothesized to identify those with reduced anti-cancer immunity and increased immunosuppression. **Methods:** Women with incident stage I to III BC were prospectively enrolled into the Women’s Health after Breast Cancer Study prior to BC treatment at Roswell Park Comprehensive Cancer Center. Participants provided blood samples and completed a survey assessing BC risk factors at the time of diagnosis and survivorship outcomes one-year post. Symptoms of being persistently and inappropriately cold as well as the occurrence of hot flashes and sweats were assessed using a Likert scale patterned on the validated Multidimensional Assessment of Fatigue Scale. A total of 424 women who had questionnaire data and plasma samples were included in the study. A panel of 27 Th1, Th2, Th9, and Th17 cytokines were assayed using a multiplex Luminex bead-based approach. Perceived symptoms of thermal discomfort were evaluated using logistic regression over cytokine tertiles (T1, T2, T3). Principal component analysis (PCA) was used to identify clusters of cytokines associated with symptoms of thermal discomfort. Cytokine composite scores were further refined based on their role with anti-tumor or pro-tumor activity. Multivariate models were adjusted for age, race, menopausal status, body mass index, stage, estrogen receptor status, grade, and treatment received. **Results:** Forty-six percent (195/424) of patients reported symptoms of feeling cold while 65% (275/424) experienced hot flashes and night sweats. There were no differences in patient or tumor characteristics between women who reported feeling cold versus those who did not, with women receiving chemotherapy more likely to report feeling cold ($p = 0.01$). Importantly, menopausal onset occurring after BC diagnosis or receipt of hormonal therapy were not associated with symptoms of feeling cold, but as expected were associated with experiencing hot flashes indicating that feeling cold is a distinct symptom from hot flashes. Higher pre-treatment levels of IL-6 was associated with 40-55% lower risk of feeling inappropriately cold 1-year post-diagnosis (T3 vs T1: OR=0.58, 95% CI: 0.34-1.00, $p=0.01$). PCA analysis identified a composite cytokine score at 1-year post diagnosis, which included the Th1 cytokines IL-12p70 and TNFα, IL-9 and IL-21 as cytokines involved in Th9 antitumor immunity, and the type 3 interferon IFN-λ2/IL-28α, which are all associated with increased CD8+ T cell activity. Increased scores were associated with reduced odds of feeling cold (T3 vs T1: OR=0.42, 95% CI: 0.23-0.77, $p=0.02$). Hot flashes in contrast were not associated with individual cytokine levels or composite scores. **Conclusions:** Symptoms of cold discomfort are less likely to be reported by BC survivors with a composite cytokine pattern associated with increased anti-tumor immunity. Further research is needed to determine if this symptom is associated with increased adrenergic stress and worse BC outcomes as observed in preclinical models.

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Sar439859, a novel selective estrogen receptor degrader (serd), demonstrates effective and broad antitumor activity in wild-type and mutant er-positive breast cancer models

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Primary treatment for estrogen receptor-positive (ER+) breast cancer is endocrine therapy. However, substantial evidence indicates a continued role for ER signaling in tumor progression. Selective estrogen receptor degraders (SERDs), such as fulvestrant, induce effective ER signaling inhibition, although clinical studies with fulvestrant report insufficient blockade of ER signaling, possibly due to suboptimal pharmaceutical properties. Furthermore, activating mutations in the ER have emerged as a resistance mechanism to current endocrine therapies. New oral SERDs with improved drug properties are under clinical investigation, but the biological profile that could translate to improved therapeutic benefit remains unclear. Here we describe the discovery of SAR439859, a novel, orally bioavailable SERD with potent antagonist and degradation activities against both wild-type and mutant Y537S ER. Driven by its fluoropropyl pyrrolidinyl side chain, SAR439859 has demonstrated broader and superior ER antagonist and degrader activities across a large panel of ER+ cells, compared with other SERDs characterized by a cinnamic acid side chain, including improved inhibition of ER signaling and tumor cell growth. Similarly, *in vivo* treatment with SAR439859 demonstrated significant tumor regression in ER+ breast cancer models including MCF7-ESR1 wild type and mutant-Y537S mouse tumors, and HCI013, a patient-derived tamoxifen-resistant xenograft tumor. These findings indicate that SAR439859 may provide therapeutic benefit to patients with ER+ breast cancer, including those have resistance to endocrine therapy with both wild-type and mutant ER. This presentation will highlight the global profile and key features of new SERD and its translation to patient.

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Real-world efficacy of ribociclib + aromatase inhibitor/fulvestrant, or endocrine monotherapy, or chemotherapy as first-line treatment in women with HR-positive, HER2-negative locally advanced or metastatic breast cancer: Third interim analysis from the RIBANNA study

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**Background:** In MONALEESA-3 and MONALEESA-7 trials, ribociclib (RIB, a selective CDK4/6 inhibitor) in combination with endocrine therapy (aromatase inhibitor [AI] or fulvestrant [FUL]) demonstrated a significant prolongation of overall survival among patients with breast cancer (BC), regardless of menopausal status and treatment-line. In the premenopausal or perimenopausal women, RIB + AI/FUL should be combined with a luteinizing hormone-releasing hormone agonist. The real-world evidence for the effectiveness, safety, and tolerability of RIB + AI/FUL in the routine clinical practice is needed to support the use of this combination. **Methods:** RIBANNA is a prospective, non-interventional study ongoing in Germany since October 2017. Pre-, peri- and postmenopausal women (planned, n = 3020) treated with RIB + AI/FUL, or endocrine monotherapy (ET), or chemotherapy (CT) as the first-line treatment for HR+/HER2- aBC in accordance with German guidelines were included. Data from routine clinical practice in all 3 cohorts, including further lines of sequential therapy, were collected. Updated data on baseline demographics and safety analysis will be presented. Additionally, first experience with CANKADO, an innovative digital and patient-friendly application for electrocardiogram (ECG) measurement, are described. By combining this app to Kardia mobile (AliveCor's single lead device), single-lead ECG can be recorded and sent via the CANKADO app for a cardiologist to read over. The cardiologist reviews the measurements, and reports the corrected QT interval by Fredericia (QTcF) results towards the trial site. Impact of the use of CANKADO onto the clinical routine will be analyzed. **Results:** For the second interim analysis, 1141 patients were enrolled until July 12th, 2019, while the full analysis set comprised 813 patients (Table 1). Median duration of RIB exposure in patients on RIB + AI/FUL vs total population was 151 vs 150 days respectively. At cut-off date, patients received first-line (89%, n = 1016), second-line (7%, n = 82), and third-line treatments (1%, n = 11). A starting dose of 600 mg per day for RIB in the first-line setting was seen in most of the patients (85%); data of second-line patients will be reported later. The first-line mean daily dose of RIB was 451.6 mg/day RIB was prescribed mainly in combination with letrozole (75%), fulvestrant (12%), anastrozole (7%), and exemestane (6%). A total of 62% of patients in the study were documented as therapy-naïve for ET. Of 424 patients with early breast cancer, 129 (30%) had documented prior CT without ET. The most common all-grade adverse events frequently noted in RIB + AI/FUL cohort in comparison with other cohorts were nausea (RIB [19%] vs ET [9%] vs CT [11%]), neutropenia (19% vs 1% vs 10%), fatigue (17% vs 9% vs 14%), and leukopenia (14% vs 4% vs 12%). The usage of CANKADO application to assess QTcF was initiated in the year 2019 and first data will be presented. **Conclusion:** RIBANNA study showed diverse population characteristics among the patients who received RIB treatment in a real-world setting. The third interim analysis is planned in October 2020, and the updated baseline data, information on safety, digital ECG measurement using CANKADO application will be presented.

Baseline Demographic Characteristics as of Second Interim Analysis

| **Demographic Variable** | **RIB + AI/FUL (n = 658)** | **Endocrine Therapy (n = 78)** | **Chemotherapy (n = 77)** |
|---|---|---|---|
| **Mean age, years (SD)** | 67 (11) | 72 (12) | 62 (10) |
| **Mean time since initial diagnosis, years** | 6.1 | 7.2 | 3.6 |
| **T stage at baseline*, n (%)** | | | |
| TX | 204 (31) | 28 (36) | 18 (23) |
| T0+T1 | 132 (20) | 12 (15) | 11 (14) |
| T2-T4 | 302 (46) | 35 (45) | 42 (54) |
| **N stage at baseline*, n (%)** | | | |
| NX | 212 (32) | 29 (37) | 28 (36) |
| N0+N1 | 317 (48) | 36 (46) | 35 (46) |
| N2+N3 | 108 (16) | 10 (13) | 8 (10) |
| **M stage at baseline*, n (%)** | | | |
| MX | 6 (1) | 0 (0) | 0 (0) |
| M0 | 18 (3) | 1 (1) | 1 (1) |
| M1 | 616 (94) | 75 (96) | 71 (92) |
| **Metastatic location at baseline*, n (%)** | | | |
| CNS, liver, lungs | 258 (39) | 14 (18) | 42 (54) |
| Bone only | 181 (28) | 42 (54) | 11 (14) |
| Skin, lymph nodes, other | 149 (23) | 16 (20) | 14 (18) |
| *Remaining cases are missing.<br>CNS, central nervous system. | | | |

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Utility of rapid autopsy in cancer research: Unexpected findings and lessons learned from warm autopsies of metastatic breast cancer patients

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Metastatic disease is understudied largely because of inaccessibility to quality specimens for research use. The Legacy Project, a rapid or “warm”, autopsy program at City of Hope, seeks to overcome this challenge by collecting tissue from metastatic patients immediately (within 6 hours) after their death. This paradigm serves as a specimen resource to address many clinically relevant questions, such as disease heterogeneity and mechanisms driving disease progression. Using this model, we uncovered clinically relevant disease information that is normally unavailable while a subject is alive. In this study, 9 metastatic breast cancer patients and their families were approached and consented prior to death. The cohort includes a diversity of clinical presentations in terms of disease subtype, progression history, organ involvement, and final cause of death. A total of 533 specimens were collected across 9 subjects. The average time from death to specimen acquisition was 6.1 hours (range: 4.03 - 7.66 hours; median: 5.71 hours). Total number of specimens collected from each participant ranged from 38-75, with an average of 60 across all patients; the mean number of tumor-positive specimens collected was 29 (range 12-46); the mean number of non-cancer specimens collected was 31 (range 25-45). In patients with primary estrogen receptor (ER) positive disease, we observed variable heterogeneity in estrogen, progesterone, and ki67 status across metastatic lesions. Furthermore, we observed a profound shift in disease phenotype towards end of life, trending towards complete loss of hormone receptor expression and stark increase of Ki67 levels. At the time of procurement, one third of subjects exhibited clinically unidentified diseased sites in organs not commonly associated with breast cancer metastases a, including ovary, kidney, and pancreas. In two other instances, “resolved” bone specimens (as measured by absence of FTG uptake in PET/CT imaging) were later determined to be >30% tumor positive when assessed by H&E. While these preliminary findings generate more questions than answers regarding mechanisms of metastatic progression and resistance to therapy, they highlight the utility of rapid autopsy in a research setting. We suggest that many unanswered clinical questions can be addressed through interrogation of post-mortem tissues and we urge research institutions to thoughtfully consider adoption of the “rapid autopsy” model.

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# Identifying the most relevant descriptors when evaluating ultrasound images in breast cancer diagnostics: A secondary analysis of an international multicenter trial

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Background and objectives: The Breast Imaging Reporting and Data System (BI-RADS) provides a standardized way to describe ultrasound images in breast cancer diagnostics. However, there is little information which descriptors are most strongly associated with malignancy and to which extend the single descriptors (tissue composition, shape, orientation, margin of lesion, echo pattern, posterior features, and calcifications) should be considered for the final evaluation of risk of malignancy. Thus, we aimed to identify which BI-RADS descriptors are most strongly associated with malignancy when evaluating ultrasound images in breast cancer diagnostics.
Methods: This multicenter, prospective trial took place at 11 trial sites in Austria, France, Germany, Japan, Netherlands, Portugal, and the US from February 2016 to March 2019. The trial enrolled 1288 women presenting with a lesion ≥0.5 and ≤5 cm in 2D B-mode ultrasound. The examiner conducted a routine 2D B-mode ultrasound examination and had additional standard information about the patients' disease history and family history. The examiner described the ultrasound images according to BI-RADS. All patients underwent histopathological confirmation which was the gold standard against which the clinical examiner was compared. We performed univariate and multivariate analyses using descriptive statistics, Chi-Square test, and logistic regression to identify which image descriptors are associated with malignancy.
Results: Histopathologic evaluation showed malignancy in 368 of 1288 lesions (28.6%). The descriptors most strongly associated with malignancy were spiculated margins (rate of malignancy 84.9%; 79 of 93), calcification (69.9%; 51 of 73), un-parallel orientation (65.9%; 187 of 284), angular margins (64.6%; 64 of 99), posterior shadowing (62.4%; 88 of 142), irregular shape (55.2%; 208 of 377), and indistinct margins (52.0%; 185 of 356). Different tissue compositions and echo patterns were least useful to distinguish between malign and benign lesions. Upon multivariate analysis, calcifications (OR 5.52; 95% CI 1.94-15.87) and posterior shadowing (OR 16.13; 95% CI 2.75-90.91) remained significantly ($p<0.05$) associated with malignancy.
Conclusion: We identified which BI-RADS descriptors are most strongly associated with malignancy when evaluating ultrasound images in breast cancer diagnostics. Future research may look into providing not only a standardized image description but also a standardized final evaluation for the rate of malignancy with respect to the different predictive usefulness of the single descriptors. This may further standardize and objectify the risk evaluation in breast cancer diagnostics.
Trial registration: NCT02638935

Table 1: Association of BI-RADS descriptors with final histopathologic results

| | benign pathology | malignant pathology | p-value |
|---|---|---|---|
| **tissue composition** | | | p<0.0001 |
| homogeneous background texture; fat -no. (%) | 185 (60.3) | 122 (39.74) | |
| homogeneous background texture; fibroglandular -no. (%) | 378 (77.3) | 111 (22.7) | |
| heterogeneous background texture -no. (%) | 356 (72.7) | 134 (27.4) | |
| **shape of lesion** | | | p<0.0001 |
| oval -no. (%) | 659 (86.1) | 106 (13.8) | |
| round -no. (%) | 89 (62.7) | 53 (37.3) | |
| irregular -no. (%) | 169 (44.8) | 208 (55.2) | |
| **orientation of lesion** | | | p<0.0001 |
| parallel -no. (%) | 806 (82.6) | 170 (17.42) | |
| not parallel -no. (%) | 97 (34.15) | 187 (65.9) | |
| **margin of lesion** | | | p<0.0001 |
| circumcised -no. (%) | 644 (89.0) | 80 (11.0) | |
| indistinct margin -no. (%) | 171 (48.0) | 185 (52.0) | |
| angular margin -no. (%) | 35 (35.4) | 64 (64.6) | |
| microlobulated margin -no. (%) | 117 (60.0) | 78 (40.0) | |
| spiculated margin -no. (%) | 14 (15.1) | 79 (84.9) | |
| **echo pattern** | | | p=0.02 |
| anechoic -no. (%) | 7 (100) | 0 (0.0) | |
| hyperechoic -no. (%) | 30 (79.0) | 8 (21.0) | |
| complex cystic and solid -no. (%) | 52 (82.5) | 11 (17.5) | |
| hypoechoic -no. (%) | 645 (71.0) | 264 (29.0) | |
| isoechoic -no. (%) | 40 (78.4) | 11 (21.6) | |
| heterogeneous -no. (%) | 136 (64.8) | 74 (35.2) | |
| **posterior features** | | | p<0.0001 |
| none -no. (%) | 590 (73.2) | 216 (26.8) | |
| enhancement -no. (%) | 249 (83.3) | 50 (16.7) | |
| shadowing -no. (%) | 53 (37.6) | 88 (62.4) | |
| combined pattern -no. (%) | 20 (58.8) | 14 (41.2) | |
| **calcification** | | | p<0.0001 |
| no calcification -no. (%) | 894 (73.8) | 317 (26.2) | |
| calcification -no. (%) | 22 (30.1) | 51 (69.9) | |

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# Long-term personal, social and financial impact of advanced breast cancer: Results from the invisible woman 2.0, a pan-European patient and carer survey

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**Background.** There is currently no cure for advanced breast cancer (ABC) and patients living with the disease are faced with many challenges influencing their ability to work and carry out daily tasks. ABC also imposes significant direct and indirect costs to the society. Healthcare systems vary considerably across Europe in equal high-quality care for all, with discrepancies in clinical outcomes and access for patients. A European patient and carer survey (The Invisible Woman) in 2013 showed that many women with ABC in Europe were suffering with psychological, social and financial hardships. A replication of the survey (2.0) was performed in 2019 to assess the progress made since 2013 and the work that still needed to be done. **Methods.** A cross-sectional survey via computer-assisted web interviews was conducted in eight countries (Italy, Spain, France, Sweden, Poland, Belgium, the Netherlands, Israel), involving 98 participants, 36% of whom were patients (n=35) and the rest carers (n=63). All patients were female with Stage IIIB-IV breast cancer and were fully aware of their condition. **Results.** The mean age of patients was 45 (range 18□69) years, 77% of whom were married or in a relationship and 82% with children. In 2019, 60% of women saw their household income drop as a result of their illness. 74% (vs 50% in 2013, n=304) of women had to make changes to their employment; 26% (vs 17% in 2013) were earning less than 11,778 € a year. The reduction in income led to 55% (vs 24% in 2013) of women having difficulty contributing financially and 69% (vs 38% in 2013) having to spend less. Furthermore, 69% of women admitted the change in their financial situation had caused psychological or physical problems, compared with 39% in 2013. The percentage of women who felt they had become isolated from the early-stage breast cancer community almost doubled from 18% in 2013 to 33% in 2019; 27% felt they received less support than when they were first diagnosed with breast cancer, a sharp increase from 15% in 2013. Findings on the emotional and physical impact of ABC in 2019 were largely comparable to those in 2013, with around 60% of women experiencing anxiety, depression, pain and discomfort which interfered with daily life; however, the proportion of women who lost confidence increased from 37% in 2013 to 58% in 2019. Similar to 2013, quality of life, followed by access to the treatment, was identified as the greatest unmet need. Information provision also requires improvement, with only 39% of participants finding the information provided by healthcare professionals useful, compared with 71% in 2013.**Conclusions.** The Invisible Woman 2.0 (2019) confirms the findings of the previous survey in 2013, and highlights that, despite several actions have been put in place for six years, several unmet needs remain unaddressed. ABC has a profound personal, societal and economic impact on patients and carers. The survey highlights the worsened practical financial situations of women with ABC and the need for improved workplace policies, as well as the impact on quality of life and a continued lack of provision of information and support. It is paramount that all relevant stakeholders work together to optimise the care of women with ABC and that the initiatives created are given more visibility and made known to patients and carers.

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# Novel iodine nanoparticle micro-localization and resultant radiotherapy-enhancement of triple negative human breast cancer growing in the brains of athymic nude mice

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About 30% of breast cancers metastasize to brain; those widely disseminated are fatal typically in 3-4 months, even with the best available surgery, drugs, and radiotherapy. To address this dire situation, we have developed iodine nanoparticles (INPs) that target brain tumors after intravenous (IV) injection. The iodine then absorbs X-rays during radiotherapy (RT), creating free radicals and local tumor damage, effectively boosting the local RT dose at the tumor. Efficacy was tested using the very aggressive human triple negative breast cancer (TNBC, MDA-MB-231 cells) growing in the brains of athymic nude mice. With a well-tolerated non-toxic IV dose of the INPs (7 g iodine/kg body weight), tumors showed a heavily iodinated rim surrounding the tumor having an average uptake of 2.9% iodine by weight (peaks at 4.5%), calculated to provide dose enhancement factors of ~5.5 (peaks at 8.0) -- the highest ever reported for any radio-enhancing agents. With 15-Gy, single dose RT, all animals died by 72 days; INP pretreatment resulted in longer-term remissions with 40% of mice surviving 150 days and 30% surviving > 280 days (Hainfeld et al., 2020). Fluorescence confocal microscopy revealed most INP staining co-localized with CD31 in the tumor center and tumor periphery. Greatest INP and CD31 staining was in the tumor periphery, the region of increased Micro CT contrast. Tumor cells are seen to line irregularly-shaped spaces (ISS) with INP and CD31 staining very close to or on the tumor cell surface and with PAS stain on their boundary and may represent a unique form of CD31-expressing vascular mimicry in intracerebral 231-tumors. INP and CD31 co-staining is also seen around ISS formed around tumor cells migrating on CD31 positive blood-vessels. We hypothesize that breast cancer cells secrete a CD31 containing scaffold to which IV-injected INPs bind; tumor cells proliferate along the scaffold forming the boundaries of the ISS creating a form of vascular mimicry. The significant radiation dose enhancement to the prolific INP-binding ISS found throughout the tumor but concentrated in the tumor rim, may contribute significantly to the life extensions observed after INP-RT; vascular mimicry could represent a new nanoparticle, particularly INP, tumor-homing target.

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# Impact of drug-drug interaction on palbociclib serum levels: Interest of therapeutic drug monitoring

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Background: The CDK4/6 inhibitors palbociclib is prescribed in association with hormonal therapy for the management of metastatic breast cancer patients. Like most oral targeted drug, therapeutic drug monitoring may be used for personalize their dosage. Using a recently published dosing technique (LC-MS/MS), we aimed at evaluating the correlation between first-cycle palbociclib plasma exposition and co-medications in order to evaluate drug-drug interaction (DDI) impact under palbociclib treatment.Methods: This is an open-label phase 4 study conducted in female subjects with first-line metastatic breast cancer (NCT04025541) treated with a palbociclib-aromatase inhibitor association. Plasma concentration of palbociclib was assessed at 24 hours postdose (plasma trough concentration $C_{trough}$) at day 15 of first cycle of treatment. A dedicated pharmacist consultation allowed the determination of clinical covariates of interest, such as weight, body surface area, ethnicity, food intake, co-medications use and DDI before Palbociclib initiation and retrospectively at the end of clinical trial. Patients were classified then according to their risk of DDI potentially leading to inhibition of CYP3A4 and/or P-glycoprotein and gastric pH increase by gastric acid-suppressive (GAS) agents (such as proton pump inhibitors, histamine H2-receptor blockers or alginic acid). Relevant drug known to have an inhibition of CYP3A4 and/or P-glycoprotein or pH-modification activity were checked in databases (e.g. DDI predictor®, Drugs.com®, Pubmed®). Results: To date, after $C_{trough}$ analysis of the 35 first cases, the geometric mean (± standard deviation [min-max]) of palbociclib plasma $C_{trough}$ was 79.5 ng/ml (± 26.1% [43.6 ng/mL - 133 ng/mL]) at day 15, similar to what reported in the PALOMA trials. No correlation between plasma concentration and body weight, body area or also age of the patients was found in our cohort. Regarding ethnicity, all the included patients were from Caucasian origin. 31% of patients (11/35) were identified of taking drugs that could cause DDI CYP3A4 and P-glycoprotein inhibition mediated (amlodipine n=3, simvastatin n=3, losartan n=2, fluconazole n=1, atorvastatin n=1, ivabradine n=1). These potential DDI interactions were associated with a significantly higher palbociclib concentration DDI subgroup (102 ng/mL vs 69 ng/mL) (p=0.000272) (Table 1). No CYP3A4 and/or P-glycoprotein inductor were reported in cohort. 1.4% of patients (5/35) were identified of taking GAS agents (pantoprazole n=2, ranitidine n=2, alginic acid n=1). We found a significantly reduction of palbociclib concentration (59.2 ng/mL vs 79.8 ng/mL) (p=0.048) in patients taking GAS medications (Table 1).

| | |
|---|---|
| **Plasma palbociclib concentrations (ng/ml), global cohort (n=35)** | |
| Geometric mean (CV%) (min;max) | 79.5 (26.1%) (43.6;133) |
| **Plasma palbociclib concentrations (ng/ml), cohort with DDI CYP3A4 and P-gp mediated (n=11)** | |
| Geometric mean (CV%) | 102 (24.3%) |
| **Plasma palbociclib concentrations (ng/ml), cohort without DDI CYP3A4 and P-gp mediated (n=24)** | |
| Geometric mean (CV%) | 69 (19.8%) |
| **Plasma palbociclib concentrations (ng/ml), cohort with GAS treatment (n=5)** | |
| Geometric mean (CV%) | 59.2 (15.9%) |
| **Plasma palbociclib concentrations (ng/ml), cohort without GAS treatment (n=30)** | |
| Geometric mean (CV%) | 82.9 (26.1%) |

Table 1: Patients' plasma palbociclib concentration (day 15 of cycle 1 of treatment).Conclusion : These preliminary results, in real-life settings, obtained with our recently-published HPLC-MS/MS method, give important information on palbociclib monitoring and pharmacokinetic variability. DDI appear to have a significant impact on palbociclib plasma exposure, GAS agents are already know to modified palbociclib absorption. Additional studies are needed to characterize palbociclib plasma concentration variations between patients, and their clinical impact on efficacy and safety. The study is ongoing and will evaluate additional potential clinical and biological impact of DDI on neutropenia occurrence, on a larger population of patients.

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Differences in the benefit of multi-gene panel (MGP) genetic testing between African American and white women with invasive breast cancer

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**Background:** Up to 10% of breast cancers are hereditary. Pathogenic variants (PV) in the *BRCA1*/2 genes are responsible for two thirds of hereditary breast cancer (BC). Additional non-*BRCA* genes (*ATM*, *CHEK2*, *PALB2*, etc.) have been identified as predisposing for BC. While genetic testing(GT) for hereditary BC traditionally involved testing mostly for mutations in the *BRCA1/2* genes, next generation sequencing has enabled multiple BC genes to be simultaneously tested at a cost often lower than testing for BRCA1/2 alone. Consequently, MGP testing has been rapidly replacing *BRCA1*/2 only testing. Studies have demonstrated that MGP testing doubles the detection of PV. Because prior studies examining MGP findings have been mostly conducted in predominantly white populations, it is unknown if the use of MGP testing in African-American (AA) patients also results in increased detection of non-*BRCA* mutations and whether there are significant differences in the prevalence of PV between AA and white women with invasive BC. In this study, we sought to compare the rate and spectrum of PV between AA and White women with invasive BC undergoing MGP testing. **Methods:** In this retrospective study, we assessed the prevalence of PV and spectrum of mutations among a cohort of 680 racially diverse women diagnosed with invasive BC who underwent GT with a MGP between 2014 and 2019 at a single cancer center. This analysis included participants who had a documented diagnosis of invasive BC and completed MGP testing. Fisher's exact tests were used to analyze differences between racial groups. Subjects previously signed informed consent to participate in research. **Results:** 680 women with invasive BC were included in the study. The study population was 79.4% non-Hispanic white, 10.6% AA, and 10% other. PV were identified in 13.4 % of the overall population. The prevalence of PV was 15.5% (84/540) in AA compared to 8.3% (6/72) in white women, but this difference was not statistically significant (p=0.14). In white women, the prevalence of PV was 5.9% (32/540) in *BRCA1/BRCA2* and 9.6% (52/540) in non-*BRCA* genes. MGP testing allowed for the detection of 52 non-*BRCA* PV, including BC genes (*CHEK2*-17, *ATM*-7, *PALB2*-4, *CDH1*-2, *BARD1*-1, *TP53*-1, *RAD50*-1) and non-BC genes (*MUTYH*-8, *NTHL1*-2, *BRIP1*-2, *PMS2*-2, *RAD51C*-1, *RAD51D*-1, *MSH6*-1, *FH*-1, *MITF*-1). In AA patients, the prevalence of PV was 6.9% in *BRCA1*/2 and 1.4% in non-*BRCA* genes. MGP testing in AA women with invasive BC detected only one non-*BRCA* mutation in the gene *MUTYH*. VUS rates were higher in AA, 29.2% compared to whites, 19.3% with a trend towards a statistically significant difference (p=0.07). **Conclusions:** While MGP testing more than doubled the detection rate of PV in white patients with BC by detecting various non-*BRCA* PV, for AA patients the use of MGP testing did not result in many additional non-*BRCA* PV being identified in this analysis. However, MGP testing did result in a high VUS rate, 19.3%, without the added value of detecting additional PV that could be helpful to the patient and their family members by expanding opportunities for cancer prevention and early detection. We acknowledge that in this study sample of 10.6% AA women, this is an under-representation. Large population-specific studies should be done to confirm those findings. Given the known psychological harms to the patient and their family members in response to the uncertainty of VUS findings as well as the possible mismanagement of VUS results, well-designed studies should investigate the selection of who to consider for MGP testing rather than BRCA1/2 testing for hereditary BC to ensure that the benefits of MGP testing over *BRCA1/2* only testing outweigh the risks associated with panel testing.

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# Outcomes for metaplastic breast cancer differ by histologic subtype

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**Background:** Metaplastic breast carcinoma (MBC) is a rare, aggressive subtype of breast cancer. The majority of MBC has triple negative (TN) receptor status and has been associated with poorer overall survival compared to other TN breast cancers. MBCs constitute a histopathologically distinct and diverse entity, which can be further classified into subtypes. In this study, we report the largest single-institution study of MBC. We aimed to compare survival outcomes among the histologic subtypes of MBC and to compare MBC to a cohort of non-metaplastic TN breast cancer patients.
**Methods:** All pure MBC patients undergoing surgery from 1995-2017 were identified from our prospectively maintained institutional database. Based upon the World Health Organization classification of MBC, tumors were classified by subtype: squamous, spindle, heterologous mesenchymal, or mixed. Primary endpoints included overall survival (OS), breast cancer-specific survival (BCSS), and recurrence-free survival (RFS). A contemporary cohort of non-metaplastic TN breast cancer patients was also identified from our institutional database. Clinicopathologic, treatment, and survival outcomes were compared between the 2 groups.
**Results:** In total, 132 MBC patients were included: 45 heterologous mesenchymal (34.1%), 26 squamous (19.7%), 26 spindle (19.7%), 30 mixed (22.7%), and 6 other (4.5%). Median follow-up time among survivors with MBC was 5.8 years (0-19.4 years). Five-year OS rate was 76% (95% CI 0.68-0.84). Five-year BCSS rate was 79% (95% CI 0.71-0.87). OS and BCSS varied among MBC subtypes. Patients with heterologous mesenchymal subtype had the best OS and BCSS rates, 88% (95% CI 0.78-0.98) and 88% (95% CI 0.78-0.99), respectively. Patients with squamous subtype had the worst OS and BCSS rates, 50% (95%CI 0.26-0.73) and 56% (95%CI 0.32-0.79), respectively. No difference in locoregional recurrence was seen between the groups. TN breast cancer patients presented with smaller tumors than patients with MBC (1.7 vs 2.35 cm, $p < 0.001$) (Table). However, they were more likely to be pathologically node positive (40% vs 24%, $p < 0.001$). Kaplan-Meier survival analysis demonstrated improved OS, DSS, and RFS for patients with TN breast cancer compared to MBC. The RFS hazard ratio for MBC compared to TN breast cancer, adjusted for age, year of surgery, type of surgery, and pathologic tumor and nodal staging, was 2.38 (range 1.63-3.26, $p < 0.001$). Of the 10 MBC patients who received neoadjuvant chemotherapy, 4 progressed while on treatment and 3 had no response.
**Conclusions:** Metaplastic breast cancer is associated with poor survival outcomes compared to TN non-metaplastic breast cancer. The heterologous mesenchymal subtype is associated with the highest BCSS, while the squamous subtype is associated with the lowest BCSS. These data suggest that standard-of-care therapy for TN is not effective for MBC and that research is needed to identify therapies tailored to the unique biology of MBC.

Table. Patient, tumor, and treatment characteristics

| | | **Metaplastic (n = 132)** | **Non-Metaplastic TN (n = 1767)** | **p-value** |
|---|---|---|---|---|
| Median Age at Surgery (range) | | 56 years (46, 65) | 54 years (44,63) | 0.13 |
| Tumor Size (range) | | 2.4 cm (1.5, 3.5) | 1.7 cm (1.0, 2.5) | < 0.001 |
| Breast Procedure | Mastectomy | 62 (47%) | 787 (45%) | 0.65 |
| | Lumpectomy | 70 (53%) | 980 (55%) | |
| Tumor Subtype | HR-/HER2- | 114 (97%) | 1767 (100%) | < 0.001 |
| | HR-/HER2+ | 1 (0.9%) | 0 (0%) | |
| | HR+/HER2- | 2 (1.7%) | 0 (0%) | |
| | Unknown | 15 | 0 (0%) | |
| Family History of Breast Cancer | No | 70 (55%) | 914 (52%) | 0.6 |
| | Yes | 58 (45%) | 849 (48%) | |
| | Unknown | 4 | 4 | |
| Genetic Mutation | BRCA1 Pathogenic Mutation | 9 (27%) | 145 (31%) | 0.11 |
| | BRCA2 Pathogenic Mutation | 3 (9.1%) | 42 (9%) | |
| | Other mutation | 1 (3%) | 0 (0%) | |
| | Negative | 20 (61%) | 279 (60%) | |
| | Not Tested | 99 | 1301 | |
| Menopausal Status | Postmenopausal | 83 (63%) | 1007 (57%) | < 0.001 |
| Axillary Procedure | Sentinel Lymph Node Biopsy | 91 (69%) | 1018 (58%) | < 0.001 |
| | Axillary Dissection | 37 (28%) | 742 (42%) | |
| | None | 4 (3%) | 7 (0.4%) | |
| Pathologic Tumor Stage | t0 | 1 (0.8%) | 32 (1.8%) | < 0.001 |
| | t1 | 56 (42%) | 1082 (61%) | |
| | t2 | 59 (45%) | 585 (33%) | |
| | t3 | 11 (8.3%) | 51 (2.9%) | |
| | t4 | 5 (3.8%) | 17 (1.0%) | |
| Pathologic Nodal Stage | n0 | 100 (76%) | 1065 (60%) | < 0.001 |
| | n1 | 25 (19%) | 486 (28%) | |
| | n2 | 2 (1.5%) | 126 (7.1%) | |
| | n3 | 1 (0.8%) | 86 (4.9%) | |
| | nx | 4 (3%) | 4 (0.2%) | |
| Radiation Therapy | No | 59 (45%) | 585 (33%) | < 0.001 |
| | Yes | 71 (55%) | 1164 (67%) | |
| | Unknown | 2 | 18 | |
| Chemotherapy | Adjuvant | 118 (92.2%) | 1358 (77.6%) | < 0.001 |
| | Neoadjuvant | 10 (7.8%) | 81 (5%) | |
| | No | 0 | 312 (17.8%) | |
| | Unknown | 4 | 16 | |
| HR, hormone receptor; TN, triple negative | | | | |

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Fine-sliced neurocognitive assessments and high-resolution neuroimaging biomarkers to diagnose cancer- and chemotherapy-induced cognitive deficits (CCICD) - a pilot study

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***Background:*** Significant progress has been made in cancer survival, however there is much room for improvement in supportive cancer care. "*Chemo-brain*" is the lay language that some patients use to describe a cognitive fog or mental fuzziness that they experience soon after chemotherapy (CT) and that can last more than a decade after CT has ended. In this study, we examine the notion of accelerated cognitive aging as a potential side effect of cytotoxic CT.While CCICD has been widely researched, its underlying biological mechanisms are yet to be sufficiently elucidated. The long-range goals of this study are to (a) yield clinically valid diagnostic criteria for CCICD by the identification of fine-sliced neurocognitive measures that can reliably capture within-subject, nuanced, cognitive changes pre/post CT; and (b) identify brain-based biomarkers that can leverage future systemic therapies or adjunctive medications that are neuroprotective. ***Trial design:*** The study takes advantage of greater clarity offered by high-resolution neuroimaging (7Tesla) to delve into biomarkers associated with the neurotoxic effects of the common chemotherapeutic agents doxorubicin, paclitaxel, docetaxel, and cyclophosphamide on brain metabolism and iron homeostasis, which may result in CCICD. We innovate by harnessing magnetic resonance spectroscopy (MRS) together with quantitative susceptibility mapping (QSM) and diffusion tensor imaging (DTI), a trio that has rarely been combined in 7T imaging, to uncover biomarkers related to CCICD. In this high-resolution imaging environment, we hope to individually isolate and track changes in key neuronal metabolites such as glutamate and glutamine using MRS (pre- and post-CT), in a prospective, longitudinal study. At these two time-points, we simultaneously use QSM to identify regions of increased iron deposits (associated with doxorubicin) in the brain along white matter tracts as well as DTI to assess white matter degeneration.We selected fine-sliced measurements of cognitive updating, mental flexibility and impulse control, the key executive function (EF) deficits associated with CCICD. These and other global EF measures are administered pre/post-CT (within a period of 4-6 months), while assessments of depression, anxiety, sleep, and pain will be administered via a weekly online questionnaire during CT.**Eligibility criteria:** Eligible patients are adults (age ≥18) with either early stage HER2 negative breast cancer or diffuse large B-cell lymphoma who will receive curative-intent combination CT, to include cyclophosphamide. Patients are excluded if they have a prior history of cancer diagnosis or treatment. Patients would have to be 7T MRI compatible.**Specific Aims:** To obtain preliminary estimates of the change in EF measures, brain metabolite, iron concentrations, and white matter degeneration in patients pre- and post-CT, to inform a subsequent larger trial.**Statistical methods:** The proposed sample (N=9) size achieves 74.8% power to detect a 1 SD change with a significance level of 0.05 using a two-sided, one-sample t-test for the pairwise difference. Estimates and 95% confidence intervals will be reported. Additionally, the relationship between executive function, brain metabolite, iron concentrations and white matter degeneration will be explored.
**Present and Target accrual:** Accrual has thus far been delayed, partially due to due to COVID-19 restrictions on clinical research, beginning in March 2020. Target accrual is 9 patients.Contact information: Kanchna-ramchandran@uiowa.edu, Phone: 319-356-0535.

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Pharmacokinetic evaluation of an oral paclitaxel DHP107 (Liporaxel®) in patients with recurrent or metastatic breast cancer (MBC): Phase II study (OPERA, NCT03326102)

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**Background**: Paclitaxel is a microtubule stabilizing anticancer therapy used to treat multiple cancers including breast cancer. DHP107 is an oral paclitaxel solubilized in lipid components using DaeHwa-Lipid bAsed Self-Emulsifying Drug delivery system (DH-LASED) technology. It demonstrated comparable efficacy and safety to IV paclitaxel in a phase 3 study for patients with advanced gastric cancer (Ann Oncol 2018) leading to regulatory approval in Korea, and also met the primary endpoint (ORR 54.5%) as first-line therapy (ESMO 2019) in the OPTIMAL Phase II study in patients with HER2 negative metastatic breast cancer (MBC). The confirmatory OPTIMAL Phase III study is ongoing in Asia and Europe. The OPERA Phase II study was designed as multinational, multicenter, randomized, open-label study to establish pharmacokinetic (PK) profile and efficacy of DHP107 in patients with MBC in the U.S. **Method**: A total of 72 patients with metastatic HER2 negative (HR+/HER2- or triple-negative breast cancer (TNBC)) will be randomized in a 2:1 fashion to receive DHP107 (200mg/m$^2$ orally twice a day on Days 1, 8, and 15 in a 28-day cycle) or IV paclitaxel (80 mg/m$^2$ on Days 1, 8, and 15 in a 28-day cycle) until disease progression or unacceptable toxicity. Tumor assessments are performed every 8 weeks. PK analyses were performed in a subset of patients receiving DHP107. A total of 103 blood samples were collected on Day 1 of Cycle 1 at predose and 1, 2, 3, 4, 6, and 10 hours post dose (before the 2nd dose administration on Day 1), and at predose on Day 8 of Cycle 1. All PK parameters were calculated by non-compartmental analysis using Phoenix WinNonlin version® 8.1. **Results**: A total of 13 subjects were enrolled in the PK substudy, All 13 patients were female and of Caucasian, non-Hispanic, ethnicity. Median $T_{max}$ was 2.17 h (range 1.92-4.08). Mean $C_{max}$ and $AUC_{0\text{-}10h}$ and their coefficient of variations (CV) were 330 ng/mL (31.1%) and 1233 ng·h/mL (30.3%), respectively (Table 1). The PK parameters of DHP107 were similar to those in a previous Phase I study in Korean cancer patients where $C_{max}$ and $AUC_{0\text{-}48h}$ were 235 ng/mL (43.9%) and 1348 ng·h/mL (19.7%) (Invest New Drugs 2012).

**Conclusion**: PK profiles were well characterized from plasma concentrations in 13 Caucasian patients with MBC up to 10 hours after oral 200mg/m$^2$ BID administration. DHP107 was rapidly absorbed and eliminated and inter-individual variability in exposure such as $C_{max}$ and $AUC_{last}$ was considered low. Compared to previous phase I PK results in Korean patients, $C_{max}$ and AUC parameters were similar after dosing with DHP107, demonstrating no clinically significant differences between Asian and Caucasian patients. Safety and efficacy will be evaluated in the ongoing OPERA and OPTIMAL studies.

Table 1

| Statistic | $T_{max}$(h) | $C_{max}$(ng/mL) | $AUC_{last,\ 0\text{-}10h}$(ngh/mL) | $AUC_{inf}$(ngh/mL) |
|---|---|---|---|---|
| N | 13 | 13 | 13 | 11 |
| Mean(SD) | | 330(103) | 1233(374) | 1462(411) |
| CV% | | 31.1 | 30.3 | 28.1 |
| Median[Min-Max] | 2.17[1.92-4.08] | | | |

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Comparing survival differences between breast-conserving therapy and mastectomy in patients with early-stage breast cancer undergoing upfront surgery

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Background: Over the last decade, patients with early-stage breast cancer have been undergoing total mastectomy (TM) with increasing frequency. Our center reported that local recurrence rates with breast conserving therapy (BCT) declined throughout the 27-year period: from 7.1% for patients treated during 1970–1984 to 1.3% for patients treated during 1994–1996. More recently, several groups have published slightly improved survival rates in patients undergoing BCT compared with TM. The aim of this study was to evaluate trends in TM rates and compare overall survival (OS), distant metastasis-free survival (DMFS), local-regional recurrence (LRR) and disease-specific survival (DSS) between BCT and TM in patients with early-stage breast cancer undergoing upfront surgery. Methods**:** We identified women with clinical stage T1–2, N0–1, M0 breast cancer who underwent surgery as first treatment modality from 1/1/2000 to 12/31/2014 at our center. TM rates and survival outcomes were evaluated. Because the decision for surgery for those patients was not random, differences in patient, tumor and treatment characteristics with respect to surgery types were adjusted using inverse probability weighting (IPW) based on propensity scores. Variables in the model included age at diagnosis, clinical tumor T category, clinical nodal category, estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2) status and year of surgery, and a multinomial logit model was used for surgery treatment assignment and a Gamma model was used for the time to censor. IPW models were used to adjust for impact of surgery types on survival outcomes. Similar analysis was used in 6 subsets: Stage I & hormone receptor (HR)+/HER2-, Stage I & HER2+, Stage I &triple negative breast cancer (TNBC), Stage II & HR+/HER2-, Stage II & HER2+, Stage II & TNBC. Patients undergoing TM with RT were excluded from subset analysis due to small sample size.
Results**:** A total of 8,256 patients were included, of them, 4701 (56.9%) underwent BCT, 2862 (34.7%) underwent TM without RT and 693 (8.4%) underwent TM+RT. Patients who underwent TM were younger and were more likely to have larger tumors, positive lymph nodes, higher grade, and HER2-positive tumors. TM rates increased in patients <=50 years old from 2006-2013. At a median follow-up time of 6.1 years, multivariable Cox model showed that patients who underwent BCT had improved OS (HR: 0.8,95%CI: 0.7-0.99, P=0.02) and had a similar DSS, DMFS, and LRR compared to patients who underwent TM without RT. After IPW adjusting, patients undergoing BCT had a slightly worse DSS (RR: 1.2, 95%CI: 1.02-1.4, P=0.03) and similar OS, DMFS and LRR compared to patients underwent TM without RT in the whole cohort. In subset analyses, after IPW adjusting, there were no survival differences in OS, DSS, and DMFS between TM without RT and BCT. Patients with TNBC undergoing BCT had a lower LRR compared to TM (RR: 0.4, 95% CI: 0.3-0.6, P<0.001) regardless of clinical stage. Conclusions: In whole cohort**,** after IPW adjusting, patients undergoing BCT had a slightly worse DSS compared to patients underwent TM without RT, and those differences in DSS have disappeared in the subset analysis. LRR was lower in patients with TNBC breast cancer undergoing BCT although there as a similar OS, DSS and DMFS compared with TM in subset analysis. These contemporary data may help physicians in surgical decision making for patients who are candidates for either TM or BCT.

Table 1. Results from multivariable Cox models for factors associated with survival outcomes and IPW adjusted models for factors associated with survival outcomes

| | Cox Model | | | | IPW adjusting models | | |
|---|---|---|---|---|---|---|---|
| Factors | HR | P | 95%CI | | RR | P | 95% CI |
| OS | | | | | | | |
| Surgery type | | | | | | | |
| TM without RT | | | | | | | |
| BCT | 0.8 | 0.02 | 0.7 | 0.99 | 1.0 | 1.0 | 0.9-1.1 |
| TM with RT | 1.0 | 0.96 | 0.8 | 1.3 | 1.1 | 0.6 | 0.9-1.3 |
| DSS | | | | | | | |
| Surgery type | | | | | | | |
| TM without RT | Ref | | | | | | |
| BCT | 1.1 | 0.4 | 0.8 | 1.5 | 1.2 | 0.03 | 1.02-1.4 |
| TM with RT | 1.7 | 0.005 | 1.2 | 2.6 | 1.3 | 0.02 | 1.04-1.6 |
| DMFS | | | | | | | |
| Surgery type | | | | | | | |
| TM without RT | Ref | | | | | | |
| BCT | 1.1 | 0.4 | 0.9 | 1.4 | 1.0 | 0.5 | 0.9-1.2 |
| TM with RT | 1.7 | 0.002 | 1.2 | 2.4 | 0.9 | 0.7 | 0.7-1.2 |
| LRR | | | | | | | |
| Surgery type | | | | | | | |
| TM without RT | Ref | | | | | | |
| BCT | 1.3 | 0.1 | 1.0 | 1.7 | 1.0 | 0.7 | 0.7-1.2 |
| TM with RT | 0.4 | 0.02 | 0.2 | 0.9 | 0.8 | 0.1 | 0.6-1.1 |
| Subsets IPW adjusted models for factors associated with LRRBCT vs. TM without RT | | | | | | | |
| Stage I & HR+/HER2- | No. of patientsTM without RT/BCT | | | | RR | P | 95% CI |
| Stage I & HER2+ | 1469/2945 | | | | 1.0 | 0.9 | 0.8-1.3 |
| Stage I & TNBC | 199/285 | | | | 0.7 | 0.3 | 0.3-1.5 |
| Stage II & HR+/HER2- | 128/317 | | | | 0.4 | <0.001 | 0.3-0.6 |
| Stage II & HER2+ | 690/745 | | | | 1.1 | 0.7 | 0.7-1.8 |
| Stage II & TNBC | 102/108 | | | | 0.9 | 0.5 | 0.5-1.4 |
| Stage I & HR+/HER2- | 110/157 | | | | 0.5 | 0.048 | 0.3-0.99 |
| HER2 – human epidermal growth factor receptor 2; HR – hormone receptor; TNBC – triple negative breast cancer | | | | | | | |

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# cGAS-STING pathway protein expression in human primary breast cancer

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**Background:** The DNA-sensing nucleotidyl transferase enzyme cyclic GMP-AMP synthase (cGAS), its second-messenger product cyclic GMP-AMP (cGAMP), and the cGAMP sensor Stimulator of interferon Genes (STING) form a major cytoplasmic DNA-sensing mechanism in human cells [Barber GN. Nat Rev Immunol, 2015]. cGAMP-activated STING oligomers bind TANK-binding kinase 1 (TBK1), translocate from the endoplasmic reticulum to perinuclear vesicles, and phosphorylate transcription factor interferon (IFN) regulatory factor 3 (IRF3), resulting in IRF3 nuclear translocation to induce expression of type I IFNs such as IFNβ. This pathway is critical for controlling innate antiviral immune responses, and is implicated in anti-tumor adaptive immunity, yet little is known regarding its function in human primary breast cancer (BC). **Methods:** Immunohistochemistry (IHC) staining for cGAS (ab224144), STING (CST13647), TBK1 (HPA045797), IRF3 (ab25950) and IFNβ (ab238675) was performed on tissue microarrays constructed from 18 normal human breast tissue samples and 197 primary BC samples to characterize *in-situ* protein expression. Positive controls were normal colon, MCF10A cells, testis tissue, MCF-7 cells and normal colon for cGAS, STING, TBK1, IRF3 and IFNβ, respectively. Substitution of primary antibodies with 0.5% normal goat serum served as negative controls. Scoring of extent of the IHC-stained area was 0 for no IHC signal, 1 for <10%, 2 for 10% to 50%, and 3 for >50% of tumor cells. IHC intensity was scored as 0 for no IHC signal, 1 for weak, 2 for moderate, and 3 for strong. A final IHC score was the product of extent score and intensity score, as described [Xia T, et al. Cell reports, 2016]. Categorical classification of high versus low final IHC scores was determined using the median as an unbiased cutoff. Associations between cGAS-STING pathway protein constituents was interrogated by Pearson's test, and associations between STING pathway IHC expression and breast tumor clinicopathological features were by Chi-square. **Results:** Among 197 primary BCs, 51.5% were estrogen receptor (ER) positive/ human epidermal growth factor receptor 2 (HER2) negative, 28.4% were HER2 positive and 19.8% were triple negative BC (TNBC). Distinct cGAS-STING pathway expression patterns were observed among three BC subtypes (Table 1). Frequent high expression of cGAS-STING pathway constituents was observed in ER+/HER2- BC. By contrast, high cGAS expression was not associated with high STING expression or effector protein IFNβ in either HER2+ BC, or in TNBC. IRF3 and IFNβ expression was significantly positively associated with hormone receptor status (both P< .001); IFNβ expression was significantly inversely associated with higher grade (P=0.008) and higher mean Ki67 index (18 vs 10, P=0.005). High expression of IFNβ was positively correlated with higher levels of TBK1 and IRF3 (R=0.262 P<.001; R=0.347, P=<.001, respectively). **Conclusion:** To our knowledge, this is the first study to report cGAS-STING pathway *in situ* protein expression in primary BC, and demonstrates distinct expression patterns amongst different primary BC clinical subtypes. A limitation of this study is that IHC methods were insufficient for detecting post-translational modifications or translocation of STING pathway proteins. These results provide foundation for understanding the mechanisms of innate immune response in BC, as well as for developing new therapeutic strategies aimed at facilitating adaptive immune anti-tumor responses.

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Baseline characteristics of women enrolled in the POSITIVE trial (**p**regnancy **o**utcome and **s**afety of **i**nterrupting **t**herapy for women with endocrine respons**IVE** breast cancer)

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**Background:** Pregnancy is a major concern for young breast cancer (BC) survivors. Conception after BC in women with hormone receptor positive (HR+) disease is affected by the standard 5-10 years of adjuvant endocrine therapy (ET) during which pregnancy is contraindicated and fertility may be waning. The POSITIVE Trial (IBCSG 48-14/BIG 8-13/Alliance A221405/NCT02308085) investigates the impact of temporary ET interruption to allow pregnancy.
**Methods:** POSITIVE enrolled premenopausal women with stage I-III HR+ early BC, ≤42 years of age, who had received adjuvant ET (SERM alone, ovarian function suppression (OFS) plus SERM or AI) for 18 to 30 months, and wished to interrupt ET to attempt pregnancy. An interruption of ET for up to 2 years was foreseen to allow pregnancy (after a 3-month ET washout period), delivery, and breastfeeding if desired/feasible. Resumption of ET to complete 5-10 years of treatment was planned as soon as pregnancy/breastfeeding was completed or after it was ensured conception was not possible. We report baseline characteristics of participants enrolled in POSITIVE by region of enrollment.
**Results:** From 12/2014 to 12/2019, 518 participants were enrolled at 116 centers in 20 countries across 4 continents. The table shows the baseline characteristics of the enrolled women.

| Characteristic | |
|---|---|
| Region: Europe / North America / Asia-Pacific | 61% / 23% / 16% |
| Median age at enrollment, yrs (IQR) | 37 (33-39) |
| Caucasian race | 77% |
| No children prior to enrollment | 74% |
| Prior fertility preservation measures taken | 51% |
| Stage I / II | 46% / 45% |
| 0 / 1 positive nodes | 65% / 21% |
| Grade 2 / 3 | 48% / 33% |
| HER2-negative | 74% |
| Mastectomy | 46% |
| Chemotherapy | 61% |
| ET: SERM alone / SERM+OFS / AI+OFS | 41% / 35% / 16% |
| Median duration of prior ET, mos (IQR) | 23 (20-27) |

Several differences were seen across regions: A higher proportion of participants <35 yrs (43%) enrolled in North America than in Europe (33%) or Asia (26%). Eighty-one percent of Asian women had no children at enrollment compared to 75% and 68% of European and North American women, respectively. Consistently, a greater percent of women in Asia (56%) had used fertility preservation measures, compared to Europe (53%) and North America (43%). Stage distribution was also different across continents: a greater percent of Asian participants had stage I, grade 1 and node-negative disease (51%, 29% and 76 %, respectively) compared to European (46%, 14% and 67%) and North American (43%, 16% and 55%) women. Only 19% of Asian women had either 1-3 positive nodes and grade 3 tumors, the proportion increased to 28% and 35% in Europe and to 41% and 38% in North America, respectively. North American women were more likely to have had mastectomy (60% vs. Asian (44%) and European (41%)); European women were more likely to have had chemotherapy (69% vs. North American (56%) and Asian (42%)). ET administration prior to enrollment differed substantially by region: Most North American women had SERM (T) alone (58%), and when OFS was added to oral ET, it was combined with AI in 19% and with T in 8% of participants, respectively. In Asia most women received T + OFS (55%), followed by T alone (36%), and AI + OFS (6%). In Europe, T + OFS was the most frequent treatment (40%), followed by T alone (37%) and AI + OFS (17%). Median duration of ET before enrollment was similar across regions (22-24 months).
**Conclusion**: Regional variation of baseline characteristics of women enrolled in the POSITIVE trial may provide important insights into different medical and sociocultural attributes and attitudes of the study participants and investigators from those regions.
**Affiliation:** POSITIVE Investigators, International Breast Cancer Study Group, Alliance for Clinical Trials in Oncology, Breast International Group, North American Breast Cancer Group

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS10-17

Palbociclib (P) in combination with fulvestrant (F) or letrozole (L) in endocrine-sensitive patients (pts) with hormone receptor (HR)[+]/HER2[-] metastatic breast cancer (MBC): detailed safety analysis from a multicenter, randomized, open-label, phase II trial (PARSIFAL)

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**Background:** P led to a meaningful improvement in clinical outcomes when used in combination with endocrine therapy for first- or later-line regimen in HR[+]/HER2[-] MBC. Grade 3-4 neutropenia was the most common adverse event (AE) in the P-containing regimens. Although venous thromboembolic events (VTE) have been rarely reported in registrational trials, a systematic review and meta-analysis of randomized controlled trials demonstrated a higher rate of these AEs. Moreover, rare but severe cases of interstitial lung disease (ILD)/pneumonitis have been observed during post-approval use of P. Here, we present a comprehensive toxicity profile of pts included in the PARSIFAL study, with particular emphasis given to AEs of special interest of the overall safety population. **Methods:** A total of 486 pts with HR[+]/HER2[-] MBC with no prior therapy in the advanced setting and endocrine sensitive criteria (relapse >12 months [mo] after the end of adjuvant endocrine therapy or diagnosed with *de novo* metastatic disease) were randomly assigned 1:1 to receive P (oral 125 mg/day [d]; 3 weeks on/1 week off) plus either F (intramuscular injection 500 mg/d; d 0, 14, 28, and then every 28 ds) or L (oral 2.5 mg/d). Pts were stratified by visceral involvement and type of disease presentation (*de novo*/recurrent). Safety assessments included blood analysis and collection of vital signs at screening, d1 of each cycle, and end of treatment/withdrawal. Severity was graded as per the NCI Common Terminology Criteria for Adverse Events v.4.03. **Results:** The incidence rate of any grade, grade 3-4, and serious AEs was 99.6%, 80.9%, and 29.9%, respectively, in the FP arm, and 99.2%, 78.5%, and 21.1% in the LP arm. Discontinuations due to AEs were 5.4% in the FP arm and 2.1% in the LP arm. Neutropenia, leukopenia, anemia, asthenia, arthralgia, fatigue, and diarrhea were the most frequent AEs in both arms. Febrile neutropenia was reported in 1.2% (3 pts) and 0.4% (1 patient) in the FP and LP arms, respectively. The rate of VTE of any grade was 5.8% (14 pts) in the FP arm and 4.5% (11 pts) in the LP arm ($p = 0.531$). Among 18 pts who had grade ≥ 3 pulmonary embolism (PE), the incidence reported in the FP and LP arms was 5% (12 pts) vs 2.5% (6 pts), respectively, and many of them (n=16, 88.9%) were unrelated PE. Asymptomatic grade 3 PE was reported in 10 pts of the entire study population on every 3-mo CT scan. Further, in 5 pts PE was detected in the context of progressive disease. Median time from the first dose of study drugs to occurrence of PE was 4.1 mo (range 1.4-32.0 mo) in the FP arm and 7 mo (range 1.8-19.3 mo) in the LP arm. Analysis of baseline characteristics in the whole population revealed that older pts had a significantly increased risk for developing PE (69.5 years [range 47-84 years]; $p < 0.01$). ECOG performance status, menopausal status, metastatic disease, visceral involvement, number of disease sites, and prior therapies including antithrombotic agents did not significantly increase the risk for developing PE. Grade 3 ILD/pneumonitis was rarely observed in the FP and LP arms (0.8% vs 1.2%, respectively) with no grade 4 AE. **Conclusions:** First-line treatment with FP and LP for HR[+]/HER2[-] MBC in the PARSIFAL study confirmed the favorable safety profile, with neutropenia representing the most common AE. Although rare, ILD/pneumonitis can be a side effect of P-based regimens. VTE and PE incidence rates were low and consistent with age-specific analyses from PALOMA trials and breast cancer population. Early detection of these AEs may assist in optimizing their management.

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# Pregnancy-associated breast cancer: Does timing of presentation affect outcome?

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**Background:** Pregnancy-associated breast cancer (PABC) comprises breast cancer diagnosed during the gestational period or within the first year post-partum. PABC is associated with worse prognosis, especially for women diagnosed in the postpartum period.
**Methods:** This is an IRB-approved retrospective review of an institutional database of women with stage 0-III PABC diagnosed between 1992 and 2019. Clinicopathologic features, treatments, and clinical outcomes were compared between women who were diagnosed with PABC during pregnancy and those who were diagnosed during lactation (1-12 months after delivery). Comparisons were made using Fisher's exact tests and chi-square tests of independence.
**Results:** A total of 341 women were identified; 131 (38%) diagnosed during pregnancy (pregnancy associated, PA) and 210 (62%) diagnosed post-partum during lactation (lactation associated, LA). Median age for the cohort was 36 (25-46). Median follow-up was 73 months (range, 11-325). Among women with PA diagnoses, 35% (n = 46) presented with breast masses during first trimester, 32% (n = 42) and 33% (n = 43) presented during second and third trimester, respectively; 28% (n = 36) of pregnancies ended in miscarriage or abortion. Fifty-five percent (n = 116) of LA diagnoses were within 6 months of delivery while 44% (n = 92) were between 6-12 months of delivery. The study population was Caucasian (n = 272, 80%), Black (n=26, 7.6%) and Asian (n = 27, 7.9%). Presenting T-stage, N-stage, and AJCC stage were similar between groups. HR+/HER-2-was the most common subtype in both groups (PA n = 49, 37% vs LA n = 71, 34%, p = 0.6). Distribution of other breast cancer receptor profiles were similar between groups (Table). Chemotherapy was administered to 94% (n = 321) of women; 229, 67% as adjuvant and 92, 27% as neoadjuvant (NAC). 72% of women received ddAC-T. Median time to chemo was 3 weeks (range 1-13) for NAC compared to 4 weeks (range 1-16) for adjuvant. Breast cancer treatment was deferred until after delivery for the PA group in 85 women, 65%. Median time from histologic diagnosis to any treatment was 4 weeks (range, 1-22) for PA group and 4 weeks (range 1-17) for LA group. Radiation therapy was received by most women (n = 194, 57%). Endocrine therapy receipt was also common (n = 168, 93% of women with hormone receptor (HR) positive tumors). Patterns of recurrence were similar between groups with most patients in both groups experiencing no recurrence (PA n = 82, 63% vs LA n = 158, 75%, p = 0.10). Differences were observed in disease status with PA having higher rates of women alive with disease (PA n = 16, 12% vs LA n = 12, 5.7%, p = 0.002) and a lower rate of women with no evidence of disease (PA n = 87, 66% vs LA n = 172, 82%, p = 0.002).
**Conclusions:** Clinicopathologic features were similar between women in both PA and LA groups. Despite these similarities, PA appeared to be associated with higher rates of women alive with disease and lower rates of women with no evidence of disease. Although median time from histologic diagnosis to treatment was similar between PA and LA groups, 65% of women in the PA group had treatment delayed until after delivery, which could potentially impact oncologic outcomes. This highlights the balance between fetal and maternal factors in treatment decisions including possible patient or physician reluctance to treat during pregnancy. Further study is necessary to evaluate this finding.

Table 1. Clinicopathologic features and outcomes associated with PABC

| Characteristic | | Pregnancy Associated, n=131* | Lactation Associated, n=210* | p-value** |
|---|---|---|---|---|
| Presenting T | 0 | 2 (1.5%) | 2 (1.0%) | 0.3 |
| | 1 | 47 (36%) | 98 (47%) | |
| | 2 | 67 (51%) | 85 (40%) | |
| | 3 | 10 (7.6%) | 19 (9.0%) | |
| | 4 | 5 (3.8%) | 6 (2.9%) | |
| Presenting N Stage | 0 | 54 (41%) | 97 (46%) | 0.2 |
| | 1 | 77 (59%) | 109 (52%) | |
| | 2 | 0 (0%) | 4 (1.9%) | |
| AJCC Stage | 0 | 2 (1.5%) | 2 (1.0%) | 0.5 |
| | 1 | 26 (20%) | 54 (26%) | |
| | 2 | 61 (47%) | 99 (47%) | |
| | 3 | 42 (32%) | 55 (26%) | |
| Subtype | TN | 45 (34%) | 59 (28%) | 0.3 |
| | HR+/HER2- | 49 (37%) | 71 (34%) | 0.6 |
| | HR+/HER2+ | 21 (16%) | 30 (14%) | 0.8 |
| | HR-/HER2+ | 10 (7.6%) | 31 (15%) | 0.072 |
| Recurrence | Contralateral Breast | 3 (2.3%) | 5 (2.4%) | 0.10 |
| | Distant | 33 (25%) | 31 (15%) | |
| | Ipsilateral LRR | 9 (6.9%) | 13 (6.2%) | |
| | No Recurrence | 82 (63%) | 158 (75%) | |
| | Simultaneous LRR and Distant | 4 (3.1%) | 3 (1.4%) | |
| Disease Status | AWD | 16 (12%) | 12 (5.7%) | 0.002 |
| | DOC | 3 (2.3%) | 0 (0%) | |
| | DOD | 25 (19%) | 26 (12%) | |
| | NED | 87 (66%) | 172 (82%) | |
| *Statistics presented: n (%); **Statistical tests performed: Fisher's exact test; chi-square test of independence | | | | |

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Mdm2 inhibition synergises with endocrine therapy or cdk4/6 inhibition for the treatment of estrogen receptor-positive breast cancer

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**Background:** Resistance to endocrine therapy is a major clinical challenge in the management of estrogen receptor (ER)-positive breast cancer. In this setting p53 is frequently wildtype and its activity may be suppressed via upregulation of its key regulator MDM2. This underlies our rationale to evaluate MDM2 inhibition as a therapeutic strategy in treatment resistant ER-positive breast cancer.
**Methods:** We used the MDM2 inhibitor NVP-CGM097 to treat *in vitro* and *in vivo* models alone and in combination with fulvestrant or palbociclib. We perform cell viability, cell cycle, apoptosis and senescence assays to evaluate antitumor effects in p53 wildtype and p53 mutant ER positive cell lines (MCF-7, ZR75-1, T-47D) and MCF-7 lines resistant to endocrine therapy and to CDK4/6 inhibition. We further assess the drug effects in patient-derived xenograft (PDX) models of endocrine-sensitive and -resistant ER positive breast cancer.
**Results:** We demonstrate that MDM2 inhibition results in cell cycle arrest and increased apoptosis in p53-wildtype *in vitro* and *in vivo* breast cancer models, leading to potent anti-tumour activity. We find that endocrine therapy or CDK4/6 inhibition synergises with MDM2 inhibition but does not further enhance apoptosis. Instead, combination treatments result in profound regulation of cell cycle-related transcriptional programmes, with synergy achieved through increased antagonism of cell cycle progression. Combination therapy pushes cell lines resistant to fulvestrant or palbociclib to become senescent and significantly reduces tumour growth in a fulvestrant resistant patient derived xenograft model.
**Conclusions:** We conclude that MDM2 inhibitors in combination with ER degraders or CDK4/6 inhibitors represent a rational strategy for treating advanced, endocrine resistant ER-positive breast cancer, operating through synergistic activation of cell cycle co-regulatory programs.

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Capecitabine maintaining treatment improves progression-free survival in metastatic breast cancer: A prospective observational study of 669 cases

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**Background**: Metastatic breast cancer (MBC) has poor prognosis, and the 5 yr-OS is less than 20%. Maintaining treatment post the chemotherapy could improve the OS and the life quality. However, we lack clinical consensus for the maintaining treatment. In this study, we aim to investigate the treatment outcome of capecitabine maintaining treatment. **Methods**: The study recruited 669 consecutive MBC patients who received chemotherapy from January 2016 through August 2019. 256 patients received capecitabine maintaining treatment after chemotherapy, including 163 patients with maintaining treatment after the first-line chemotherapy and 67 patients with maintaining treatment after the second-line chemotherapy. 413 patients did not receive capecitabine maintaining treatment after capecitabine-based chemotherapy. Kaplan-Meier curves were plotted and COX proportional hazards models with candidate risk factor analyses stratified by chemotherapy lines and maintaining treatment were assessed the impact of each candidate on progression-free survival (PFS). Circulating tumor DNA (ctDNA) analysis was performed to screen genetic aberrations that might lead to maintaining treatment response. **Results**: Capecitabine maintaining treatment group showed a significant improvement in PFS compared with non-maintaining group [hazard ratio = 0.53 (95% confidence interval = 0.41-0.68); log-rank test p<0.0001]. The median PFS was 19.9 months (95% CI: 15.6, 22.6) and 10.4 months (95% CI: 8.5, 14.9) in capecitabine-maintaining group and non-maintaining group, respectively. The 1$^{st}$ line maintaining treatment could achieve an optimal PFS (median 21.3, 95% CI: 16.1, 36.3). The median PFS of 2$^{nd}$ and 3$^{rd}$ line were 17.2 months and 10.8 months, respectively. Compared to the 2$^{nd}$ and 3$^{rd}$ line therapy, the 1$^{st}$ line maintaining therapy could significantly improve PFS [hazard ratio = 0.66 (95% confidence interval = 0.45-0.96); log-rank test p=0.03]. In addition, compared to non-maintaining group, more maintaining group benefited from capecitabine-based chemotherapy (CR+PR+SD: 99% vs 56%, p<0.0001). Patients with hormone receptor (HR)-positive would be more benefited from capecitabine-based chemotherapy. ctDNA analysis showed that in maintaining group, *PIK3CA* helical domain mutation (33%) and *TP53* mutation (42.9%) concentrated in patients with poor PFS. **Conclusion**: Capecitabine maintaining treatment significant improves PFS in MBC patients. Treatment at earlier lines would be more efficient. While HR-positive patients benefited more from capecitabine-based chemotherapy, *PIK3CA* helical domain mutation and *TP53* mutation might be responsible for the poor response to capecitabine maintaining treatment.

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Hypofractionated versus conventional intensity modulated postmastectomy radiotherapy: Toxicity and quality of life in patients with tissue-expander breast reconstruction

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Introduction: Hypofractionation (HF) in breast cancer is a radiotherapy regimen frequently used in recent years. Greater toxicity has been described in irradiated patients with heterologous breast reconstruction procedures, but it is unknown if this greater toxicity could be avoided by using hypofractionated intensity modulated radiotherapy (IMRT). The objective of this study is to describe the toxicity and complications presented in breast cancer patients that were reconstructed with a tissue expander (EXP) treated with IMRT and to determine if there are differences according to the used fractionation regimen.
Method: All patients with breast cancer reconstructed with expander and treated with adjuvant IMRT to the chest wall and regional lymph nodes were included, using conventional fractionation (CF) dose of 50 Gy in 25 fractions or hypofractionated (HF) regimen dose of 45 Gy in 20 fractions. Acute and late toxicity, during treatment and at the end of follow-up, were recorded according to RTOG / EORTC and CTCAE 4.0 criteria and the BREAST Q 2.0 quality of life survey postoperative reconstruction module (QoL) was applied in the last follow-up visit.
Results: 33 patients were analyzed. With a median follow-up of 17 months, 31 were treated with Tomotherapy and 2 with VMAT. CF was used in 20 and HF in 13. There was no G3 acute toxicity, and G2 was observed in only 1 patient with HF (7.6%) and in 3 with CF (15%), mainly determined by radiodermatitis. Regarding late toxicity (LT), there was only one G3 event which occurred in a patient with CF and full axillary irradiation. Grade 2 LT was not observed in patients treated with HF, whereas with CF 2 cases (10%) were reported. During the expander period, 1 patient with HF presented a complication (7,6%) and 3 with CF (15%), 2 of the latter required unscheduled surgical intervention (USI). 12 patients in the HF group underwent prosthetic replacement (92%) and 15 in the CF group (75%). After the replacement 4 patients with CF required an USI (26.6%) and none of the patients in the HF group had post replacement complications that required hospitalization. None of the previously mentioned differences were statistically significant. Regarding QoL, the patients with HF had a better late toxicity score, with an average of 96.7 vs. 82.4 points ($p < 0.005$), and better physical well-being of the chest, with an average of 81.7 vs. 66 points, which did not reach statistical significance ($p = 0.052$). The rest of the scales within the module did not show any differences. Conclusions: Postmastectomy IMRT in patients with heterologous reconstruction is associated with low toxicity and complications. The use of hypofractionation presents a toxicity profile similar to that of conventional fractionation, with a tendency to less frequent complications associated with reconstruction. HF is also associated with a better QoL score in late toxicity and physical well-being of the chest. Prospective studies are required to confirm whether hypofractionation using IMRT could decrease complications and improve quality of life in patients undergoing total mastectomy and tissue-expander breast reconstruction.

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Association of neutrophil-to-lymphocyte ratio with pathological complete response in locally advanced breast cancer

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**Background:** Neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential inflammatory blood biomarker for breast cancer (BC) outcomes. Prior analysis suggests that NLR is a reliable prognostic factor for patients with locally advanced breast cancer (LABC) receiving adjuvant chemotherapy. However, the prognostic value in patients receiving neoadjuvant chemotherapy (NAC) remains unclear. We aimed to evaluate the association of baseline NLR with pathological complete response (pCR) among patients with LABC treated with NAC. **Methods:** We retrospectively analyzed 253 patients with stage II and III BC that received NAC followed by surgery at Montefiore Einstein Cancer Center from 2005 through 2017, and had information regarding baseline NLR and pCR at surgery. Demographic, clinicopathological, laboratory and treatment characteristics were obtained from electronic medical records. Laboratory parameters included absolute neutrophil count and absolute lymphocyte count. pCR was defined as absence of residual invasive carcinoma in both the breast and the lymph nodes (ypT0/ypN0 or ypT*is*/ypN0) at the time of surgery. The association between NLR and pCR was assessed using the multivariate logistic regression model. The association between NLR and disease free survival (DFS) and overall survival (OS) was assessed using Cox proportional hazards models. **Results:** Median age at diagnosis was 54 years [interquartile range (IQR)=45-63]. Patients were predominantly non-Hispanic (58%). The most common race was Black (49%) followed by White (32%) and Asian (6%). Pre/perimenopausal and postmenopausal status corresponded to 42% and 59% of patients, respectively. The most common histological subtype was ductal (88%) followed by lobular (7%) adenocarcinoma. High, intermediate and low histological grades were seen in 57%, 36% and 2%, respectively. Triple negative, human epidermal growth factor receptor 2-HER2(+), and hormone receptor-HR(+)/HER2(-) tumors corresponded to 39%, 31% and 30% of patients, respectively. Taxanes and anthracyclines were administered to 96% and 68% of patients, respectively. Mastectomy (63%) was the most common type of surgery followed by breast conserving (37%) surgery. pCR was achieved in 30% of patients. Median NLR was 2.2 [IQR=1.6-3.1] and dichotomized into $NLR^{HIGH}$ (>=2.2) and $NLR^{LOW}$ (<2.2). In the bivariate analysis, there was no statistically significant association between $NLR^{HIGH\ vs.\ LOW}$ and pCR (p=0.78). When adjusted for age, race, histological grade, HR status and HER2 status, no statistically significant association was found between NLR and pCR (Odds ratio: 0.82, p=0.51). When adjusted for age, race, histological grade, HR status and HER2 status, no statistically significant association was found between NLR and DFS (Hazard ratio (HR): 0.75, p=0.3) or OS (HR: 0.61, p=0.19). **Conclusions:** In our study, the baseline NRL was not an independent prognostic factor for pCR, DFS or OS in patients with stage II and III BC treated with NAC. These findings are consistent with prior studies. Patients of Black race have lower baseline neutrophil counts, which could lead to different NLR values than other racial groups. Notably, our population was predominantly Black, in which scarce data exists concerning the association between NLR and BC outcomes. Further studies are needed to elucidate the prognostic value of NLR in the neoadjuvant setting among multiracial groups.

**Publication Number:** OT-06-01

Open-label, phase 1 study to evaluate duration of severe neutropenia after same-day dosing of eflapegrastim in patients with breast cancer receiving docetaxel and cyclophosphamide (NCT04187898)

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**Background**: Eflapegrastim (Rolontis®, Efla) is a long-acting granulocyte-colony stimulating factor (G-CSF), consisting of a recombinant human G-CSF analog conjugated to a human IgG4 Fc fragment via a short polyethylene glycol linker. Efla is not a biosimilar and represents the first myeloid growth factor innovation in more than 15 years. In preclinical studies with chemotherapy-induced neutropenic rats, Efla showed ~3-fold higher exposure in serum and higher exposure in bone marrow at similar doses compared to pegfilgrastim (Peg). The duration of neutropenia (DN) was shown to be significantly shorter with Efla vs Peg when administered on the same day and 24-hours post-chemotherapy. Additionally, the DN after Efla administered on the same day as chemotherapy was similar to the DN 24 hours post-chemotherapy. Moreover, in two Phase 3 studies that randomized a total of 643 patients with early-stage breast cancer (ESBC) to either Efla (3.6 mg G-CSF n=314) or Peg (6 mg G-CSF n=329) given ~ 24 hours after docetaxel and cyclophosphamide (TC) administration, the duration of severe neutropenia (DSN) was statistically noninferior in patients treated with Efla compared to Peg. As a standard of practice, G-CSF products require administration 24 hours after chemotherapy. Since Efla preclinical and clinical results suggest that the increased activity of Efla may provide effective prophylaxis against chemotherapy-induced neutropenia when administered on the same day as chemotherapy, the purpose of this study is to assess the feasibility of Efla same-day (3 different dosing timepoints) in patients receiving TC for treatment of ESBC. **Trial Design:** This is a randomized, schedule finding, multicenter, Phase 1, open-label study evaluating the same-day administration of 13.2 mg/0.6 mL Efla (3.6 mg G-CSF) following IV infusion of docetaxel (75 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$) in patients with ESBC. Patients will be randomized 1:1:1 to Efla dose schedules of 0.5, 3, and 5 hours after TC. The primary endpoint is DSN (ANC $<0.5\times10^9$/L) in Cycle 1. The secondary endpoints for Cycle 1 administration include the incidence of SN, time to recovery from SN, incidence of Grade 3 febrile neutropenia, incidence of neutropenic complications, and pharmacokinetics (PK) of Efla. Blood for hematology will be drawn daily for the first 10 days and then on Day 1 of Cycles 2-4. **Eligibility Criteria:** This study is enrolling histologically confirmed (operable stage I-IIIA) patients with ESBC, who are ≥18 years of age, are candidates for neoadjuvant or adjuvant TC chemotherapy, have an ECOG of ≤2, with adequate hematological, renal, and hepatic function. Patients will be excluded if they have a known sensitivity or previous reaction to E. coli derived products, exposure to a G-CSF agent within 3 months, history of bone marrow or hematopoietic stem cell transplant, radiotherapy or surgery within 30 days, are pregnant, or are breast-feeding. **Statistical Methods:** A sample size of 15 patients per dosing schedule arm was determined to provide adequate precision for the 95% CI of the DSN and secondary endpoints, including PK parameters. The sample size produces a 2-sided 95% CI with a distance from the mean DSN to the limits that is equal to 0.554 using t-distribution when the estimated standard deviation is 1.0 days. A safety evaluation will be performed once the first three patients in each arm have completed Cycle 1. **Target Accrual**: 45 patients (15 subjects/arm). Enrollment began in April 2020.

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# Pml mediates tumor-associated macrophages to promote breast tumor progression

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**Introduction:** Tumor-associated macrophages (TAMs) are major immunosuppressive cells that accumulate in tumor microenvironment (TME), and are associated with poor outcome in breast cancer patients. Although TAMs have been directly implicated in tumor cell proliferation, motility, invasiveness and chemoresistance, the underlying mechanisms by which TAMs promote tumor progression remains poorly elucidated. **Methods:** MCF-7 cells were cultured alone or co-cultured with human monocyte-derived macrophages (MDMs) or polarized TAMs (pol-TAMs). Genome-scale RNA-seq analysis from these samples showed that promyelocytic leukemia (PML) gene was significantly upregulated in pol-TAMs co-culture samples ($P$=0.0250). The upregulation of PML was further verified by qRT-PCR and immunohistochemistry (IHC) in tissue microarray (TMA, BR6161, US Biomax) containing 294 cases of primary breast tumor tissues, 19 cases of adjacent normal tissue and 9 cases of normal tissue, with duplicate cores per case of cancer, and single core per case of adjacent normal and normal tissue. To evaluate the infiltration of CD 68+ TAMs and its association with the upregulation of PML, IHC in the same TMA samples was performed. Kaplan-Meier survival plots were generated to assess effect on patient prognosis. **Results:** Global transcriptome analysis revealed that co-culture with pol-TAMs significantly upregulated PML expression in MCF-7 cells, which was confirmed by qRT-PCR. Further, the protein level of PML was detected by IHC in TMA tissue samples. As expected, both the maximal immunoreactivity and the percentage of stronger immunoreactivity of PML were higher in breast tumor than those in benign tissue ($P$<0.0001). The positive correlation between TAMs infiltration and PML expression in breast tumor tissue was further confirmed by IHC in the same TMA ($P$<0.0001, $R^2$=0.2074). When compared among breast carcinoma tissue, a higher percentage of stronger immunoreactivity of PML was observed in lymph node metastasis cases ($P$=0.0369). Further, high PML expression resulted in worse relapse-free survival (RFS), overall survival (OS), distant metastasis-free survival (DMFS) and palliative performance scale (PPS) survival curve (*logrank P* =9.3e-11, 0.0012, 0.00012 and 0.00065 respectively). **Conclusion:** Promyelocytic leukemia (PML) gene is upregulated in a subset of breast tumor and has been identified as breast cancer oncogene. Here, we demonstrate that PML expression in tumor cells is induced by TAMs, and is enriched in lymph node metastasis. High PML expression also exhibited worse prognosis in patient outcome, consistent with lymph node metastasis cases. Thus, PML upregulation mediates TAMs activity to promote breast cancer progression, suggesting PML as a potential therapeutic target in breast malignancies.

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Identification of cell-free microRNA signatures in pre-operative plasma from breast cancer patients

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**Background:** Breast cancer (BC) is a heterogeneous disease and difficult to treat once metastasis occurs. Thus, determining blood molecular biomarkers that allow for early diagnosis would help to identify BC patients at higher risk. MicroRNAs (miRs) are short sequences (18-22 base pairs) and promising candidates as biomarkers due to their high stability in blood. Using a direct blood cell-free miR (cfmiR) next generation sequencing (NGS) -based assay that requires no extraction, we assessed 2083 cfmiRs in plasma samples from BC patients. We *hypothesize* that specific cfmiR signatures detected in plasma from BC patients are associated with early BC diagnosis. Those cfmiRs represent unique patterns that may allow for monitoring BC tumor burden and early detection.**Methods:** Two cohorts of pre-operative plasma samples from BC patients (n= 158), one cohort of pre-operative plasma samples from patients with BC brain metastasis (BCBM, n= 5), and a cohort of female normal donors' plasma samples (n=20) were assessed by HTG EdgeSeq miR whole transcriptome assay. All primary BC tumors were histopathology staged (TNM, AJCC $8^{th}$) after surgery and divided into two different cohorts: the BC-1 cohort (n= 80, including stage I= 39, II= 37, and III= 4 patients), and the BC-2 cohort (n= 78, including stage I= 42, II= 33, and III= 3 patients). All of the samples were analyzed using DESeq2 normalization and interrogated for differentially expressed (DE) miRs using a cut-off of 30 counts, FC>1.2 or <-1.2, and FDR ($p$<0.05). We utilized the BC-1 group as the training cohort and the BC-2 and the BCBM cohorts were used to validate the observations in BC-1.
**Results:** In a retrospective study the cfmiR profiles obtained from BC-1 patients were compared to the cfmiR profiles obtained from normal donors' plasma samples. Briefly, 328 cfmiRs were DE in plasma samples from the BC-1 cohort compared to normal donors' plasma samples, of which 184 were upregulated and 144 were downregulated. To validate our findings, we screened the plasma samples from the BC-2 cohort (n=78). The results showed that 181 of 361 DE cfmiRs were downregulated and 180 were upregulated. By comparing both BC cohorts we found 269 DE cfmiRs consistently changing, which included 82% and 74.5% of the cfmiRs identified in BC-1 and BC-2 cohorts, respectively. In addition, we compared the cfmiR expression of BCBM (n=5) and normal donors' plasma samples. Of the 300 DE cfmiRs, 30 were downregulated and 270 were upregulated. By integrative analysis, a 59 cfmiR signature observed in BCBM plasma samples was consistently identified in both BC-1 and BC-2 cohorts. Also, 172 cfmiRs were found exclusively in BCBM and not in primary BC tumors. Receiving operative characteristic curve analysis showed that the 59 cfmiR signature was able to distinguish primary BC from female normal donors' (BC-1 AUC= 0.910, $p$<0.05 and BC-2 AUC= 0.922, $p$<0.05, respectively). Using the 59 cfmiR signature, the first five components of the principal component analysis showed 85.26% and 85.27% mean cumulative variance for BC-1 and BC-2 respectively.**Conclusions:** Specific cfmiR patterns were associated with primary BC tumors and may have potential utility for early BC diagnosis, including disease recurrence. A 59 cfmiR signature detected in primary BC patients was able to detect BCBM and may have potential clinical utility in monitoring patients at higher risk of metastasis. Further analysis are in progress to validate our observations.

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The role of myoglobin in breast cancer

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Breast cancer today is typically seen as malignancy with longer survival due to early-detection diagnostics, yet the cancer remains by far the most common tumor type in adult females. Recently, our group co-discovered myoglobin (MB) to be expressed in luminal cells of healthy and cancerous breast epithelia of human and mice. In human patients, MB positivity emerged as hallmark of the luminal subtype and was directly correlated with estrogen receptor alpha positivity and hence a significantly better prognosis. Cancerous cells' MB also appears to interact with the known tumor suppressor p53. However, if and how myoglobin itself restricts mammary tumorigenesis is completely unclear. To understand how MB exerts its alleged tumor-suppressive effects and if it impacts response of mammary tumors to chemo- and/or radiotherapy, we examine the molecular role of MB in breast tumor formation and progression through a) *in vitro* studies (MCF7 breast cancer BrCa cell clones; wildtype (wt) controls versus CRISPR/Cas9-engineered clones of a MB and/or p53 knockout (MBko/p53ko), b) *in vivo* mouse models to obtain spontaneously forming breast tumors, with or without MB, in a p53 deficient background. Comparing MCF7 BrCa MBko and p53ko clones vs. their corresponding wildtype counterpart supports our hypothesis of a feed forward loop between MB and p53 proteins, besides interfering with estrogen receptor expression. In addition to that, loss of MB was noticed to exert p53-independent upregulation on cell cyclins with more S phase cell population. That was reflected by a significant increase in survival of the MBko cells, in presence or absence of p53. Hypoxic MBko cells exhibited a partial epithelial to mesenchymal transition and hence a more migratory phenotype, relative to MBwt controls. Additionally, MB seems to stimulate apoptosis of the normoxic cancer cells. On the other hand, murine tumors were found to phenocopy human BrCa in the extent of their MB expression. Interestingly, MB-devoid tumors showed a significantly higher proliferation index and fat accumulation. Further studies will look into the clinical significance of that. In conclusion, MB seems to occupy unknown roles in cancer cells beyond or different from its classical $O_2$ storage/transport functions. Unraveling these novel roles in governing tumor development and virulence will hopefully provide innovative strategies for future breast cancer interventions.

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# Nurse navigation in the ambulatory oncology clinic: Patient-centered findings from a survey of 50 breast cancer patients

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**Introduction** A nurse navigator is a registered nurse who serves as a patient advocate, educator, and coordinator for newly referred cancer patients. Nurse navigators assist with the coordination of care before a patient's first appointment with their provider. In some healthcare centers, they are also the point-person throughout a patient's entire treatment process. The nurse navigator role is designed to promote cancer patient empowerment through advocacy, educational support, resource navigation, and psychosocial care. Our study attempted to assess the impact of a newly implemented nurse navigator program, in an academic setting, and measure the effect on patient knowledge, care coordination, and emotional well-being before their breast oncology appointment.

**Methods** A mixed-methods approach was implemented. We provided an Institutional Review Board-approved 9-question survey created from items adapted from Patient Satisfaction with Interpersonal Relationship with Navigators (PSN-I) to UCSF Breast Care Center patients before their first appointments with a breast oncology provider. After survey completion, patients were asked to participate in an open-ended interview about their patient experience with a member of the study team.

**Results** 50 patients were surveyed. 22 (44%) patients surveyed had nurse contact and 28 (56%) did not have prior nurse contact before their appointment. With regards to patient knowledge prior to the oncology appointment, 16 out of 22 (73%) of patients with nurse contact felt informed compared to 16 out of 28 (57%) of patients without nurse contact. With regards to having initial questions answered before their visit, 11 out of 22 (50%) of patients with nurse contact strongly agreed compared to 4 out of 28 (14.3%) of patients without nurse contact. In response to the statement, "my care is coordinated effectively in the Breast Care Center," 15 out of 22 (68%) of patients with nurse contact strongly agreed compared to 12 out of 28 (43%) of patients without nurse contact.

Patients with nurse contact were asked whether speaking with a nurse *did 1)* improve their patient experience and 2) better deal with stressful emotions. Among 22 patients with nurse contact, 16 (73%) of patients with nurse contact strongly agreed to statement 1, and 20 (91%) agreed with statement 2. Patients without nurse contact were asked to predict

whether nurse contact *would 1)* improve their patient experience and 2) better deal with stressful emotions. Out of 28 patients, 14 (50%) strongly agreed to both statements.

From our open-ended interviews, we found the following themes: appreciation for preliminary knowledge, identification of knowledge gaps, appointment scheduling, and insurance coverage barriers, and humanistic care from nurse navigators. Patients reported that they appreciate not only a nurse navigator's facilitation in coordination and education but also their companionship during their cancer journey.

**Conclusions** Nurse navigators can play a vital role in improving patient knowledge, workflow/care coordination, and emotional well-being at cancer centers. A greater proportion of patients with initial nurse contact felt informed before their appointment and believed their care was effectively coordinated than those without nurse contact. The majority of patients with nurse contact believed their nurses improved their patient experience and relieved anxiety and stress. Based on this study, we will fully implement initial contact with patients to provide information and coordinate services for in-person visits. Given the changes brought by COVID, that first contact could also be with a nurse or physician via video consult prior to an in-person appointment. Future studies should investigate the impact of a longitudinal nurse navigator in providing continuity of care beyond the first referral.

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Exploring global clinical trial enrollment opportunities in high breast cancer mortality regions

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**BACKGROUND** Globally, breast cancer is the most commonly diagnosed cancer and the most common cause of cancer death for women. Access to high quality treatment and novel therapies vary significantly based on geographic regions and countries. Mortality rate is considerably higher women in developing and low-income regions compared to high income regions. While many factors contribute to disparities in breast cancer specific outcomes, access to clinical trials provide high quality and evidence-based cancer care. Therefore, we evaluated the availability of breast cancer treatment clinical trial among global regions with the highest breast cancer incidence and related mortality.
**METHODS** In this study, we reviewed clinical trials registered with clinicaltrials.gov and published in 3 high impact journals: The New England Journal of Medicine, Lancet Oncology and the Journal of Clinical Oncology between January 2018 and May 2020. For each trial, the countries from which patients enrolled were captured and compared to the countries in the top 5 regions for highest breast cancer incidence and breast cancer related mortality globally per the GLOBOCAN 2018 estimates.
**RESULTS** A total of 77 clinical trials meet this criteria and enrolled patients in 67 different countries. As most trials enrolled in multiple countries, the enrollment countries for every trial was recorded with a total of 697 enrolled countries in these 77 clinical trials. The global regions with the high breast cancer mortality are Melanesia, Micronesia and Polynesia (Hawaii excluded), Northern Africa, Caribbean and Western Africa. These regions together had only 8 clinical trials that accrued patients during this time frame: one trial in Egypt, 4 in New Zealand and 3 in Puerto Rico. This represents about 1% of country accruals in the trials analyzed (8 of 697). The most frequently enrolling countries were the United States, Canada, Belgium, United Kingdom, Italy, France, Germany, and Spain which have high incidence of breast cancer but lower mortality rates compared to other global regions.
**CONCLUSIONS** High impact breast cancer trials currently enroll patients from areas with high incidence of breast cancer but not from areas with high mortality rates. Barriers that lead to these disparities have not been extensively explored and would be of interest in future studies. Exploring creative ways to bridge this gap, such as working with local governments to help develop clinical centers with ability to run clinical trials and train local medical staff, may be part of an effort to decrease global breast cancer mortality.

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Combination PI3K and NOS targeted therapy for metaplastic breast cancer

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Metaplastic breast cancer (MpBC) is a rare subset accounting for less than 1% of all breast cancers. MpBC exhibits the worst prognosis in comparison to triple-negative breast cancer (TNBC) with a dismal poor survival rate in patients with metastatic disease. The main therapeutic options for MpBC remain surgery and systemic chemotherapy, despite known resistance to most systemic chemotherapy. A common molecular alteration in MpBC is hyperactivation of the phosphoinositide 3-kinase (PI3K) pathway. Recently, we published that MpBC displays a gain-of-function oncogenic mutation in ribosomal protein L39 (RPL39), which is responsible for treatment resistance, stem cell self-renewal, and lung metastasis. The mechanistic function of RPL39 is mediated through inducible nitric oxide synthase (iNOS)-mediated nitric oxide production. In addition, we demonstrated that inhibiting this nitric oxide synthase (NOS) pathway using pan-NOS inhibitor NG-methyl-L-arginine acetate (L-NMMA) may represent a highly effective therapeutic option for MBC patients. Therefore, we hypothesize that the combinatorial approach of inhibiting the two major pathways implicated in MpBC, namely PI3K/Akt/mTOR and NOS pathways would lead to significant tumor regression. Alpelisib, an FDA-approved, isoform-specific PI3K inhibitor, is currently used with the antiestrogen, fulvestrant, to treat hormone receptor (HR)-positive, *PIK3CA*-mutated breast cancer patients. We used MpBC cell lines Hs578t and BT549 and MpBC patient-derived xenograft (PDX) models in our preliminary studies. Using flow cytometry to detect Annexin V+/DAPI+ cells, we found increased cell death in MpBC cell lines treated with L-NMMA+alpelisib combination treatment in comparison to monotherapy. Immunoblotting of samples from single (L-NMMA or alpelisib) or combination treated cell lines and PDXs showed increased PARP degradation and cleaved caspase 3/9 with combination treatment. *In vivo* data using PDX models showed that combination treatment of L-NMMA+alpelisib was most effective at reducing tumor volume in comparison to monotherapy. We performed preliminary bulk-RNA sequencing analysis of tumor samples collected from PDX BCM-4664 treated with vehicle control, monotherapy of L-NMMA or alpelisib, and combination therapy. Gene set enrichment analysis found that E2F and Hedgehog signaling pathways were the top two enriched pathways in BCM-4664 tumors treated with combination therapy. Pathway-focused RT-PCR of MpBC PDXs confirmed GSEA results and showed significant gene expression alterations involving E2F signaling and cell cycle regulation. Further studies are currently ongoing to elucidate the molecular mechanisms involved in enhanced cell death and decreased tumorigenesis with L-NMMA and alpelisib dual therapy. Our results support the concept that LNMMA and alpelisib combination therapy has therapeutic potential in the treatment of MpBC, which may enable rapid translational into clinical trials, and impact the exceeding poor prognosis of women with MpBC.

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Rapamycin inhibits stem cell function and diminishes inflammation and senescence markers in human mammary gland

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Gene expression profiles of some subtypes of breast cancer were shown to correspond to the profiles of the basal or luminal mammary stem/progenitor cell-enriched epithelial cells implicating the mammary stem cells (MaSCs) as tumor-initiating cells for certain types of breast cancer. Moreover, there is growing evidence that MaSCs may initiate neoplastic transformation when dysregulated in mouse models. We have previously reported an increased frequency of the MaSC-enriched $Lin^{-}/CD49f^{high}/CD24^{+}$ basal cells in old mice (>27 month) compared to young ones (2-4 month) along with an increase of hyperplasic lesions. Gene expression profile revealed an increase of immune and inflammatory responses in old basal cells and stroma cells indicating that aging-induced immune and inflammatory responses might initiate basal cell expansion and transformation. Our preliminary data on mice using rapamycin, an immune and inflammation inhibitor, were very encouraging so we decided to start a clinical window trial (NCT02642094) to test whether rapamycin could reduce biomarkers associated with progression to invasive breast cancer and MaSC numbers in postmenopausal patients with atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS). The patients enrolled in the trial took rapamycin (sirolimus, 2mg/day) for 5-7 days with 3-7 days of washout before surgery. The adjacent non-tumor surgical tissues were used for the measurements of sphere formation efficiency (SFE) of the basal and luminal cells. The control group were patients with ADH/DCIS who did not take the drug. Rapamycin treatment significantly diminished the SFE of the basal MaSC. Immunohistochemical staining of the biopsies and surgical tissues showed that rapamycin treatment significantly decreased the levels of COX2 (an inflammation marker) and p16 (a senescence marker), and moderately increased p62 (an autophagy marker). Furthermore, rapamycin significantly reduced the proliferation marker Ki67 staining. In conclusion, rapamycin inhibits MaSCs function and senescence and inflammation features in human mammary glands. Whether the suppression of the senescence-associated inflammatory responses is the mechanism by which rapamycin suppresses MaSC function is under investigation.

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Patient and provider determinants of breast cancer screening among Ontario women age 40-49: A population based retrospective cohort study

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**Background:** For women aged 40-49, Canadian guidelines recommend individualized-decision making (based on risk assessment, values, and preferences) rather than routine screening mammography (SM). In this age group, family physicians are the gatekeepers to access SM; however, studies indicate substantial variability in practice patterns. There are few population-based data regarding uptake and patient/provider determinants of SM in this age group. We describe the uptake and frequency of SM and identify patient and provider level associations with SM in Ontario women aged 40-49. We hypothesized that SM would vary by provider characteristics and women's demographics, suggesting lack of guideline-concordant care.
**Methods:** This population-based retrospective cohort study linked health administrative databases to form a cohort of all Ontario women aged 40-49 between April 1, 2009 to March 31, 2019. Mammograms were identified using Ontario Health Billing codes. In order to identify mammograms that were specifically for screening, women were excluded if they had any prior breast MRI, mammogram, cancer diagnosis, oncologist visit, or breast surgical procedure. Sub-cohorts were created to identify women who had (a) at least one SM ("screen cohort") and (b) 3 or more SM ("routine screen cohort"). Following SM, women were censored from cohorts if they had any cancer diagnosis, breast surgical procedure, oncologist visit, or death; however, breast cancer related outcomes were tracked for 6 months following SM, regardless of whether a censoring event occurred. Patient and provider characteristics were extracted for women in each cohort. A multivariable regression model was used to identify predictors of routine SM.
**Results:** Of 2 million eligible women, 743 274 (35.6%) received a mammogram, 532 782 (25.5%) received at least one SM, and 90 651 (4.3%) received routine SM (3 or more). Table 1 demonstrates cohort characteristics. There were 0.32 and 0.52 mammograms per woman per year in the screen and routine screen cohort respectively. Call-backs were similar for women after the first SM compared to the third SM (9.5% vs 9.3%); however, there were more biopsies (3.2% vs 1.8%) and breast cancers diagnosed (1.2% vs 0.45%) within six months of the first SM. Compared to the full cohort, women in the routine screen cohort were more likely to have a family physician at cohort entry, be in higher-income quintiles, receive annual health exams, and receive have pap smears (p<0.001). Women in the screen cohort were more likely to have female providers and providers that were primarily paid fee for service versus capitation (p<0.001). Multivariable analysis will be reported at the meeting.
**Conclusions:** Less than 5% of Ontario women 40-49 undergo routine SM. SM is associated with patient demographics related to higher socioeconomic status which could be related to higher risk of breast cancer and/or increased access to care. SM is also associated with some provider demographics which could be independent of breast cancer risk, suggesting lack of individualized risk assessment. Qualitative work is ongoing to explore this hypothesis. This information can inform guideline implementation strategies.

**Table 1: Patient and Provider Characteristics of Screening**

| **Characteristic**percent (%) unless otherwise noted | **All Women 40-49** | **Screen Cohort (1 or more SM)** | **Routine Screen Cohort (3 or more SM)** |
|---|---|---|---|
| **Patient Characteristics** | | | |
| Age at Cohort entryMean (median) | 42.5 (40) | 42.8 (42) | 41.7 (41) |
| Age at Cohort exitMean (median) | 47.3 (50) | 48.5 (50) | 49.1 (50) |
| Family Physician at Cohort entry | 90.0 % | 92.3% | 94.8% |
| Income – top quintile | 20.7% | 22.3% | 24% |
| Rurality Category – most urban | 76.3% | 79.0% | 81.2% |
| Birth Location – Canada | 74.4% | 72.2% | 71.6% |
| Annual Health Exams: at least one | 51.1% | 72.1% | 75.3% |
| Pap Smear: at least one | 68.4% | 86.6% | 92.9% |
| **Provider Characteristics** | | | |
| Female | 44.8% | 47.2% | 52.1% |
| Canadian Graduates | 70.3% | 70.3% | 72.1% |
| Fee for Service model | 48.0% | 55.0% | 58.8% |

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Assessing effect modification of obesity-associated genes variants in *FTO*, *MC4R*, *BDNF*, and *CREB1* on weight loss among breast cancer survivors enrolled in the randomized lifestyle, exercise, and nutrition (LEAN) study

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**Background:** Obesity is a leading risk factor for breast cancer in post-menopausal women and is associated with greater risk of recurrence and cancer-specific mortality. There are over 3 million female breast cancer survivors in the United States, and nearly 65% are either overweight or obese. Lifestyle intervention studies have been shown to be effective in achieving clinically meaningful weight loss for breast cancer survivors with a BMI > 25 kg/m2. However, individual variability in body weight response to diet or exercise interventions has been previously reported among carriers of common obesity-genetic variants. Our study examined whether common variants of obesity-associated genes *FTO, MC4R, BDNF*, and *CREB* moderated the effects of an exercise and nutrition intervention on weight change among breast cancer survivors. **Methods:** A total of 151 breast cancer survivors with a body mass index (BMI) ≥ 25 kg/m2 at baseline were randomly assigned to a 6-month weight loss intervention (n=93) or usual care group (n=58). The weight loss intervention included eleven 30-min counseling sessions on improving nutrition and increasing physical activity. Height, weight and body composition (via dual energy X-ray absorptiometry) were measured at baseline and six months. Genotyping of FTO rs9939609, *MC4R* rs6567160, *BDNF* rs11030104, *CREB1* rs17203016 was performed using Taqman® SNP genotyping assays. Association analyses were performed in SAS version 9.4, separately for each SNP and assuming a dominant genetic model. Linear mixed models were used to analyze the main effects of genotype and the intervention on weight, BMI, and percent body fat changes at 6 months, with adjustment for age. Appropriate cross product terms were included in each regression model to analyze the potential interaction between genotype and treatment arm. All statistical tests were evaluated against a Bonferroni-corrected alpha of 0.0125. **Results:** The genetic distributions of the *FTO* SNP rs9939609, *MC4R* SNP rs6567160, *BDNF* SNP rs11030104, *CREB1 SNP* rs17203016 did not differ significantly by treatment arm. Changes in weight, BMI, and percent body fat did not differ significantly between carriers of the *FTO* SNP rs9939609, *MC4R* SNP rs6567160, *BDNF* SNP rs11030104, *and CREB1 SNP* rs17203016 risk alleles compared to non-carriers (p-interaction > 0.0125 for each SNP and across all outcomes). Women in the intervention group achieved significantly greater weight loss than the usual care group (-4.8 kg vs -0.6 kg, p < 0.001) regardless of genotype. **Conclusions:** Common variants of known obesity-associated genes (*FTO, MC4R, BDNF, and MC4R)* did not modify the effect of the nutrition and exercise intervention on changes in body weight and body fat. Women who are genetically predisposed to obesity and recently diagnosed with breast cancer may benefit from lifestyle changes similarly to women who are not genetically predisposed to obesity. Our findings may help guide the incorporation of lifestyle interventions and weight loss counseling into breast cancer survivorship care.

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Clinical utility of a biologic signature to assess DCIS recurrence risk in patients meeting ‘good-risk’ criteria (RTOG 9804, ECOG 5194): Interim analysis of the DCISionRT PREDICT study

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**BACKGROUND:** When considering health-related, quality-of-life and monetary costs associated with post-surgical treatments for women diagnosed with Ductal Carcinoma In Situ (DCIS), there remains a need for prognostic and predictive tools to help design individual treatment planning. DCISionRT (PreludeDx, Laguna Hills, CA) is a validated biologic signature to assess the 10-year event risk for DCIS patients managed with breast conserving surgery (BCS). The 10-year risks are provided separately for patients treated with and without adjuvant radiation therapy (RT) after BCS. The study was designed to measure the change in adjuvant RT recommendation. This is a planned interim analysis of the study, which will eventually comprise up to 2,500 patients and 100 sites.
**METHODS:** The registry includes females over the age of 25 who are candidates for breast conserving surgery and eligible for RT. Survey forms are completed pre- and post-DCISionRT test to capture treatment recommendations and patient preferences. This interim analysis was performed to assess changes in RT recommendation for patients treated with BCS in different clinicopathologic subgroups. Specifically, ‘good risk’ profiles were based on the RTOG 9804 and ECOG 5194 study designs. RTOG 9804 like criteria was screening detected tumors with nuclear grade of 1 or 2, size of ≤ 2.5 cm, and clear (≥ 2 mm) surgical margins. ECOG 5194 like criteria was tumors with nuclear grade of 1 or 2, size of ≤ 2.5 cm, and clear surgical margins, or nuclear grade of 3, size of ≤ 1 cm, and clear surgical margins. Statistics were provided as percentages and counts, and McNemar’s test was used to assess change in RT with a p-value of <0.05 considered statistically significant.
**RESULTS:** There were 513 patients from 32 sites with testing completed after treatment with BCS. Of these patients, 16% were ≤ 50 years of age, 60% were ≥ 60 years of age, and 26% were ≥ 70 years of age. The DCIS tumor nuclear grade was high in 32% of patients, and the size of the tumor was ≤ 1 cm for 68% of patients. There were 49% of patients who met RTOG 9804 like criteria, 51% who met the ECOG 5194 (grade 1 or 2) criteria, and 45% of patients who met the ECOG 5194 (grade 3) criteria. RT was recommended to 52% and 53% patients for RTOG 9804/ECOG 5194 (grade 1 or 2) criteria pre-testing, and 42% post-testing. For ECOG 5194 (grade 3) like criteria, 64% of patients were recommended RT pre-test, and 40% were recommended RT post-test. In all criteria groups, for patients whom were initially recommended RT pre-test, 51% to 54% were not recommended RT post-test, while patients initially not recommended RT pre-test, 25% to 37% were recommended RT post-test. Overall, the post-test RT recommendation was significantly changed from between 42% and 46% for patients with ‘good-risk’ clinicopathologic criteria.
**CONCLUSIONS:** The PREDICT study interim analysis demonstrates a significant absolute overall change post DCISionRT testing for RT recommendation in patients with ‘good-risk’ clinicopathology. RT recommendations were changed post-test for 42% to 46% of patients meeting RTOG 9804/ECOG 5194 like criteria. Integration of DCISionRT testing had a significant impact on the RT recommendations aimed at reducing overtreatment and minimizing undertreatment.

**Table 1.** Pre-Post DCISionRT Impact by ‘good-risk’ criteria.

| | **n** | **% RTPre-testYes** | **% RTPost-test Yes** | **% RTPre-Yes, Post-No** | **% RTPre-No, Post-Yes** | **% Total Decision Change** | **95% CI** | **p-value** |
|---|---|---|---|---|---|---|---|---|
| **RTOG 9804 criteria** | | | | | | | | |
| Grade 1 or 2, Size ≤ 2.5 cm, screen detected, wide margins | 252 | 52 | 42 | 54 | 37 | 46% | 40 - 52% | 1.2E-02 |
| **ECOG E5194 criteria** | | | | | | | | |
| Grade 1 and 2, Size ≤ 2.5 cm, wide margins | 262 | 53 | 42 | 53 | 36 | 45% | 39 - 51% | 0.010 |
| Grade 3, Size ≤ 1 cm, wide margins | 231 | 64 | 40 | 51 | 25 | 42% | 36 - 48% | 2.4E-08 |

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# A physician survey evaluating real-world practice patterns and attitudes towards de-escalation of bone-modifying agents in patients with bone metastases from breast cancer

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**Background:** Despite extensive use of bone modifying agents (BMA) in patients with bone metastases from breast cancer (BC), the optimal choice, frequency, and duration of BMA treatment remains unclear. A physician survey was performed to identify current practices and attitudes towards performing trials of de-escalation after 2 years of treatment, where very little prospective data exists.
**Methods:** Canadian oncologists treating breast cancer were surveyed from May to June 2020 via an anonymized online survey. Physicians were approached by e-mail invitation, and a follow-up e-mail was sent 2 weeks later. The study was approved by the Ontario Cancer Research Ethics Board. The survey collected physician demographics, current practice patterns, perception on risk of symptomatic skeletal events (SSE) and BMA-associated toxicity. It also assessed attitudes towards conducting a study evaluating further de-escalation of BMAs after 2 years of treatment.
**Results:** Of 238 potentially eligible breast oncologists on initial screening, 40 responded (response rate 16.8%; 97.5% medical oncologist). The most common BMA regimens during the first 2 years in patients with no limitations in drug coverage were denosumab q4wks for 3-4 months then q12wks [13/40 physicians (32.5%)], denosumab q4wks [7/40 (17.5%)], and zoledronate q12wks [8/40 (20%)]. For patients with no public funding for denosumab, the most common regimens were zoledronate q4wks for 3-4 months then q12wks [14/40 (35%)] and zoledronate q12wks [12/40 (30%)]. Most physicians [33/40 (82.5%)] routinely de-escalated BMA, with the most common approaches being de-escalation from the start of treatment [9/33 (27.3%)], after 3 months [7/33 (21.2%)], 6 months [6/33 (18.2%)], or 12 months [5/33 (15.2%)]. In terms of continuing BMA after 2 years, 11/40 (27.5%) felt there was benefit, 5/40 (12.5%) felt there was no benefit, and 24/40 (60%) were unsure. There was no consensus on the perceived risk of SSE or BMA-related toxicity after ≥ 2 years of BMA in breast cancer. Most physicians treating breast cancer-related bone metastases felt a de-escalation study after more than 2 years of BMA would be clinically important [i.v. bisphosphonate (BP) q12wks vs q24wks: 65%; i.v. BP q12wks vs. discontinue: 70%; denosumab q12wks vs q24wks: 57.5%; denosumab q12wks vs. discontinue: 67.5%]. Most physicians would accept SSE rate increase of < 5% with BMA de-escalation. If a study of BMA de-escalation showing non-inferiority in terms of SSE rate was not feasible, physicians would consider changing practice to de-escalated therapy if: BMA toxicity was reduced (64.1%), pain was no worse (48.7%), physical function was no worse (48.7%), or cost-utility or cost-effectiveness was improved (41%). 38.5% would only change practice if the SSE rate was not significantly worse.
**Conclusion:** Despite their extensive use and costs, questions around optimal use of BMAs still exist. It is evident that practice varies according to patient insurance coverage, however most physicians are de-escalating BMAs. There is interest amongst clinicians in performing trials of de-escalation, especially after 2 years of treatment.

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# Protective-2 (bpi-2358-106): A confirmatory trial to demonstrate superiority of the plinabulin+pegfilgrastim (plin/peg) combination versus standard of care pegfilgrastim for the prevention of chemotherapy-induced neutropenia (cin) in breast cancer (bc) patients (pts)

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**Introduction**. BC is a potentially curable cancer condition, with more favorable outcomes with avoidance of CIN. Peg is the standard of care for the prevention of CIN, but does not fully prevent CIN (Masuda 2015). Plin is a novel, small molecule, non-G-CSF agent, given as a single dose per cycle, by 30 min IV infusion, 30 min after Chemotherapy (Chemo), on the same day of Chemo. In contrast to Peg, Plin does not cause bone pain or thrombocytopenia. The mechanism of action (MoA) of Plin exerts its CIN preventive effects predominantly in week 1 of the cycle, whereas Peg primarily in week 2. This was the rationale to combine these two agents, to obtain superior CIN protection throughout the entire cycle (Blayney ASCO 2019). Data from Phase (Ph) 2 portion of PROTECTIVE-2 (NCT0329457) with the Plin/Peg combination demonstrated superiority in CIN protection vs Peg alone, with a favorable safety/tolerability profile (Blayney, St Gallen 2019). Additionally, the addition of Plin to Peg almost eradicated the Peg-induced bone pain. The Ph 3 portion of PROTECTIVE-2 aims to confirm superiority of the Plin/Peg combination vs Peg standard of care for avoidance of CIN and Bone Pain-prevention.

**Trial Design**

PROTECTIVE-2 is a global, multicenter, randomized, double-blind Study to Evaluate Plin 40 mg + Peg 6mg (Arm 1) versus Peg 6mg + Placebo (Arm 2) in preventing Severe Neutropenia ( defined as Absolute Neutrophil Count (ANC) of <0.5×10E9/L) in early stage (Stage I and II) and Stage III BC (node positive or node negative with a high risk of recurrence) pts with ECOG status 0 or 1 (target of approximately n=222 pts) receiving myelosuppressive Chemo with Docetaxel (75 mg/m2), Doxorubicin (50 mg/m2), and Cyclophosphamide (500 mg/m2) (TAC). A non-binding Interim Analysis was a planned at approximately n=100 pts completing Cycle 1. TAC and Plin were given on Day (D) 1 and Peg on D2.ANC (Covance Central Laboratory) was assessed before and after during Cycle 1 on D 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, and 15. Bone Pain was assessed by a validated at regular timepoints in Cycle 1 with a validated PRO questionnaire.

**The Primary objective** was to compare the percentage of pts with a Duration of Severe Neutropenia (DSN) of 0 days in treatment Cycle 1 between the Plin/Peg vs Peg alone.

**Secondary objectives** in Cycle 1 included mean DSN, mean ANC NADIR, average change in Bone Pain from baseline, the rate of composite risk (infection, FN, hospitalization, significant disability, life threatening and death), and over 4 Cycles, the percentage of patients with Relative Dose Intensity (RDI) < 85%.

Following the pre-planned Interim Analysis, the DSMB recommended the trial to continue without modifications. Current Status: Patient accrual has been completed.

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**Publication Number:** PS4-18

# Real-world PD-L1 test utilization and analytical concordance of the PD-L1 IHC 28-8 and 22C3 assays in patients with breast cancer

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**Background:** Programmed death-1/programmed death ligand 1 (PD-[L]1) inhibitors are approved for use in a range of cancers. PD-L1 expression in the tumor microenvironment, assessed with an FDA-approved PD-L1 immunohistochemistry (IHC) diagnostic assay such as the Dako PD-L1 IHC 28-8 and 22C3 pharmDx or Ventana PD-L1 SP142 and SP263 assays, is associated with improved PD-(L)1 inhibitor treatment outcomes in some tumor types, including breast cancer (BC). In March 2019, the FDA approved atezolizumab + nab-paclitaxel for the treatment of patients with advanced triple-negative BC and immune cell (IC) PD-L1 expression ≥ 1% using the SP142 assay. Here, we investigated test utilization, test turnaround time (TAT), PD-L1 expression prevalence by assay and biopsy location, and analytical concordance between assays in real-world BC samples.
**Design:** The study included samples from patients with BC that were tested for PD-L1 expression between Oct 2015 and Sep 2019 at NeoGenomics Laboratories, a US national reference laboratory. Patient characteristics from Symphony Healthcare Solutions were matched to PD-L1 test results using unique identifiers. Test volume and TAT were assessed for the 28-8, 22C3, SP142, and SP263 assays. PD-L1 expression was determined by trained pathologists using the 28-8, 22C3, or SP142 assays. Results for the 28-8 assay for the entire study period and for the 22C3 assay until Dec 2018 were reported as the percentage of tumor cells (% TC) with PD-L1 expression. From Jan 2019 onwards, 22C3 assay results were reported as a combined positive score (CPS). All SP142 assay results were reported as the percentage of ICs (% IC) with PD-L1 expression. Analytical concordance between assays was assessed in patients with matched samples (biopsies from the same site and collected on the same date). BioStat Solutions performed statistical analyses.
**Results:** 2955 PD-L1 tests were performed on samples from 2508 patients with BC. The volume of PD-L1 tests on BC samples increased > 100-fold over the study period. Mean TAT was < 5 days for all 4 assays pooled. Table 1 shows PD-L1 expression prevalence in patients with a 28-8, 22C3, or SP142 test result. Median PD-L1 expression did not differ between primary tumors and metastatic sites. In matched samples, overall percentage agreement (OPA) between the 28-8 (TC ≥ 1%) and 22C3 (CPS ≥ 1) assays was 94%, and OPA between the 22C3 (CPS ≥ 1) and SP142 (IC ≥ 1%) assays was 64% (Table 2). Analytical concordance between the 28-8 and 22C3 assays for % TC scoring in matched samples from 27 patients was high (Kendall's tau = 0.997 [95% CI, 0.883-1.000]).
**Conclusion:** Mean PD-L1 test TAT for BC samples remained < 5 days across all tests despite a large increase in test volume over the study period. Prevalence of PD-L1 expression ≥ 1(%) was higher with the CPS and % IC algorithms than the % TC algorithm, although differences could be due to multiple confounding factors. Despite a small sample size, analytical concordance between the 28-8 and 22C3 assays in matched samples was high. These data provide real-world context for the PD-L1 testing landscape in BC.

**Table 1. Prevalence of PD-L1 expression in patients with BC**

| PD-L1 expression[a] | 28-8 and 22C3[b] % TC, n (%) (N = 608) | 22C3[c] CPS, n (%) (N = 609) | SP142 % IC, n (%) (N = 1080) |
|---|---|---|---|
| < 1(%) | 390 (64) | 253 (42) | 367 (34) |
| ≥ 1(%) | 218 (36) | 356 (58) | 713 (66) |

All patients had a single test result or ≥ 2 identical results. [a]The CPS algorithm is reported on a scale of 0-100, not as a percentage; [b]Samples tested with the 22C3 assay between Q4 2015 and Q4 2018 were scored using the % TC algorithm; [c]Samples tested with the 22C3 assay between Q1 2019 and Q4 2019 were scored using the CPS algorithm.

**Table 2. Agreement between assays on matched samples from patients with BC**

| **Agreement between 28-8 (TC ≥ 1%) and 22C3 (CPS ≥ 1) (N = 18)[a]** | | |
|---|---|---|
| | 28-8 as reference | 22C3 as reference |
| OPA (n/N) | 94 (17/18) | |
| PPA (n/N) | 100 (6/6) | 86 (6/7) |
| NPA (n/N) | 92 (11/12) | 100 (11/11) |
| **Agreement between 22C3 (CPS ≥ 1) and SP142 (IC ≥ 1%) (N = 33)[b]** | | |
| | 22C3 as reference | SP142 as reference |
| OPA (n/N) | 64 (21/33) | |
| PPA (n/N) | 86 (12/14) | 55 (12/22) |
| NPA (n/N) | 47 (9/19) | 82 (9/11) |

[a]Data are presented for 28-8 and 22C3 tests on matched samples with 22C3 tests performed between Q1 2019 and Q4 2019; [b]Data are presented for 22C3 and SP142 tests on matched samples with 22C3 tests performed between Q1 2019 and Q4 2019. N, total number of samples; n, number of samples with the same results with the 2 tests; NPA, negative percentage agreement; PPA, positive percentage agreement.

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Predicting breast cancer response to neoadjuvant therapies using a mathematical model individualized with patient-specific magnetic resonance imaging data: Preliminary Results

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**Background**: This study evaluates the ability to predict the response of locally advanced breast cancers to neoadjuvant therapy (NAT) using patient-specific magnetic resonance imaging (MRI) data and a biophysical mathematical model. The 3D mathematical model consists of three parts: tumor cell proliferation, tumor spread (diffusion), and treatment. In particular, the tumor cells proliferate according to logistic growth, and the diffusion term is coupled to the mechanical properties of the surrounding fibroglandular and adipose tissues to inform individual tumor growth patterns (specific to each patient's anatomy). The model's treatment term accounts for tumor cell reduction according to approximate local drug delivery for each patient.
**Methods**: Patients (N = 21) with intermediate to high grade invasive breast cancers with varying receptor status, who were eligible for NAT as a component of their clinical care, were recruited. Each patient was treated with standard-of-care consisting of one or two NAT regimens in sequence followed by surgical resection of any residual tumor. MRI data are acquired at four time points: 1) prior to initiation of NAT, 2) after 1 cycle of NAT, 3) after 2-4 cycles of NAT, and 4) 1 cycle after scan 3. The MRI data is processed and evaluated using our semi-automated pipeline. Specifically, diffusion-weighted MRI data is utilized to characterize the cellularity throughout the tumor tissue, and dynamic contrast-enhanced (DCE-) MRI data is used to segment the breast tissue and analyze the local drug delivery using pharmacokinetic analysis and population-derived plasma curves of drug concentrations. The model's predictive ability is assessed using three different strategies. First, the model is calibrated using each patient's first two scans to enable predictions of the total tumor cellularity, volume, and longest axis that are directly compared to the values measured from their third scan. Second, the model's predictions for tumor response are compared to the corresponding response evaluation criteria in solid tumors (RECIST) results. Third, the model is re-calibrated using scans 3 and 4 and simulated to the time of surgery to compare the model's predictions to each patient's response status determined by surgical pathology.
**Results**: Calibrating the model with MRI data for one cycle of therapy yields predictions strongly correlated with tumor response measured from each patient's third scan, concordance correlation coefficients of 0.91, 0.90, and 0.86 for total cellularity, volume, and longest axis, respectively (p < 0.01, N = 18). The model's predictions are significantly (p < 0.01) correlated with tumor response as designated by RECIST for the cohort. Specifically, the model predicts greater percent reduction in the longest axis for the RECIST designated responder group (i.e., complete response and partial response) compared to non-responders. At the time of surgery, the model predicts changes in total tumor cellularity from baseline that are significantly (p < 0.01) correlated with pathological response status—an area under the receiver operator characteristic curve of 0.92 and a sensitivity and specificity of 1.0 and 0.74, respectively.

**Discussion**: These preliminary results suggest that this clinical-mathematical approach can be predictive of tumor response very early in the course of NAT on a patient-specific basis. Moreover, the study was performed in the community-care setting across a heterogenous group of patients, indicating the approach may be practical for wide-spread application.
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Describing the cancer spectrum in families with CHEK2 pathogenic and likely pathogenic variants by mutation type

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**Background:** Deleterious CHEK2 variants have well-defined risks for breast and colorectal cancers. Some studies have also suggested association with a variety of other cancers, including leukemia, kidney, prostate, thyroid and gastric cancers. However, most CHEK2 studies are based on European founder mutations, and there is a lack of data on non-founder mutations. Here, we describe the cancer family histories of patients with both founder and non-founder CHEK2 mutations. **Methods:** This is a retrospective review of patients who underwent germline testing of 31 cancer risk genes. All pathogenic (P) and likely pathogenic (LP) variants in CHEK2 were selected from our database and categorized as founder or non-founder mutations. Personal and family histories of cancer reported by the ordering provider were recorded for each case. Cancer rates were calculated as the number of patients with a personal and/or family history of each cancer divided by the total number of patients. Ethnicities in our CHEK2+ cohort and our overall database were calculated as a percentage. **Results:** A total of 132 patients were found to have P/LP variants in CHEK2. This CHEK2+ cohort was largely Caucasian (79.5%), despite our overall database being ethnically diverse (56% Caucasian). Nineteen different mutations were identified, 75% of which were founder and 25% were non-founder mutations. Personal histories of cancer were identified in 7% of patients. Twenty-eight different cancers were reported in patients' personal/family histories. The rates of select cancers in the total cohort, founder mutation group and non-founder mutation group are reported in Table 1. **Discussion:** These findings support previous reports that prostate, gastric and kidney cancers may be part of the CHEK2 cancer spectrum, which has typically only included breast and colorectal cancer. We also identify ovarian and pancreatic cancer as potential CHEK2-associated cancers. Cancer rates are similar between CHEK2 patients with founder and non-founder mutations. Differences in cancer rates were observed between these two groups, but this cohort was too small to determine significance. Additional studies are needed to understand the overlap of cancer risk with non-founder mutations and those well-described for founder mutations.

| | **Breast Female** | **Ovarian** | **Prostate** | **Colorectal** | **Pancreatic** | **Uterine** | **Gastric** | **Kidney** |
|---|---|---|---|---|---|---|---|---|
| **All** | 80.3% | 39.4% | 25% | 23.5% | 13.6% | 8.3% | 8.3% | 6.1% |
| **Founder** | 81.8% | 40.4% | 30.3% | 23.2% | 18.2% | 9.1% | 9.1% | 8.1% |
| **Non-founder** | 75.8% | 36.3% | 9.1% | 24.2% | 0% | 6% | 6% | 0% |

**Table 1:** Select cancer rates by CHEK2 mutation type

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# Metformin exhibits cytotoxicity effects on triple-negative cancer cells via TRAIL-mediated apoptosis

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**Introduction:** Triple-negative breast cancer (TNBC) does not respond to conventional targeted therapy, necessitating novel treatment options. Metformin possesses unique anti-proliferative and pro-apoptotic properties in TNBC cells. However, the molecular mechanism through which metformin may induce apoptosis is incompletely understood. In the current study, we aim to determine whether tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptotic signaling is involved in metformin-induced cytotoxicity on TNBC cells.
**Methods:** TNBC cell lines HCC70, MDA-MB-468, BT549 and MDA-MB-231 were used in the study. A cell death detection ELISA kit was used to quantitatively measure cytoplasmic histone-associated DNA fragments (mono- and oligonucleosomes). Western blot analyses were carried out to assess the expression of TRAIL, TRAIL receptors DR5 and DR4, and apoptosis-related proteins (PARP, Caspase-8 and Caspase-3). Flow cytometric analyses were performed to define the expression of cell surface TRAIL receptors DR5 and DR4. Secreted TRAIL protein level in the conditioned medium (CM) of cell culture was measured by using a highly specific ELISA and western blot. MDA-MB-231 cells were treated with concentrated CM from metformin-treated cells to test the activity of secreted TRAIL in inducing cell apoptosis. A soluble recombinant TRAIL decoy receptor, which contains a normal extracellular domain of death receptor 5 (DR5) but a truncated intracellular domain and thus is unable to transduce death signals, was used to block TRAIL function. Infection with lentivirus containing specific shRNAs was performed to knockdown TRAIL expression.
**Results:** Metformin induced apoptosis in a panel of TNBC cell lines in a dose-dependent manner, as evidenced by the increase of cytoplasmic histone-associated DNA fragments and the cleavage of PARP, caspase-8 and caspase-3. Interestingly, during the process of TNBC cells undergoing apoptosis, metformin elicited a dose-dependent upregulation of TRAIL protein levels (both cellular TRAIL and secreted TRAIL) without altering the expression of TRAIL receptors DR5 and DR4. The secreted TRAIL from concentrated CM of metformin-treated cells showed activity in inducing apoptosis of MDA-MB-231 cells. To determine if the
induction of TRAIL was essential for metformin-induced cytotoxicity effects on TNBC cells, we examined whether inhibition of TRAIL function by a decoy receptor or specific knockdown of TRAIL expression with shRNAs would affect metformin-induced apoptosis. In all three cell lines (HCC70, MDA-MB-468, BT549) we tested, both the TRAIL decoy receptor and TRAIL-specific shRNAs significantly attenuated metformin-induced DNA fragmentation and cleavage of PARP, caspase-8, and caspase-3.
**Conclusion:** We demonstrate that metformin promotes TNBC cells undergoing apoptosis via induction of TRAIL expression. Our data suggest that TRAIL-mediated apoptosis critically contributes to metformin's antitumor activity against TNBC.
**Keywords:** Metformin, TRAIL, Apoptosis, triple-negative breast cancer

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Association of factors of the obesity phenotype with breast cancer recurrence risk measured by oncotype recurrence score and short-term response to neoadjuvant endocrine therapy

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Background:Increased body mass index (BMI) and metabolic syndrome are associated with an increased risk of breast cancer recurrence. The mechanism(s) responsible for this increased risk are not known, though multiple mechanisms including resistance to endocrine therapy have been proposed. We sought to determine whether obesity and/or metabolic syndrome were associated with intrinsic tumor risk as determined by the Oncotype recurrence score (RS), or with resistance to neoadjuvant endocrine therapy, as determined by Ki67 response after short-term presurgical treatment. Methods:To investigate whether BMI was associated with increased intrinsic recurrence risk, we analyzed a cohort of 779 patients treated at Vanderbilt for early stage breast cancer and who had Oncotype test results. Medical records were reviewed to record BMI at the time of breast cancer diagnosis. We compared the Oncotype RS between patients with BMI greater or less than 27, and in normal, overweight, and obese ranges. To investigate whether the increase in breast cancer recurrence risk associated with obesity could be identified by a surrogate marker of short-term response to endocrine therapy, we analyzed data from a presurgical trial of endocrine therapy in early stage breast cancer patients previously completed at Vanderbilt. In this study patients were treated with 1-2 weeks of letrozole prior to surgery, then the surgical specimen was analyzed for Ki67. The original goal of the study was to compare endocrine sensitive tumors with endocrine resistant tumors as a platform for discovery of resistance mechanisms to endocrine therapy. We retrospectively analyzed medical records for 143 patients in that study who had post-treatment Ki67 values available, and for whom BMI at the time of surgery could be obtained. We also reviewed medical records for components of the metabolic syndrome (hypertension, hyperglycemia or anti-hyperglycemic medications, low HDL, high triglycerides or statin use, and BMI > 30 as a surrogate for waist circumference). Metabolic syndrome was defined as 3 or more of the 5 components. For endocrine therapy response, a cutoff of 1 for the natural log Ki67 expression was defined as sensitive (approximately 2.5%) and tumors with natural log of Ki67 expression between 1 and 2 (approximately 7.5%) were categorized as intermediate sensitivity. Results:We did not find any significant association between BMI and recurrence score and the distribution of risk scores was similar across all BMI groups. We did not observe any correlation between RS and BMI. However we did observe a difference in the proportion of endocrine sensitive and resistant tumors in overweight and obese groups (only a minority of patients in this cohort, 18%, had normal weight). In patients with overweight, 70% of the tumors had a post-treatment Ki67 level classified as sensitive, whereas only 40% of the tumors in patients with obesity were endocrine sensitive (chi square = 0.0518). Similarly, 72% of patients without metabolic syndrome had sensitive tumors, but only 51% of patients with metabolic syndrome had sensitive tumors (relative risk 1.408, chi square = 0.0154). Conclusions:Our findings suggest that the association between obesity and/or metabolic syndrome and increased recurrence risk is not reflected in tumor-intrinsic properties present at the time of diagnosis. Rather, the effect of obesity and metabolic syndrome appears to be in response to treatment, at least as measured by a short-term surrogate marker of long-term endocrine sensitivity. Importantly, this suggests that interventions to reverse obesity and/or metabolic syndrome may be effective in improving outcomes for breast cancer recurrence, at least in part by improving sensitivity to endocrine therapy.

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# Microsatellite instability high (MSI-H) detection utilizing targeted plasma based genotyping in metastatic breast cancer

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**Background:** Microsatellite instability (MSI) occurs in some tumors from defects in mismatch repair genes. Immune checkpoint inhibition is approved for treatment of MSI-high (MSI-H) tumors. Plasma-based genotyping assays are being used more commonly in breast cancer to identify targetable mutations. The objective of this study was to evaluate MSI-H detection by plasma-based genotyping in metastatic breast cancer (MBC) and understand the co-existing genomic landscape. In selected cases, correlations of MSI-H with clinical characteristics were determined.

**Methods:**Patients who had MSI-H detected by cell-free DNA (cfDNA) analysis via Guardant360™ testing (next-generation sequencing (NGS), up to 74 gene panel) between 9/27/2018 and 3/12/2020 with a diagnosis of breast cancer reported on the test requisition form were identified from a de-identified database. MSI detection is based on plasma NGS of 90 microsatellite sites and combining observed read sequences and molecular barcoding information in a probabilistic model (Willis, 2019). A retrospective review was conducted to identify demographic and genomic characteristics of patients with MSI-H findings. For 11 patients, clinical data was provided by the treating physician for evaluation of demographics and response to immunotherapy.

**Results:**Of 7824 patients with breast cancer with alterations in plasma NGS, 40 (0.5%) were MSI-H. Of these 40 patients, 40 (100%) were female. The median age was 61 (range 39-92). The median number of genomic alterations per sample was 13 (range 4-69), and the median maximum allelic fraction (MAF) was 15.9% (range 0.92-54.2), compared to 4 and 2.7%, respectively, in all breast cancer samples reported in this time period. Table 1 depicts the most common co-existing non-synonymous mutations, which included DNA damage repair genes (*ATM* and *BRCA2*).

Clinical data was available for 11/40 MSI-H patients with MBC. Of these 11 patients, 4 (36%) had triple-negative MBC (mTNBC), and 7 (64%) had hormone receptor positive (HR+)/HER2- MBC. None had known Lynch syndrome. Seven patients received treatment with an immune checkpoint inhibitor (2 atezolizumab/nab-paclitaxel, 3 pembrolizumab, 1 pembrolizumab/capecitabine followed by pembrolizumab/eribulin, and 1 nivolumab). Treatment duration was available for 5 patients, and the median duration of treatment was 108 days (range 65-273 days). Two patients had durable benefit (1 with stable disease for 10 cycles, and another on treatment for > 152 days), both of whom had mTNBC and were treated in the first-line setting with atezolizumab/nab-paclitaxel.

**Conclusions:**Plasma-based genotyping assays can identify the presence of MSI-H in breast cancer, including in patients with mTNBC and HR+/HER2- MBC. MSI-H breast cancers had a higher number of somatic alterations and MAF, suggesting higher tumor burden and genomic instability. The co-existing genomic landscape is heterogeneous, and mutations in *TP53, PI3KCA, ESR1, RB1, NOTCH1,* and *ARID1A*, and DNA damage repair genes (*ATM* and *BRCA2*) may be present. Since plasma based genotyping is increasingly being utilized to identify actionable mutations including *PI3KCA*, the ability to detect additional genomic alterations such as MSI-H extends the potential clinical application. However, the clinical utility of MSI detection by cfDNA needs to
be determined and further prospective research is needed to validate the use of immunotherapy in cfDNA detected MSI-H MBC.

**Table 1.**

| Gene | Number (%) of MSI-H patients with ≥ 1 mutation |
|---|---|
| *TP53* | 31 (78) |
| *PI3KCA* | 25 (63) |
| *ESR1* | 20 (50) |
| *RB1* | 16 (40) |
| *NOTCH1* | 15 (38) |
| *ARID1A* | 15 (38) |
| *ATM* | 14 (35) |
| *BRAF* | 14 (35) |
| *EGFR* | 13 (33) |
| *PDGFRA* | 11 (28) |
| *PTEN* | 11 (28) |
| *APC* | 11 (28) |
| *MET* | 10 (25) |
| *KIT* | 10 (25) |
| *FGFR2* | 10 (25) |
| *BRCA2* | 10 (25) |

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Relative risk of various endocrinopathies associated with the use of chemoimmunotherapy for triple-negative breast cancer: A systematic review and meta-analysis

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**Background:** Chemoimmunotherapy (CPI+C) is an important addition to the triple-negative breast cancer (TNBC) treatment. However, immune checkpoint inhibitors (CPIs) are frequently associated with significant endocrine toxicities. We conducted a systematic review and meta-analysis of phase 3, randomized controlled trials (RCTs) to determine the relative risk of various endocrinopathies associated with use of CPI+C regimens for the treatment of TNBC.
**Methods:** We conducted a comprehensive search in the PUBMED, MEDLINE, EMBASE, San Antonio Breast Cancer Symposium, and American Society of Clinical Oncology meeting abstracts as per PRISMA guidelines from inception until June 2020. We included phase 3 RCTs used CPI+C in the intervention arm for the treatment of TNBC and reported the number of events for various endocrinopathies. We used the Mantel-Haenszel method and the random effects model to calculate the pooled risk ratio (RR) with a 95% confidence interval (CI). Heterogeneity was tested with the $I^2$ value and Cochran's Q statistics. An RR of < 1 was considered to be favorable for the CPI+C, and an RR of > 1 was considered to be unfavorable for the CPI+C. A P-value ≤ 0.05 was considered statistically significant.
**Results:** Two phase 3 RCTs — IMpassion130 and KEYNOTE-522 — were included in the final analysis. The CPI+C arm included 1233 patients, and the placebo-chemotherapy (P+C) arm included 827 patients. While the IMpassion130 was done in unresectable, locally advanced or metastatic TNBC patients at the first-line setting, the KEYNOTE-522 was done in early stage TNBC patients. For the KEYNOTE-522 study, we used data from the neoadjuvant phase, as in the adjuvant phase, only CPI was continued. The number of patients in the adjuvant phase also differed from the neoadjuvant phase which made it difficult to select appropriate denominator for the RR calculation. Some important characteristics of these studies are included in the table 1. The incidence of any-grade hypothyroidism was 15% in the CPI+C arm vs 3.86% in the P+C arm. The pooled RR of any-grade hypothyroidism was 4.03 (95% CI: 2.79-5.82, P < 0.00001, $I^2$ = 0%). The incidence of any-grade hyperthyroidism was 4.54% in the CPI+C arm vs 1.2% in the P+C arm. The pooled RR of any-grade hyperthyroidism was 3.73 (95% CI: 1.89-7.34, P = 0.0001, $I^2$ = 0%). The incidence of any-grade adrenal insufficiency was 1.78% in the CPI+C arm vs 0% in the P+C arm. The pooled RR of any-grade adrenal insufficiency was 12.87 (95% CI: 1.70-97.34, P = 0.01, $I^2$ = 0%). The incidence of type 1 diabetes mellitus was 0.24% in the CPI+C arm vs 0.24% in the P+C arm. The RR for type 1 diabetes mellitus was not significantly different between the arms — RR: 0.91 (95% CI: 0.14-5.96, P = 0.92, $I^2$ = 0%).
**Conclusions:** The relative risk of hypothyroidism, hyperthyroidism, and adrenal insufficiency were significantly higher with the use chemoimmunotherapy compared to chemotherapy alone in TNBC patients. CPI induced endocrinopathies are often permanent and require long-term treatment. However, treatment discontinuation is not necessary for CPI induced endocrinopathies. A careful monitoring of symptoms and endocrine functions, and initiation of appropriate treatments are crucial to reduce endocrine related morbidities and mortalities in these patients.

Table 1. Characteristics of the included studies.

| Study | Author/Journal/Year | Setting | CPI+C arm | P+C arm | Randomization | No.of patients (CPI+C) | No. of patients (P+C) |
|---|---|---|---|---|---|---|---|
| IMpassion130 | Schmid/NEJM/2018 | Advanced TNBC | Atezolizumab + nab-paclitaxel | Placebo + nab-paclitaxel | 1:1 | 452 | 438 |
| KEYNOTE-522 | Schmid/NEJM/2020 | Stage II and III TNBC | Pembrolizumab + paclitaxel + carboplatin + adriamycin or epirubicin + cyclophosphamide | Placebo + paclitaxel + carboplatin + adriamycin or epirubicin + cyclophosphamide | 2:1 | 781 | 389 |

CPI+C: chemoimmunotherapy; NEJM: The New England Journal of Medicine; P+C: placebo + chemotherapy; TNBC: triple-negative breast cancer.

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Eribulin-mediated release of mitochondrial DNA activates the cGAS-STING innate immune signaling pathway

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Triple-negative breast cancer (TNBC) patients have a higher response rate to immune checkpoint inhibitors as compared to patients with other types of breast cancer. This higher response rate is thought to be due to higher mutational burdens, the prevalence of PD-L1/PD-1 expression, and immune cell infiltration in TNBC. However, less than half of TNBC patients respond to these drugs as single agents, which has prompted their use in combination with chemotherapy, including microtubule targeted agents (MTAs). Multiple clinical trials now show that the combination of PD-1/PD-L1-targeted immune checkpoint inhibitors with chemotherapy, including the MTAs paclitaxel or eribulin, can improve clinical responses in both late and early-stage TNBC. Previous studies have demonstrated that MTAs can activate innate immune sensing pathways that could potentially mediate their efficacy in combination with immunotherapies, including the ability of paclitaxel to promote TLR4 signaling. However, there has not been a direct comparison of the immunogenic effects elicited by each of the five MTAs that are used to treat TNBC to inform on how agents of this class could differentially alter the tumor immune microenvironment. In the current study, we determined the concentration and time-dependent effects of paclitaxel, docetaxel, ixabepilone, eribulin, and vinorelbine on the cytokine expression profiles in both immune and TNBC cells. Our results demonstrate that the microtubule destabilizers, eribulin, and vinorelbine, but not the microtubule stabilizers, paclitaxel, docetaxel, and ixabepilone, promote upregulation of type 1 interferons (IFNα/β) and downstream interferon-stimulated-genes. A time-course analysis in the human monocytic THP-1 cell line and primary murine bone-derived macrophages found that the induction of IFNβ by eribulin occurred within 2-6 hours and was independent of mitotic arrest. A pharmacological and genetic-based assessment of the signaling pathways responsible for the eribulin-mediated expression of IFNβ revealed a dependency on the cGAS-STING cytosolic DNA-sensing innate immune signaling pathway in both immune and TNBC cells. Moreover, we demonstrate that the mechanism for the promotion of cGAS-STING-dependent interferon induction by eribulin is due to the release of mitochondrial DNA (mtDNA) into the cytoplasm. Together, these results provide evidence that different MTAs have distinct immunomodulatory properties and highlight the ability of eribulin to promote the release of mtDNA to activate the cGAS-STING pathway, which has been previously shown to enhance the efficacy of immunotherapy in TNBC. These studies were funded by Eisai.

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# Clinical utility of genomic testing for early stage breast cancer patients treated with APBI brachytherapy

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**Background:** Adjuvant radiation after breast conserving surgery (BCS) remains the standard of care for management of patients with early-stage breast cancer (ESBC). Whole breast irradiation (WBI) after lumpectomy for ESBC has demonstrated a 50% reduction in the 10-year rate of recurrence (ROR). NSABP B-39 determined that accelerated partial-breast irradiation (APBI) was effective at reducing the ROR by treating ESBC directly at the tumor bed and that a rigorous course of WBI may not be necessary in select patients. In this study, we determined the impact of genomics and tumor biology on the decision to escalate or de-escalate therapies and on subsequent outcomes beyond anatomic staging for APBI patients. **Methods:** This analysis included 91 patients with biopsy confirmed invasive ESBC treated with BCS followed by APBI intracavitary brachytherapy at a dose of 34.0 Gy in 10 fractions from 2007 to 2018 who received either MammaPrint (MP) or Oncotype DX (ODx) testing. Clinicopathological risk assessment was performed using MINDACT criteria for clinical guidelines to classify patients as either clinical low risk (CLR) or clinical high risk (CHR). MP stratified patients into either MP Low Risk (MLR) or MP High Risk (MHR). ODx was used with TAILORx-defined cutoffs to stratify patients into either ODx Low Risk (OLR), which is women >50 years of age with HR+, HER2-negative, node-negative breast cancer, Recurrence Score (RS) of 0 to 25 or ODx High Risk (OHR), RS 26-100. If both methods were concordant, the genomic test could not be determined to have impacted the treatment decision. Clinical utility was established in discordant cases when the genomic test guided treatment. Differences in overall survival (OS) were assessed by Kaplan Meier analysis and log-rank test. Relevant clinical data was abstracted from the electronic medical record. **Results:** Patients (n=91) were 60% CLR and 40% CHR. Of the CLR patients with MP testing, 36% reclassified as MHR; 25% of these (3/12) omitted chemotherapy (CT) despite the discordant result, one of whom (33%) had a local recurrence within 0.25 years of follow-up (FU). Of CHR patients, 54% were MHR, 62% of whom received CT in line with the CHR/MHR result. Of the CHR patients who reclassified as MLR (46%), 91% omitted CT from treatment plans, in alignment with MP results. There were no distant or local recurrences or deaths to date in these groups. About 96% of CLR patients were OLR with 2 events (BC related death). One patient that reclassified as OHR omitted CT despite a discordant CLR/OHR result and has not had a recurrence within 3.9 years of FU. Of the CHR patients who reclassified as OLR (83%), 90% omitted CT in alignment with ODx results; 22% of whom had distant metastases and subsequent death within 1.1 years of FU. **Conclusion**: 9/11 (82%) of Oncotype discordant patients followed the genomic test recommendation, of whom 22% could not safely do so without impairing outcome. 19/23 (83%) of MammaPrint discordant patients all safely followed this genomic test recommendation. These data suggest that the addition of a genomic signature may allow de-escalation of radiotherapy to APBI even in select high risk patients, provided they follow the systemic therapy recommended by the genomic test result.

| | **CLR/MLR (n=21)** | **CHR/MLR (n=11)** | **CLR/MHR (n=12)** | **CHR/MHR (n=13)** |
|---|---|---|---|---|
| **Followed MP YES** | 21 (100%) | 10 (91%) | 9 (75%) | 8 (62%) |
| **Followed MP NO** | 0 | 1 (9%) | 3 (25%) | 5 (38%) |
| **EVENT** | 0 | 0 | 1 LRR | 0 |
| **3-year OS (95% CI)** | 100% | 100% | 100% | 100% |
| | **CLR/OLR (n=23)** | **CHR/OLR (n=10)** | **CLR/OHR (n=1)** | **CHR/OHR (n=2)** |
| **Followed ODx YES** | 19 (83%) | 9 (90%) | 0 | 2 (100%) |
| **Followed Odx NO** | 4 (17%) | 1 (10%) | 1 (100%) | 0 |
| **EVENT** | 2 Deaths at 6.3 and 7.9 years | 2 Deaths at 0.5 and 1.7 years | 0 | 1 Death at 6.5 years |
| | (RS 21 & 25) | (RS 17 & 23) | | (RS 32) |
| **3-year OS (95% CI)** | 100% | 77.8% (36.5-93.9) | 100% | 100% |

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Inhibition of mTOR signaling by rapamycin abrogates mammary stem/progenitor cell activity in aged mice

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Previous studies have shown an altered physiology in the mammary gland of aged mice, with mammary ducts displaying increased tertiary branching along with an enriched myoepithelial population compared to younger mice. It is the population of myoepithelial cells residing in the basal layer of mammary ducts that is thought to be responsible for the development of the mammary gland. These qualities have been attributed to the mammary stem cells (MaSCs) that reside in this population and are capable of regenerating the mammary gland when implanted in an empty mammary fat pad, indicating their bipotent nature. It is not known however, if these stem cells are responsible for the aging mammary gland phenotype and the increased risk of cancer seen in aging mammals. Our preliminary studies showed that rapamycin could be utilized as a MaSC inhibitor and clinical trials are currently under way investigating the role of rapamycin in inhibiting MaSC function and abrogating biomarkers associated with invasive BC progression. Mammalian target of rapamycin (mTOR) is a protein kinase that regulates growth, proliferation, and survival in cells and is often upregulated in cancer. Rapamycin is an extremely selective inhibitor of mTORC1 function and its downstream signaling. In this study, aged mice fed *ad lib* with microencapsulated rapamycin showed decreased mTOR activity in the mammary ducts as shown by immunohistochemistry in aged mice. Treated mouse breast tissue also displayed a decreased population of $Lin^{-}$ $CD24^{low}$ $CD49f^{hi}$ myoepithelial/basal cells along with decreased tertiary branching in the ductal morphology, effectively reversing the aged mammary gland phenotypes. MaSC inhibition by rapamycin was also shown using sphere formation efficiency (SFE) assays after sorting the luminal ($Lin^{-}$ $CD24^{hi}$ $CD49f^{low}$) and basal ($Lin^{-}$ $CD24^{low}$ $CD49f^{hi}$) epithelial cells using Florescence Activated Cells Sorting (FACS) in a free suspension culture. Together, these findings show a possible use in regulating MaSCs by rapamycin and its potential in preventing age-related diseases such as breast cancer.

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Circulating tumor DNA (ctDNA) mutation (mut) profile in relation to paboclicib (pal) efficacy in hormone receptor positive (HR+) and HER2 negative (HER2-) metastatic breast cancer (MBC)

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**Background:** Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6*i*) are now standard of care (SOC) for pts with HR+/HER2- MBC. However, aside from HR positivity, there are no biomarkers for pt selection. Although mutations (muts) in genes such as *RB1*, *FAT1*, or *FGFR*, are associated with CDK4/6*i* resistance, they are rare events in HR+/HER2- MBC. The goal of this study is to examine the ctDNA mut profile, and the impact of commonly mutated genes (*ESR1*, *TP53* and *PIK3CA*) on progression free survival (PFS) in pts received pal as SOC in a real world experience. **Methods:** Chart review was performed for pts with HR+/HER2- MBC who received pal and ctDNA Guardant360® (G360) testing between 01/2015 and 06/2020 at Siteman Cancer Center. The Kaplan-Meier method was used to generate time-to-event curves with calculated mPFS. A stratified log-rank test was used for all comparisons with P-values reported. Hazard ratios (HRs) and associated 95% confidence intervals (CI) were calculated with a stratified Cox proportional-hazards model. **Results:** Among the 73 pts identified, median age was 61.5 years (range 33.7-83.3). 15 (20.5%) pts received pal as 1$^{st}$-line, 22 (30.1%) pts as 2$^{nd}$-line, and 36 (49.3%) pts as 3$^{rd}$-line and beyond. All 73 pts had muts by G360. Top 3 mutated genes are *PIK3CA* (n=25, 34.2%), *TP53* (n=20, 27.4%) and *ESR1* (n=17, 23.3%), followed by *GATA3* (n=12, 16.4%) and *MYC* (n=6, 8.2%). For association analysis with PFS, 17 pts were excluded from further analysis due to having had multiple interim therapies between G360 testing and pal therapy, leaving 56 pts who had G360 immediately prior to pal (n=11), during pal (n=13), at progressive disease (PD) on pal (n=20), or had 1 additional therapy after PD on pal (n=12). Among the 56 pts, the median age on pal was 62.8 years (36.6-78.4). Median duration on pal was 7.7 months (mo). Pal was received as 1$^{st}$-line in 14 (25.0%), 2$^{nd}$-line in 17 (30.4%) and 3$^{rd}$-line plus in 25 (44.6%) pts. Muts in *PIK3CA*, *TP53* and *ESR1*, were identified in 18 (32.1%), 16 (28.6%), and 13 (23.2%) pts, respectively, with rates similar to the entire 73-pt cohort. Among 13 ESR1 mutant pts, 7 had letrozole and 6 had fulvestrant as pal's endocrine partner. Concurrent muts in 2 of 3 genes were observed in 11 (19.6%) pts (6 with *PIK3CA* and *TP53*, and 5 with *ESR1* and *TP53)*. The mPFS was 7.4 and 12.6 mo (p=0.03) in pts with or without *PIK3CA* mut, 7.9 and 12.8 mo (p=0.85) with or without *ESR1* mut, and 16.0 and 13.3 mo (p=0.46), with or without *TP53* mut, respectively. mPFS for pts with concurrent muts in 2 of the 3 genes was 7.4 mo, compared to 11.7 mo and 13.3 mo in pts with 1 or no mut in these 3 genes (p=0.46). In multivariate analysis that included age, visceral mets and line of therapy, the HRs for PFS were <1 for pts without mut in *PIK3CA* or *ESR1* (Table 1). Pts with 1-5 and 6-10 mut were 26% and 36% less likely to have PD compared to pts with >10 muts, respectively. **Conclusions:** In this retrospective real world experience, ctDNA muts in *PIK3CA* and *ESR1* as well as higher number of muts in ctDNA were associated with worse outcome in pts received pal. Although several studies have shown CDK4/6*i* benefit regardless of *PIK3CA* or *ESR1* mut status, our data indicates that muts in these genes render worse prognosis on CDK4/6*i* and supports *PIK3CA* and *ESR1* muts as driver events in HR+ MBC. PI3K*i* or novel ER targeted agents are combined with CDK4/6*i* in clinical trials and results are eagerly awaited. In addition, further study for pts with higher ctDNA mut number is warranted.

Multivariate Cox Proportional Hazards Regression Model on PFS

| Variables | PFS | |
|---|---|---|
| | HR (95% CI) | P-value |
| ESR1 (non-mut vs. mut) | 0.64 (0.26-1.56) | 0.32 |
| TP53 (non-mut vs. mut) | 1.70 (0.80-3.60) | 0.16 |
| PIK3CA (non-mut vs. mut) | 0.42 (0.17-1.02) | 0.06 |
| Age (<65 vs. >=65 yo) | 0.92 (0.45-1.87) | 0.81 |
| No. Lines of pal (1$^{st}$- vs. 3$^{rd}$-line) | 0.61 (0.25-1.48) | 0.28 |
| No. Lines of pal (2$^{nd}$- vs. 3$^{rd}$-line) | 0.46 (0.20-1.04) | 0.06 |
| No. of muts (1-5 vs. >10) | 0.74 (0.24-2.33) | 0.61 |
| No. of muts (6-10 vs. >10) | 0.64 (0.20-2.07) | 0.46 |
| Visceral mets (no vs. yes) | 1.25 (0.52-2.98) | 0.61 |

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**Publication Number:** PS3-18

# Differences in the diagnostic performance of breast ultrasound with or without additional patient information: A secondary analysis of an international multicenter trial

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Background and objectives: The Breast Imaging Reporting and Data System (BI-RADS) has helped to standardize radiologic reports and assessment in breast cancer diagnostics. So far, BI-RADS consists of the sole, standardized description of images. Individual patient characteristics like disease and family history or age are no part of the current BI-RADS classification system but are often subjectively considered to evaluate the risk of breast cancer in the clinical setting. It is however unclear how and to which extent such additional patient information influence the evaluation of risk of malignancy. Thus, we compared the performance in the detection of breast cancer between the sole analysis of ultrasound images by physician experts and a physician actually examining and counseling a patient in the clinical setting.
Methods: This multicenter, prospective trial took place at 11 trial sites in Austria, France, Germany, Japan, Netherlands, Portugal, and the US from February 2016 to March 2019. The trial enrolled 1288 women presenting with a lesion ≥0.5 and ≤5 cm in 2D B-mode ultrasound. In the clinical setting, the examiner conducted a routine 2D B-mode ultrasound examination and had additional standard information about the patients' disease history and family history. The final ultrasound images made in the clinical routine (annotated with size measurements) but not any other information about the patient was given to three physician experts (>15 years of experience in breast cancer diagnostics). The examiner in the clinical setting and each of the three experts evaluated the ultrasound images according to BI-RADS and gave a likelihood score for malignancy according to ACR (American College of Radiology). Following the BI-RADS definition by ACR, malignancy was assumed for a likelihood of malignancy >2% (BI-RADS 4 or higher). All patients underwent histopathological confirmation which was the gold standard against which the clinical examiner and the three experts were compared. AUC, sensitivity, specificity, negative-predictive value (NPV), and positive-predictive value (PPV) were the performance measures.
Results: Histopathologic evaluation showed malignancy in 368 of 1288 lesions (28.6%). AUC of the examiner in the clinical setting (AUC=0.94; 95% CI 0.92-0.95) was significantly better as for all three experts evaluating images only: expert one AUC=0.78 (95% CI 0.75-0.81); expert two AUC=0.81 (95% CI 0.78-0.84); expert three AUC=0.83 (95% CI 0.80-0.86). Sensitivity, specificity, NPV, and PPV of the examiner in the clinical setting were better as for all three experts evaluating images only. NPV of the examiner in the clinical setting was 98.6% (425 of 431), for expert one 87.8% (381 of 434), for expert two 91.2% (198 of 217), and for expert 3 84.1% (413 of 491).
Conclusion: Our findings suggest that information about individual patient characteristics (e.g. age, disease and family history) has great influence to accurately evaluate the risk of breast cancer. Future research may look into incorporating not only a standardized description of images into the BI-RADS classification system but also a standardized description of these individual patient characteristics to further standardize and objectify the risk evaluation in breast cancer diagnostics. Trial registration: NCT02638935

Performance of the examiner in the clinical setting and the three experts evaluating images only

| | Examiner clinical setting | Images only - Expert 1 | Images only - Expert 2 | Images only - Expert 3 |
|---|---|---|---|---|
| AUC (95% CI) | 0.94 (0.92-0.95) | 0.78 (0.75-0.81) | 0.81 (0.78-0.84) | 0.83 (0.80-0.86) |
| Sensitivity -% (no.) | 98.4% (362 of 368) | 85.6% (315 of 368) | 94.8% (349 of 368) | 78.8% (290 of 368) |
| Specificity -% (no.) | 46.2% (425 of 920) | 41.4% (381 of 920) | 21.5% (198 of 920) | 44.9% (413 of 920) |
| Negative Predictive Value -% (no.) | 98.6% (425 of 431) | 87.8% (381 of 434) | 91.2% (198 of 217) | 84.1% (413 of 491) |
| Positive Predictive Value -% (no.) | 42.2% (362 of 857) | 36.9% (315 of 854) | 32.6% (349 of 1071) | 36.4% (290 of 797) |

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**Publication Number:** PS7-18

The impact of insurance status on survival in patients with inflammatory breast cancer (IBC) and non-IBC among a unique population in Hawaii

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**Background:** Breast cancer is one of the most common types of cancer in United States women, with inflammatory breast cancer (IBC) being among the most aggressive, accounting for only 1-4% of all breast cancer cases yet causing 8-10% of breast cancer related deaths. It is reported that survival outcomes differ significantly between races and that specific races such as African-American tend to have aggressive and advanced disease. Previously, we reported that the proportion of IBC to non-IBC is significantly high in Native Hawaiian (NH) and Pacific Islander (PI) populations. The same study showed that NH and PI have shorter overall survival (OS) than Caucasians in patients with non-IBC but not in those with IBC. However, it is still not well known if poor prognosis in specifc races is due to aggressive disease biology, advanced stage at diagnosis, or socioeconomic status such as insurance status. Our primary objective was to determine the factors that predict OS after adjusting for baseline patient and disease characteristics. One of the novelties in our study is that we analyzed IBC and non-IBC, separately in our unique population in Hawaii. **Methods:** Patients with newly-diagnosed primary invasive breast cancer were identified from January 1, 2000 through December 31, 2018 using The Queen's Medical Center Tumor Registry in Honolulu, Hawaii. Patients whose baseline and disease characterics were not available were excluded from the final analysis. Clinical T4d was used to differentiate IBC and non-IBC. OS was defined as the time from diagnosis to death or last follow-up. Patients who were alive at the date of last follow-up were censored. All the variables were summarized using standard descriptive statics. Univariate and multivariate cox proportional hazards models were used to assess the effects of variables of interest on OS. P-values <0.05 were considered statistically significant. **Results:** A total of 1,442 patients were included in the final analysis. There were 44 patients with IBC. The proportions of IBC to non-IBC were significantly high in NH and PI (P=0.005, respectively), which is consistent with our previous report. In multivariate cox regression proportional hazards model adjusted for all variables that were significant in the univariate analysis, NH or PI were not significant predictive factors of OS in both IBC and non-IBC (IBC: Native Hawaiian HR 1.23, [95%CI, 0.2-7.4], P=0.82, Pacific Islander HR 1.51, [95%CI, 0.12-18.5], P=0.75; non-IBC: Native Hawaiian HR 0.75, [95%CI, 0.34-1.64], P=0.47, Pacific Islander HR 1.35, [95%CI, 0.55-3.33], P=0.52). Medicaid and no insurance were significantly associated with short OS in both IBC and non-IBC (IBC: Medicaid: HR 6.39, [95%CI, 1.21-33.9], P=0.03, No Insurance: HR 14.7, [95%CI, 1.7-127], P=0.02; non-IBC: Medicaid: HR 2.45, [95%CI, 1.12-5.34], P=0.02, No Insurance: HR 17.3, [95%CI, 3.31-89.8], P=0.001). Pacific Islanders were more often under or uninsured (P<0.001). In addition, triple-negative breast cancer subtype and advanced stage were significantly associated with short OS in both IBC and non-IBC. **Conclusions:** This is the first study to investigate the association between patient, disease characteristics and socioeconomic status in a unique population focusing on Native Hawaiians and Pacific Islanders with IBC and non-IBC, separately. Insurance status was a significant prognostic factor after adjusting for patient and disease characteristics but race was not. Our result suggests that improving social determinants such as insurance support might improve the outcomes of patients with breast cancer including IBC, regardless of race.

**2020 San Antonio Breast Cancer Symposium®**

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# Phase Ib trial of olinvacimab and pembrolizumab in patients with metastatic triple-negative breast cancer

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**Background:** Metastatic TNBC (mTNBC) has a poor prognosis. Preclinical data suggests benefit for combination therapy of immune checkpoint inhibitor and anti-angiogenesis. Olinvacimab (O) is a fully humanised monoclonal antibody (MAB) which binds to Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) and antiangiogenic and antitumor effects have been demonstrated. Pembrolizumab (P) is an anti-PD1 MAB. This study aimed to identify the safety and tolerability of O and P to establish a phase 2 recommended dose of O. **Methods:** From December 2018 to September 2020, we conducted a two-site, single arm, open-label study of O and P in pts with mTNBC. Eligible patients (pts) were >18 years, had ER, PR & HER2-negative MBC with at least one measurable lesion and adequate organ function. Pts with history of serious thromboembolism, gastrointestinal haemorrhage and prior anti-VEGF therapy were excluded. A modified Toxicity Probability Interval design was used. Pts received O 12 mg/kg q7d (dose level 1) or 16mg/kg day q7d (dose level 2) in combination with P 200mg flat dose day 1 q21d. Treatment continued until dose limiting toxicity (DLT), disease progression (PD) or treatment intolerance. **Results:** 11 pts, median age 62 (range 39-67) were recruited and received at least one dose of treatment. 8 (73%) had ECOG PS 1 and 3 (27%) had ECOG PS 2. 5 pts had previous chemotherapy for mTNBC (with 3 pts also having received immunotherapy), 6 pts were treated in the first-line metastatic setting (with all pts having received anthracycline and taxane in the adjuvant setting). 5 pts received O at 12mg/kg with P, completing a median of 6 cycles (range 1-18). As no DLTs were seen, 6 pts were treated with O at 16mg/kg with median of 8 cycles (range 2-21), with no DLTs being observed. Treatment was ceased due to PD in 6 pts, 3 pts are receiving treatment at data cut-off. Haemangiomas were seen in 8 pts accounting for 47 events of CTCAE grade 1 and 21 events of grade 2. Treatment emergent adverse events (TEAEs) of ≥grade 3 was seen in 6 pts (27 events), with 8 events being related to treatment. 4 pts (36%) had partial response (PR) as best overall response 5 pts (45%) had clinical benefit (PR+SD≥24weeks). **Conclusions:** Combination therapy of O and P was well tolerated with evidence of efficacy in mTNBC pts who had all previously received anthracycline and taxanes, with 3 pts having previously received immunotherapy. These results support the combination entering into a phase 2 study.

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# Efficacy of everolimus and exemestane for the treatment of metastatic hormone receptor-positive breast cancer in patients previously treated with CDK4/6 inhibitors

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**Background:** Everolimus in combination with exemestane (EVE+EXE) was initially FDA approved to treat metastatic hormone receptor-positive breast cancer (mHRBC) in patients previously treated with nonsteroidal aromatase inhibitors based on the BOLERO-2 trial. However, none of the patients in the BOLERO-2 trial received prior CDK4/6 inhibitors, which have become standard of care for mHRBC. There is limited data to support the use and clinical benefit of EVE+EXE in mHRBC patients previously treated with CDK4/6 inhibitors. **Methods:** We reviewed patients ≥18 years old with mHRBC treated with EVE+EXE at our institution from January 1, 2012, to April 1, 2020. Patients were excluded if they received EVE+EXE ≤30 days. Data collected included patient and tumor characteristics, prior therapies in the metastatic setting, adverse drug events, and clinical outcomes. The primary objective was to compare progression free survival (PFS) for EVE+EXE between patients with and without prior exposure to CDK4/6 inhibitors. Secondary outcomes included overall survival (OS) and safety. Group comparisons were performed by two-sample t test or Wilcoxon rank sum test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Log-rank test was used to compare the PFS and OS between groups. **Results:** One-hundred ninety two patients were included in the study; 79 patients had received prior CDK4/6 inhibitor based therapies, while 113 patients did not. Baseline patient characteristics such as histology, menopause status, de novo metastatic disease, presence of lung or liver metastases, and bone only disease were similar between groups. There was a median of 2 lines of treatment in the metastatic setting prior to receiving EVE+EXE in both groups. Fewer patients received prior chemotherapy in the metastatic setting in those who received prior CDK4/6 inhibitors (32.9% vs 49.6%, p=0.032). In patients who received a prior CDK4/6 inhibitor, median PFS was 3.9 months (95% CI: 3.5 to 4.8) compared to 5.5 months (95% CI: 4.0 to 6.3) in those who did not receive a prior CDK4/6 inhibitor (HR for progression, 1.46; 95% CI: 1.08 to 1.97, p=0.013). Overall survival between groups was not significantly different. A total of 32 (16.7%) patients discontinued EVE+EXE due to intolerance or adverse drug events. **Conclusion:** Patients who received a prior CDK4/6 inhibitor had a lower median PFS benefit from EVE+EXE compared to those who did not.

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# The accuracy of axillary node assessment of ultrasound after neoadjuvant chemotherapy in clinically node positive patients

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**Background.** Neo-adjuvant chemotherapy (NAC) is widely used as preoperative systemic therapy for operable breast cancer. However, the use of sentinel-lymph-node biopsy (SNB) following NAC for patients with clinically node positive is controversial, even if they achieve cCR in the axilla. Although preoperative axillary imaging assessment may help to decide axillary management after NAC, few data are available on whether axillary ultrasound (LN-US) is useful to assess axillary response to NAC. **Purpose.** We investigated the accuracy of axillary node assessment by ultrasound after NAC in clinically node positive patients and analyzed factors related to the accuracy of LN-US. **Methods.** From January 2012 through December 2016, patients with cT1-4, N1-2, M0 primary breast cancer who had cytologically proven axillary metastasis, and underwent axillary lymph node dissection (ALND) after NAC were retrospectively reviewed. Clinically positive lymph node by LN-US was defined as concentric cortical thickness >3mm, absent fatty hilum, or irregular morphology. **Results.** A total of 298 patients with clinical stage T1-4, N1-2, M0 primary breast cancer who had cytologically proven axillary metastasis, and underwent surgery with axillary dissection following NAC were enrolled. Of 279 eligible patients, 101 patients (36.2%) showed pathologically node-negative in the axilla (ypN0), and the rate of ypN0 was 20.2% (37/183) in hormone receptor (HR)+/human epidermal growth factor receptor-2 (HER2)-, 71.9% (23/32) in HR+/HER2+, 83.3% (20/24) in HR-/HER2+, and 52.5% (21/40) in HR-/HER2-. Sensitivity and specificity of LN-US were 65.7% and 62.3% respectively. The accurate prediction rate of node-negative status after NAC by LN-US was 49.2% in total, 29.7% in HR+/HER2-, 89.5% in HR+/HER2+, 86.7% in HR-/HER2+, and 68.8% in HR-/HER2- disease. The accuracy was highest in the HER2+, and lowest in HR+/HER2-. The median number of pathologically positive residual nodes at ALND after NAC was 2 (1-16) in total and 2 (1-15) in patients with ycN0. Of 61 patients with ycN0ypN+, 26 (42.6%) had 1 positive lymph node on the pathologic review, 9 (14.8%) had 2 positive lymph nodes, 7 (11.5%) had 3 positive lymph nodes, and 19 (31.1%) had more than 3 positive lymph nodes.The accuracy of node negative status by LN-US varies significantly by tumor subtype ($p<0.001$) and tumor response as assessed by MRI after completion of NAC ($p=0.0003$), although there was no significant difference between two groups regarding T category at diagnosis, tumor histology, and the number of positive nodes before NAC as assessed by LN-US. Of 23 patients who achieved ycN0 in LN-US and cCR in the primary lesion in MRI, the accurate prediction rate of ypN0 was 100% in patients with HR±/HER2+ and HR-/HER2- disease. **Conclusion.** The accuracy of axillary US after NAC depended on subtypes, which was highest in the HER2 disease and the accuracy increased by combing with the tumor response in the breast assessed by MRI. In the point of reducing FNR after NAC by LN-US assessment before surgery, the accuracy of NPV is especially important. We suggest that it is of clinical importance to take account of tumor subtypes and primary tumor response in the breast by MRI in combination with LN-US in selecting patients for SNB after NAC.

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Are we missing something? Ki-67 evaluation is important in African American women with an oncotype DX score< 26: A multi-institutional study

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**INTRODUCTION:** The literature suggests that there is no difference in the Oncotype DX® (ODX) recurrence score between African American (AA) women and Caucasian (CA) women; however, an analysis of clinical outcomes in participants enrolled in the TAILORx trial found that AA women had worse clinical outcomes than CA women, despite similar ODX recurrence scores. The TAILORx trial suggested that chemoendocrine therapy may not be necessary in women with hormone-positive, HER2-negative, node-negative invasive breast carcinomas with an ODX recurrence score < 26. We examine Ki-67 (a marker of tumor proliferation) in relation to an ODX recurrence score of 26 in AA and CA women from two seperate institutions. **METHODS:** A total of 851 consecutive cases of AA (n = 78) and CA women (n = 773) with ER+ invasive breast cancer and available ODX recurrence scores from the University of Rochester and the University of Louisville were included in this study. For all results, a p-value of < 0.05 was considered significant. **RESULTS:** Consistent with the previous literatuere, there was no significant difference between the average ODX recurrence score of AA and CA women (p = 0.44, Table 1), and we found no significant difference in average ER, PR, Nottingham score, or tumor size between AA and CA patients; however, the Ki-67 was significantly higher in AA patients with an ODX recurrence score < 26 compared to CA patients with and ODX recurrence score < 26 (p = 0.002, Table 2). This significant difference in Ki-67 was not evident with an ODX recurrence score ≥ 26 (p = 0.98, Table 2). **CONCLUSIONS:** Our preliminary results suggest that compared to CA women, AA patients are more likely to have a higher Ki-67 if the ODX recurrence score is < 26. AA breast cancer patients with an ODX < 26 are at increased risk for recurrence compared to CA women with an ODX < 26. Ki-67 evaluation is not routinely done as part of the breast cancer workup in many institutions. Ki-67 evaluation may be helpful to help guide treatments decisions in AA patients with and ODX < 26. Additional investigation is warranted.

**Table 1: Oncotype DX and histopathologic variables for African American and Caucasian women**

| | ODXRS* (mean) | ER** (mean) | PR** (mean) | NS***(mean) | Ki-67 (mean)**** | Tumor size (mean) | ODXRS < 26 (n) | ODXRS ≥ 26 (n) |
|---|---|---|---|---|---|---|---|---|
| ALL | 17.6 | 255.3 | 168.9 | 6.0 | 16.4 | 2.2 | 713 | 138 |
| AA | 18.3 | 250.7 | 175.9 | 6.3 | 21.4 | 2.2 | 63 | 15 |
| CA | 17.5 | 255.8 | 168.2 | 6.0 | 15.9 | 2.2 | 650 | 123 |

***Oncotype DX recurrence score** modified H-score*** Nottingham score****n = KI-67 available for 777 total patients (650 with ODXRS < 26 and 127 with ODXRS ≥ 26); KI-67 available for 71 AA patients (51 with ODXRS < 26 and 14 with ODXRS ≥ 26); KI-67 available for 706 CA patients (593 with ODXRS < 26 and 113 with ODXRS ≥ 26)**

**Table 2: Oncotype DX < 26 and ≥ 26 and associated histopathologic variables for African American and Caucasian women**

| | ODXRS* (mean) | ER** (mean) | PR** (mean) | NS*** (mean) | Ki-67 (mean)**** | Tumor size (mean) |
|---|---|---|---|---|---|---|
| ODXRS < 26 | 14.5 | 260.5 | 189.1 | 5.8 | 13.7 | 2.2 |
| AA | 15.4 | 262.8 | 200.7 | 6.0 | 19.2 | 2.3 |
| CA | 14.4 | 260.3 | 188.0 | 5.8 | 13.1 | 2.2 |
| ODX ≥ 26 | 33.8 | 228.4 | 64.4 | 7.3 | 30.5 | 2.1 |
| AA | 30.3 | 199.8 | 71.9 | 7.7 | 30.4 | 1.6 |
| CA | 34.2 | 231.9 | 63.5 | 7.3 | 30.5 | 2.2 |

***Oncotype DX recurrence score** modified H-score*** Nottingham score****n = KI-67 available for 777 total patients (650 with ODXRS < 26 and 127 with ODXRS ≥ 26); KI-67 available for 71 AA patients (51 with ODXRS < 26 and 14 with ODXRS ≥ 26); KI-67 available for 706 CA patients (593 with ODXRS < 26 and 113 with ODXRS ≥ 26)**

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# Ceralasertib (cer) in combination with olaparib (ola) in patients (pts) with advanced breast cancer (BC): Results of phase I expansion cohorts

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**Background:** Alterations in *BRCA1/2* are associated with ~9% of all BCs. Ola (a poly ADP-ribose polymerase inhibitor [PARPi]) is approved for treating pts with HER2-negative metastatic BC with germline *BRCA* mutation (g*BRCA*m), demonstrating an improvement in progression-free survival (PFS). Ceralasertib (an ataxia telangiectasia and Rad3-related protein ATR inhibitor) targets DNA damage repair and cell cycle regulation. Preclinical studies show synergistic antitumor effects of ola+cer vs ola monotherapy supporting the clinical evaluation of this combination.
**Methods:** Study 4 is a modular multicenter Phase I study of cer combinations (NCT02264678). Module 2 established the Recommended Phase 2 Dose of ola+cer as ola 300 mg bid daily + cer 160 mg qd D1-7 q 28d. We report the results of two expansion cohorts testing ola+cer in pts with triple negative breast cancer with no alterations in homologous recombination repair (HRR)-related genes (HRR wt group), and pts with advanced HER2-*BRCA*m BC (*BRCA*m group), with a data cut-off of 19th June 2019. Eligible pts had to have received 1-2 prior lines of chemotherapy for metastatic disease, and were PARPi naive. Patients may have enrolled directly based on a local *BRCA*m test result, but all pts submitted a tumor specimen for central confirmation of a deleterious (or suspected deleterious) germline or somatic *BRCA1/2* mutation. The primary objective was to investigate the safety and tolerability of the combination; secondary objectives included assessment of objective response rate by RECIST 1.1.
**Results:** Twenty-five pts were enrolled in the HRR wt group: median age 53 (31-75), ECOG PS 0/1 13 (52%)/12 (48%), median number of prior chemotherapy lines 2 of which 8 pts (32%) had received prior platinum. Thirty-seven pts enrolled in the *BRCA*m group: median age 51 (24-69), ECOG PS 0/1 20 (54%)/17 (46%), median number of prior chemotherapy lines 1 of which 19 pts (51%) had received prior platinum. The most frequent all causality Adverse Events (AEs) were nausea 43 (69%), anemia 36 (58%), diarrhea 20 (32%) and vomiting 20 (32%); CTCAE ≥ Grade 3 AEs included anemia 15 (24%), neutropenia 6 (10%) with few patients discontinuing treatment. In the HRR wt group, no responses were observed, 12 (48%) pts achieved a best response of stable disease and 13 (52%) had disease progression. The median PFS was 3.1 months (80%CI 2.0,3.9). In the *BRCA*m group, 13 (35%) pts achieved a confirmed response (including 1 complete response), 17 (46%) stable disease and 7 (19%) pts disease progression. The median PFS in pts with a centrally confirmed *BRCA*m was 11.5 months (80%CI 5.8-14.8, n=30), 7.7 months (80%CI 5.8-11.4, n=37) in all pts enrolled in the *BRCA*m group. Eleven of the 13 responders in the *BRCA*m group were on study treatment for a longer duration than their treatment immediately prior to enrollment. As of 18th June 20, preliminary data shows 10 pts are still ongoing with a treatment duration ranging 20 to 35 months.
**Conclusion:** In pts with HER2- *BRCA*m breast cancer, clinical efficacy was observed with durable radiological response despite adverse prognostic features in this Phase I population. The observations in this study are currently being tested in a global multicenter open-label randomised Phase 2 study: VIOLETTE (NCT03330847).

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Prognostic value of textural associated with metabolic parameters of baseline $^{18}$FDG-PET/CT in early triple-negative breast cancer (TNBC)

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**Background** : Triple negative breast cancer (TNBC) represents 10-17 % of all diagnosed early breast cancers, occurs more frequently in young women (< 50 years old) and has a poor prognosis. TNBC remains a clinical and therapeutic challenge dealing with a paradox: a high-risk of metastatic relapse despite a high rate of clinical and histological response after neoadjuvant chemotherapy with contrasting but disappointing results of targeted therapies. However, TNBCs are treated as a single entity and due to their phenotypic heterogeneity and various molecular pathogenesis, this subtype has a very different profile in terms of prognosis and response to treatment. Positron emission tomography/computed tomography (PET/CT) with $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) is gaining importance for the staging of patients with large or locally advanced breast cancer. TNBCs often show high 18FDG uptake and several studies demonstrate correlations between standard uptake value (SUV) and histoprognostic factors such as grade or KI67%. Recently, a new approach is growing interest in medical imaging: textural analysis. Some studies have shown correlations between metabolic parameters with overall survival (OS) and disease free survival (DFS) in other carcinoma, such as lung and head-and-neck cancers. Few studies analyzed textural features with potentially promising prognostic value that has to be confirmed. The objective of this study is to evaluate the association between metabolic and textural parameters measured at the initial $^{18}$FDG-PET/CT, disease-free survival (DFS) and overall survival (OS) in patients with non-metastatic TBNC. **Patients and Methods**: All consecutive non-metastatic TNBC women who underwent $^{18}$FDG-PET/CT at diagnosis between 2012 and 2018 were retrospectively included. Metabolic parameters (SUVmax, SUVmean, SUVpeak, MTV, TLG) in the primary tumor and lymph nodes and textural features (entropy, homogeneity, SRE, LRE, LGZE, HGZE) in the primary tumor were collected. Regression models were used to assess the correlations between PET parameters and histoprognostic factors. Cox regression models were computed to identify association with DFS and OS. **Results** : One hundred and eleven patients were enrolled. The median follow-up was 53.6 months. Thirty-six patients experienced relapse and 20 died. Homogeneity was associated with no axillary lymph node involvement and lower grade. Entropy was associated with higher grade, lymph node involvement and inflammatory tumors. SRE was only associated with higher grade. TLG and MTV were highly correlated (r =0.98, 95%CI = 0.97-0.99). TLG, MTV and Entropy of the primary tumor were associated with lower DFS (p = 0.008, p = 0.006, and p = 0.025, respectively) and lower OS (p = 0.002, p = 0.001 and p = 0.046, respectively). In the 50 patients with positive PET axillary lymph nodes, all metabolic parameters except SUVmean were correlated with DFS whereas no correlation was seen with OS. **Conclusion:** Textural associated with metabolic features of baseline $^{18}$FDG-PET/CT add prognosis value interesting to identify high risk group of relapse in early TNBC patients.

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# Comparing MammaPrint and BluePrint results between core needle biopsy and surgical resection breast cancer specimens

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**Background**: Pre-operative/neoadjuvant treatment utilization in early-stage breast cancer has been increasing, particularly during the COVID-19 pandemic. With goals of minimizing potential exposure to SARS-COV-2, as well as resource rationing, physicians are urged to triage breast cancer patients by identifying those that require urgent surgical care vs. those who may delay surgical treatment.[1] Accurate risk assessment is an integral component of this triaging process, which has recommended that genomic testing on diagnostic core needle biopsy (CNB) samples be used to assist with the identification of patients with low risk tumor biology who may be candidates for surgical delay.[1] MammaPrint (MP), a 70-gene risk of recurrence signature, and BluePrint (BP), an 80-gene molecular subtyping signature, have been routinely used in formalin-fixed paraffin embedded (FFPE) CNB and surgical resection (SR) samples since MammaPrint obtained FDA clearance for FFPE tissue in 2015[2]. In addition, over 1,500 CNB tumor samples from patients enrolled in prospective neoadjuvant treatment trials (NBRST and ISPY-2) have received successful MP & BP testing. This study compares the gene expression results between CNB and SR specimens to better elucidate how these tests perform across specimen type. **Methods:** Routine diagnostic samples submitted to Agendia, Inc. (Irvine, CA) between Feb 2017 and May 2020 for MP and BP testing were processed according to standard FFPE microarray procedures. MP was used to stratify samples into Ultra Low Risk (UL), Low Risk (LR), and High Risk (HR). BP was used to classify samples into Luminal, HER2, or Basal-type. This study included 13,603 CNB and 25,684 SR specimens. MP Index (MPI) distribution on BP defined Luminal-type tumors were compared between CNB and SR samples. Comparative “logistics metrics” (average turnaround time [TAT] and success rate) were also assessed between these specimen types. **Results:** Of the 39,287 samples included in this analysis, 35% were CNB and 65% were SR (Table). BluePrint Luminal, HER2 and Basal-type distributions were 86%, 4%, and 10% respectively for CNB samples and 94%, 1%, and 5% respectively for SR samples. Within BP defined Luminal-type tumors, the frequency of UL, LR, and HR results were 18%, 58%, and 42% for CNB, and 16%, 60%, and 40% for SR, respectively. Overall, MP Index distributions were similar between samples tested from CNB vs. SR. Average TAT between CNB and SR were 4.52 and 4.55 days, respectively. For specimens that met the minimum tumor % threshold, successful testing rates for CNB and SR were 97.5% and 98.4%, respectively. **Conclusions**: MP and BP testing were successfully performed on both CNB and SR samples in approximately 98% of all eligible specimens with rapid TAT allowing for timely pre-operative decision-making. The frequency of each MP risk group as well as the distribution pattern of MP Index were nearly identical between CNB and SR specimens, indicating comparable performance regardless of specimen type. With no meaningful difference in MPI distribution, TAT or success rate between CNB specimens and SR specimens, pre-operative use of MP+BP genomic testing is feasible, in alignment with recent COVID-19 pandemic guidelines.

**Table:**

| | (n) | (%) | | (n) | (%) |
|---|---|---|---|---|---|
| **Total CNB** | **13,603** | **35%** | **Total SR** | **25,684** | **65%** |
| CNB Ultralow | 2,175 | 16% | SR Ultralow | 3,898 | 15% |
| CNB Low Risk | 6,900 | 51% | SR Low Risk | 14,656 | 57% |
| CNB High Risk | 6,703 | 49% | SR High Risk | 11,028 | 43% |
| | (n) | (%) | | (n) | (%) |
| **Luminal-type CNB** | **10,057** | **38%** | **Luminal-type SR** | **16,311** | **62%** |
| CNB Ultralow | 1,824 | 18% | SR Ultralow | 2,588 | 16% |
| CNB Low Risk | 5,785 | 58% | SR Low Risk | 9,771 | 60% |
| CNB High Risk | 4,272 | 42% | SR High Risk | 6,540 | 40% |

**References**1.Dietz, J.R., et al. Breast Cancer Res Treat 181, 487-497 (2020).2.FDA 510(k) Clearance K141142, January 2015.

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# Characteristics of breast cancer brain metastases presentation by subtype and validation of the modified breast graded prognostic assessment

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**Purpose:** Breast cancer brain metastases (BCBM) diagnosis is increasing in frequency due to improved systemic control and imaging techniques. Differences have been noted in rates of central nervous system (CNS) relapse and biologic subtype. The modified breast graded prognostic assessment (breast-GPA) was initially validated in patients treated between 1996-2013 and considers biologic subtype. In this study, we characterize patients diagnosed with BCBM by subtype and validate the breast-GPA in a modern cohort of patients.
**Methods:** All patients with BCBM treated at our institution with radiotherapy between 2016 and 2019 were identified. Characteristics of patients' initial brain metastasis diagnosis were retrieved from the clinical chart and radiologic examinations. To test differences between cohorts, the Kruskal-Wallis and Pearson's chi-square tests were used when appropriate. Overall survival (OS) was calculated from the date of brain metastasis diagnosis to the date of death using the Kaplan-Meier (KM) method, with the log-rank test used to examine differences between groups.
**Results:** A total of 122 BCBM patients were identified. Breast cancer subtypes included hormone receptor (HR)+/HER2- (45%), triple negative (TN) (25%), HR-/HER2+ (16%), and HR+/HER2+ (14%). The first treatment for BCBM patients following diagnosis was whole brain radiation (51%), surgery followed by stereotactic radiation (28%), and stereotactic radiation (21%). The interval between breast cancer diagnosis and diagnosis of BCBM was longest for HR+/HER2- 4.5 years, followed by TN 2.8 years, HR+/HER2+ 2.3 years, HR-/HER2+ 1.9 years, p=0.003. The interval from systemic metastases to BCBM diagnosis trended towards the shortest for TN patients 6.6 months, p=0.15. A total of 34 patients (28%) were diagnosed with leptomeningeal disease (LMD) at initial brain metastases presentation. LMD was diagnosed most commonly at presentation in HR+/HER2- (36%) followed by , TN (26%), HR-/HER2+ (26%), and HR+/HER2+ (6%), p=0.06. No differences were noted based on receptor typessubtype and age, symptomatic intracranial disease, number of brain metastases, type of first intracranial treatment or concurrent systemic metastases at initial BCBM presentation, all p > 0.05. Twenty-four month KM OS rates following diagnosis of brain metastasis for breast-GPA 0-1, 1.5-2, 2.5-3, and 3.5-4 groups were 14%, 27%, 33%, and 86% (p=0.0005), respectively.
**Conclusions:** In our institutional analysis, similarities were noted in the initial presentation of BCBM based on receptor typesubtype. Significant differences were noted in OS based on the modified breast-GPA. Further investigation is needed to determine which subtypes of asymptomatic breast cancer patients are at sufficient risk to warrant brain MRI screening.

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# Metformin improves the survival in Chinese early invasive breast cancer patients with type 2 diabetes mellitus

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**Objective:** The purpose of this retrospective study was to investigate the effect of metformin on the survival of Chinese breast cancer patients with type 2 diabetes mellitus (T2DM) after surgery.**Methods:** A total of 3,553 primary breast cancer patients who underwent surgery from January 2010 to December 2013 was enrolled in this study. The patients were divided as metformin group (312 cases), insulin group (79 cases) and non-diabetes group (3139 cases) according medication treatment. The median follow-up time was 85 months. Overall survival (OS) and disease-free survival (DFS) after tumor removal were estimated with the Kaplan-Meier method followed by a log-rank test for evaluating three groups differences. Multivariate Cox proportional hazards regression model was applied to estimate the relationship between metformin and prognosis of breast cancer patients with T2DM.**Results:** Clinical and pathological features of three group patients were matched. There was a significant survival difference among metformin group, insulin group and non-diabetes group, 5-year OS was 97.1%, 73.3%, 87.3%, and 5-year DFS was 96.1%, 73.0%, 85.8% respectively (P <0.05). Through the Kaplan-Meier curve and Cox multivariate analysis, metformin was significantly associated with better OS [hazard ratio (HR) 0.386, 95% confidence interval (CI) 0.248-0.601; P =0.000] and DFS (HR 0.384, 95% CI 0.247-0.598; P = 0.000).**Conclusion:** Metformin might have a good impact on the survival of breast cancer patients with T2DM. However, due to the limitations of the retrospective design in this study, prospective studies are needed to confirm our results.

Multivariable analyses of OS and DFS in all breast cancer patients

| | OS | | DFS | |
|---|---|---|---|---|
| | HR(95.0%CI) | *P* | HR(95.0%CI) | *P* |
| Age at diagnosis | | 0.003 | | 0.013 |
| ≤55 years | 1 | | 1 | |
| >55 years | 1.302(1.094-1.549) | | 1.247(1.048-1.484) | |
| BMI | | 0.000 | | 0.000 |
| <25 | 1 | | 1 | |
| 25-30 | 1.280(1.070-1.532) | | 1.300(1.087-1.556) | |
| ≥30 | 1.696(1.300-2.213) | | 1.753(1.344-2.286) | |
| Tumour size | | 0.000 | | 0.000 |
| ≤2cm | 1 | | 1 | |
| >2cm,≤5cm | 1.261(1.053-1.511) | | 1.259(1.051-1.507) | |
| >5cm | 2.281(1.602-3.247) | | 2.234(1.569-3.182) | |
| Uncertain | 1.248(0.897-1.736) | | 1.241(0.892-1.726) | |
| Lymph node metastasis | | 0.000 | | 0.000 |
| 0 | 1 | | 1 | |
| 1-3 | 2.684(2.158-3.338) | | 2.716(2.184-3.376) | |
| 4-9 | 3.960(3.072-5.105) | | 4.096(3.178-5.280) | |
| ≥10 | 9.264(7.339-11.695) | | 9.837(7.782-12.433) | |
| ER status | | 0.012 | | 0.016 |
| Negative | 1 | | 1 | |
| Positive | 0.738(0.563-0.967) | | 0.738(0.563-0.967) | |
| Unknown | - | | - | |
| PR status | | 0.025 | | 0.017 |
| Negative | 1 | | 1 | |
| Positive | 0.745(0.580-0.958) | | 0.730(0.569-0.938) | |
| Unknown | - | | - | |
| Ki-67 | | 0.009 | | 0.007 |
| Low | 1 | | 1 | |
| High | 1.255(1.017-1.547) | | 1.285(1.042-1.584) | |
| Uncertain | - | | - | |
| Groups | | 0.000 | | 0.000 |
| Non-diabetes | 1 | | 1 | |
| Metformin | 0.386 (0.248-0.601) | | 0.384(0.247-0.598) | |
| Insulin | 1.307(0.848-2.014) | | 1.205(0.781-1.858) | |
| BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor. | | | | |

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# Preoperative selection of patients with early-stage invasive breast cancer for intraoperative radiation therapy (IORT): A single-institution experience

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**Purpose/Objective:** Intraoperative radiation therapy (IORT) is a form of accelerated partial breast irradiation (APBI) delivered at the time of lumpectomy for early-stage breast cancer. Upfront selection of patients based on favorable preoperative characteristics is important to achieve good outcomes. Here we present our single-institution experience in the management of invasive breast cancer with IORT. We focused on the classification of patient suitability for IORT by the American Society for Therapeutic Radiation Oncology (ASTRO) APBI consensus guidelines using preoperative and postoperative clinicopathologic factors, as well as treatment outcomes and recurrences.
**Materials/Methods:** We reviewed our institutional prospective registry database (AAAJ8512) to identify patients with biopsy-proven invasive breast cancer treated with breast IORT between 9/2013 and 4/2020 using the Zeiss Intrabeam™. Patients received a single dose of 20Gy delivered to the lumpectomy cavity surface at the time of planned surgery. We excluded patients from analysis with prior radiation to the breast, or triple negative disease at initial diagnosis. We reviewed preoperative and postoperative clinicopathologic factors to determine each patient's ASTRO APBI suitability (suitable, cautionary or unsuitable) based on the 2017 consensus guidelines.
Table 1

| | Reason | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ASTRO APBI Pre-Op Suitability | # | **Size** | **ER (-)** | **Age** | **T2** | **ILC** | | |
| Suitable | 191 | | | | | | | |
| Cautionary | 46 | 11 | 4 | 10 | 11 | 22 | | |
| Unsuitable | 0 | | | | | | | |
| ASTRO APBI Post-Op Suitability Change | # | **Size** | **Close Margins** | **Positive Margins** | **LVI** | **Multifocal** | **ILC** | **EIC** |
| Suitable to Cautionary | 77 | 9 | 20 | | 23 | 21 | 11 | 24 |
| Suitable to Unsuitable | 12 | 1 | | 11 | | | | |
| Cautionary to Unsuitable | 6 | 2 | | 4 | | | | |

*Abbreviations:* ER = Estrogen Receptor; ILC = Invasive Lobular Carcinoma; LVI = Lymphovascular Invasion; EIC = Extensive Intraductal Component
**Results:** 237 patients were treated with IORT for early stage breast cancer. Median age was 67 years (range 44-94 years). Median extent of disease by conventional imaging was 1.0 cm (range 0 - 3.0cm). 51/103 (49.5%) patients with heterogeneously or extremely dense breasts underwent a MRI preoperatively. Based on preoperative clinicopathologic characteristics, 191 (80.6%) patients were suitable according ASTRO APBI guidelines, 46 (19.4%) cautionary and no patients were unsuitable. APBI group suitability changed in 95 (40.1%) patients based on final pathology from the time of lumpectomy, summarized in Table 1. 17 (7.2%) patients underwent re-excision for close or positive margins. 39 (16.5%) patients received additional adjuvant whole breast radiotherapy including 10/18 (56%) of unsuitable patients. Of 212 (89.5%) patients who initiated hormone therapy (HT), 191 (80.6%) were compliant at last follow up. Median follow-up for all patients was 38.2 months (0.4 - 74.5). Five (2.1%) patients experienced ipsilateral breast tumor recurrence, 1 (0.4%) patient experienced new contralateral breast cancer, and 2 (1.6%) patients experienced distant recurrence with the median time to event of 27.8 months (range 6.3-50.4). Of the 5 patients with ipsilateral breast tumor recurrence, 2 (0.8%) were true local recurrences <2cm from the initial lumpectomy bed with the same histology as initial tumor, both cases were cautionary risk and one declined HT, 3 (1.3%) were new breast primaries occurring >2cm from lumpectomy bed with a different histology.
**Conclusion:** Breast IORT is an attractive cost-effective option for women with early stage breast cancer, and our 3-year true local recurrence rate is 0.8%. Optimal patient selection is key based on preoperative characteristics. Patients who become unsuitable or cautionary for APBI based on final pathology should be considered for additional adjuvant therapy.

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Title:peripheral blood immuneimpactsin arandomizedphase iiclinical trial ofprogrammed death 1 (pd-1) blockadecombined with platinum-based chemotherapy in patients with metastatic triple negative breast cancer (mtnbc)

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**Background:** PD-1 blockade has shown promising clinical activity in mTNBC. We designed an investigator-initiated multi-center clinical trial consisting of a Safety run-in, into a randomized phase II trial of combination pembrolizumab (P) with carboplatin (C) and gemcitabine (G) in patients with mTNBC. A detailed characterization of peripheral immune cell changes may help in understanding responses in mTNBC to immune checkpoint inhibition. Correlative studies for the purpose of understanding the effect of combining chemotherapy (CT) simultaneously with checkpoint inhibition on the peripheral immune response are planned as part of this clinical trial.
**Methods:** Patients with a diagnosis of mTNBC are recruited to this trial with a Safety Run-in (N = 6 subjects), followed by a randomized design of C + G with/without P (2:1 randomization, N = 75). Treatment consists of P 200 mg on day 1 of each 21-day cycle, and C (AUC2) + G (800mg/m$^2$) on days 1 and 8 for cohort A, and C (AUC2) + G (800mg/m$^2$) for cohort B. Patients are consented for a peripheral blood (PB) collection pre-treatment on day 1 of cycle 1, and post-treatment on day 1 of cycle 3, in order to phenotype immune changes by flow-cytometry.
**Results:** A total of 60 patients have been consented, 42 patients were enrolled (6 on safety run-in, 36 on the randomized part II). Of those on the randomized part II, blood samples from 17 patients have been analyzed from cycle 1 day 1 and cycle 3 day 3. A decreased expression of PD-1 on effector and memory subsets of both CD4$^+$ and CD8$^+$ T cells from C1D1 to C3D1 was observed in blood from both cohorts, especially cohort A. We found an increased % NK, CD4$^+$ T and CD8$^+$ T cell subsets expressing the activation marker, CD69, in cohort A, but not cohort B, reflecting activation by pembrolizumab. There was a parallel increased expression of the proliferative marker, Ki67, in CD56$^{bright}$ (immature) NK cells and effector memory CD8$^+$ T cells in blood from C1D1 to C3D1 in cohort A. We also found an increased % CD56$^{bright}$ (immature) NK and effector memory CD4$^+$ T cells expressing the exhaustion marker, CD39, which was consistent with increased expression of the activation marker, CD69.
**Conclusions:** Although comprising a limited number of patients in this early analysis, our correlative studies found evidence for effective immune stimulation upon combining CT with the PD-1 blockade. The randomized nature of this trial, with our planned pre and post treatment blood collection will be helpful in understanding response to immune check point inhibition combined with chemotherapy in mTNBC. Correlation with absolute lymphocyte counts and outcomes data is planned and will be presented.

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Whole exome sequencing and BRCAness estimation in TNBCs and their correlation with response to platinum

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**Background**: Triple-Negative Breast Cancer (TNBC) comprises approximately 30% of all breast cancers in Indian women. The hallmark of TNBC is genomic instability with very high rates of TP53 mutation. BRCAness has been defined by Ashworth et al (2004 &2014), as the phenocopying of BRCA1&2 mutation by alternate genetic or Epigenetic mechanisms. The consequence of this is DNA damage repair (DDR) deficiency. Though PARP inhibitors have been of utility in treating this subset of TNBC, trials have in general not found an unequivocal support for the use of platinum. We have developed an assay for BRCAness, the BRCA1 deficiency score (BDS) (Korlimarla et al 2016). In this study, we have applied BDS assay in tandem with whole exome sequencing to a small retrospective series of TNBC patients more than half of whom were treated with Platinum. **Methods:** 40 TNBC primary specimens along with complete clinical data from a retrospective series at the SSCHRC were obtained under all IERB approvals and informed patient consent for BDS assay and mutational analysis**.** BDS assay is a multianalyte assay involving measurement of BRCA1 (Transcript and protein) as well as additional epigenetic regulators of BRCA1, mir182 and ID4. Whole Exome Sequenced (WES) using the Agilent Sureselect V6 kit on Illumina HiSeq platform. Variant calling analysis was performed using GATK Mutect2 with Hg38 reference genome following the best practice workflow. Variants annotated as protein affecting based on their functional impact prediction and mapped to known cancer related genes (from COSMIC), were selected. **Results:** Clinical details: Mean age of patient in the series was 49. 37/40 qualified for BDS assay. 21/37 (57%) patients were treated with Carboplatin in combination with Docetaxel in an adjuvant setting. Remaining patients were treated with Cyclophosphamide Adriamycin with or without Docetaxel. 15/37 (45%) were BRCA1 deficient and10/15 were treated with Platinum and 8 (80%) were responders.

| **CHARACTERS** | **n** | **%** | **Platinum Treatment - ( n )** | **Treatment response** | | % |
|---|---|---|---|---|---|---|
| **BDS** | 37 | | 21 | | | |
| **Deficient** | 15 | 45 | 13 | BRCA1 deficient response | 8 | **61** |
| **Proficient** | 19 | 51 | 8 | BRCA1 Proficient response | 4 | **50** |
| **Undet** | 3 | 4 | | | | |

39 passed QC and considered for analysis**.** Spectrum of variants were missense mutations (86.5%), followed by stop gained (5.91%) and frame shift (3.76%). Results were compared to TCGA TNBC set (n=123). The most frequently mutated gene was *TP53 (62%)* as reported in TCGA. We also report higher frequency of deleterious mutations on DNA damage repair (DDR) genes like ATM and BRCA2 (15%). Response to Platinum therapy in this subset, correlated with Mutations in DNA damage repair genes ($p \leq 0.003$). 4/6 samples mutated were also In the BDS deficient group. BRCAness score for predicting Platinum response also correlated significantly ($p \leq 0.05$). Other genes which showed significant alterations were *KMT2A and KMT2D (15% and 13%)* which encode the histone methyl transferase and are responsible in altering the chromatin structure and *RECQL4* (10%) which is a helicase involved in DDR **Conclusion:** Both BRCAness and mutation profile identified a DDR deficient group within TNBC patients. In addition to TP53 which is the most frequently mutated gene, our small sample set has shown higher frequencies of mutations in DDR genes like *ATM* and *BRCA2.* This group of patients showed favourable response to platinum therapy. Since very little is known about the molecular heterogeneity of TNBCs in Indian patients, our analysis aids in identification of actionable mutations in TNBCs and may be of use in selection of patients for platinum therapy.

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# Exploratory biomarker analysis of Young-PEARL [palbociclib plus exemestane with GnRH agonist versus capecitabine in premenopausal women with HR (hormone receptor)-positive, HER2-negative metastatic breast cancer (MBC)] study

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Background: Young-PEARL study showed median progression-free survival (PFS) of 20·1 months in the palbociclib plus endocrine therapy group versus 14·4 months in the capecitabine group (hazard ratio 0·659 [95% CI 0·437-0·994], log-rank p=0·0235). We conducted exploratory biomarker analysis to predict the efficacy of the trial. Methods: This was a phase II trial that randomized 184 patients with HR+ MBC in premenopausal women to palbociclib plus exemestane with GNRH agonist (Arm A, n=79) versus capecitabine (Arm B, n=62). We performed targeted sequencing (CancerSCAN$^{TM}$) containing 375 cancer-related genes (141 patients) and whole transcriptome sequencing (165 patients) using baseline tumor samples to examine genomic alteration in relation to drug response in terms of PFS.
Result: By research-based PAM50 subtyping, 73% of patients classified as Luminal (Luminal A and Luminal B), and showed better prognosis in all patients and Arm A (p<0.05) in compared to no survival difference in Arm B (p=0.284). PFS difference between LumA and LumB was not statistically significant in Arm A (p=0.196). PIK3CA mutation (41%), TP53 mutation (33%), GATA3 mutation (25%), CCDN1 CNV (29%), BRCA2 mutation (14%) were the most frequently detected in this population. High TMB, TP53 mutation, ClinVar pathogenic somatic BRCA2 mutation (3.5%) showed worse prognosis in Arm A (p<0.05). Non-luminal patients with TP53 or BRCA2 mutations were poor prognosis in Arm A. Patients with BRCA2 pathogenic mutations showed worse prognosis regardless PAM50 subtypes, and luminal patients showed longer PFS compared to non-luminal patients among patients without BRCA2 pathogenic mutations in Arm A. RB1 loss, known as a resistant biomarker of CDK4/6 inhibitor was found in 4% of Arm A, and was associated with shorter PFS (log2 HR=2.26, 95% CI 0.51 to 4.01, p=0.011). AURKA mutation/amplification and RAD51C amplification were significantly associated to the patients with PFS less than 6 month. ESR1 mutations were found in 3.5% of patients, which was less than PEARL (29.4%) and PALOMA-3 (25.1%) trials. ESR1 mutations and ESR1/2 expression were not associated with shorter PFS. Notch 2/3/4 pathway expression was lower in patients with longer PFS (PFS more than 20month). ETIMATE ImmuneScore was higher in non-luminal compared to luminal patients, and didn't show survival difference in Arm A, but luminal patients with low ImmuneScore showed better prognosis. The relative proportion of 22 immune cell types was deconvoluted by CIBERSORT, and T cell CD4 memory resting, Macrophage M0 and M2 were abundant. NK cell activated was higher proportion in patients with longer PFS. Low TIL patients with low interferon and high T cell regulation expression showed worse prognosis. Germline BRCA mutation and integrated analyses of genomic and transcriptomic profiles will be reported.
Conclusions: The alteration of a few genes including Rb1 loss may be associated with resistance of palbociclib in HR-positive premenopausal population with MBC. Luminal type showed better prognosis, and BRCA2 pathogenic mutation showed worse prognosis regardless luminal/non-luminal type. ESR1 mutation was found in low population frequency because all patients didn't received AI therapy. Further exploration of molecular variables is warranted to determine and validate biomarkers of efficacy. Clinical trial information: NCT02592746.

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Evaluation of tumor-specific MHC-II expression as a biomarker

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Recently MHC-II protein expression levels in breast cancer tumor cells were shown to predict response to the PD-1 inhibitor pembrolizumab on a neoadjuvant clinical trial for ER+ and TNBC (ISPY-2). To better understand this biomarker and avoid post-market issues, we aimed to investigate possible pitfalls of MHC-II/HLA-DR quantification, prevalence of HLA-DR expression in breast cancer (BC) cells and its association with clinical data in a cohort of 372 BC patents. We assessed tumor and non-tumor HLA-DR expression by multiplex fluorescence immunohistochemistry on 8 TMAs containing 372 surgical BC samples, comprised of 239 ER+ and 123 TNBCs. Patient characteristics are shown in table 1. PanCK was used to define the tumor area and HLA-DR quantification was performed by training an object classifier on QuPath. Upon visual examination, 23 samples showed patchy panCK expression. We excluded normal breast epithelium and in situ components, which showed varying degrees of HLA-DR. 44.4% of breast cancers expressed HLA-DR, with 8.3% showing high tumor expression (HLA-DR$^{HI}$; ≥20% of tumor cells). TNBC showed higher prevalence of HLA-DR$^{HI}$ cases (35% HLADR+, 14.6% HLA-DR$^{HI}$, mean tumor HLA-DR expression (% of tumor cells) 10.3%, range 0-84%) than ER+ BC (51% HLADR+, 5.4% HLA-DR$^{HI}$, mean 7.4%, range 0-66.5%). In some cases, HLA-DR and panCK expression were mutually exclusive. In other cases the lack of panCK expression highlighted the presence of stromal cells within the tumor area that were not evident on H&E. Tumoral MHC-II expression correlated with the presence of TILs for ER+ BC (r=0.18, p=0.0158) and TNBC (r=0.20, p= 0.0450), specifically CD3 (r=0.49 p<0.0001) and CD4 (r=0.48 p<0.0001), and to a lesser extent CD8 (r=0.28, p= 0.013) in a subset of TNBCs on which these stains where performed (n=81). We found no correlation between tumoral MHC-II expression and clinical characteristics (ER and PR within ER+ BC, age, presence of lymph node metastasis, stage, neoadjuvant treatment) in ER+ or TNBC. High tumor HLA-DR expression correlated with poorer recurrence-free survival (RFS) in ER+ BC (p=0.038) but showed no correlation in TNBC. Cox proportional hazard model including clinical data determined that only stage was an independent predictor of survival in ER+. Non-tumoral HLA-DR expression was associated with better RFS (p=0.007) and overall survival (p=0.01) in TNBC; however, only stage was an independent predictor in multivariant analyses. Tumor MHC-II expression in BC has been reported to range from 22% to 48.5% in TNBC or unselected BC, and high tumoral MHC-II expression was reported to be 6.9% in unselected BC and 36.3% in TNBC. Specific rates of HLA-DR expression in ER+ breast cancer have not been extensively investigated. Here we report a similar overall prevalence, but lower number of tumors presenting high HLA-DR expression and an association with poorer survival in ER+ BC. HLA-DR IHC is a robust assay that can be easily used to identify MCH-II high expressing tumors and scoring percentage of tumoral cells should be more reproducible than PD-L1 scoring on immune cells when assessed by a trained pathologist.Table 1: Patient characteristics

| | TNBC | ER+ |
|---|---|---|
| Total number of cases | 239 | 123 |
| Median age | 48,5 | 63 |
| Treatment | | |
| treatment naïve | 26% | 45% |
| neoadjuvant chemotherapy | 74% | 4% |
| pre-surgical letrozole | - | 51% |
| Positive lymph node | 58% | 14% |
| Stage | | |
| I | 27% | 82% |
| II | 20% | 27% |
| III | 67% | 8% |
| IV | 0% | 1% |

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Gene expression profile in HER2-positive breast cancer to predict outcome in patients treated with adjuvant trastuzumab

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**Background** Trastuzumab is the cornerstone of adjuvant therapy for HER2-positive breast cancer (BC), but up to 20% of patients relapse. We performed a nested case-control study comparing the gene expression profile of relapsed cases within 5 years from the start of adjuvant trastuzumab and a group of controls not relapsed, in order to understand potential resistance mechanisms and to allow developing alternative strategies.**Methods**RNA was isolated from formalin-fixed paraffin-embedded primary tumors with AllPrep DNA/RNA FFPE Kit (Qiagen) and analyzed with nCounter Breast Cancer 360 Panel (Nanostring Technologies), according to manufacturer's instructions. The analysis of differential expression was performed by DESeq2 R package, on raw counts assuming a negative binomial distribution and using the Benjamini-Hochberg procedure to control the False Discovery Rate (FDR). Pathway enrichment analysis on Differentially Expressed Genes (DEGs) was performed by STRING database v. 11.0. Fisher's Exact test was used for categorical variables and Wilcoxon-Mann-Whitney test for the continuous ones to analyze the comparison between cases and controls for the clinical and genetic variables. **Results**Considering a median of ≥ 20 counts per gene as threshold, 653 genes were analyzed. Eight significant DEGs were found between cases and controls, with a FDR < 0,10: AGTR1, Receptor for angiotensin 2 (log2foldchange [log2FC]=-1.83; FDR=0.0017), PGR (log2FC=-2.41, FDR=0.016), ROCK1, Rho-associated protein kinase 1 (log2FC=1.26, FDR=0.042), ITPR1, Inositol 1,4,5-trisphosphate receptor type 1 (log2FC=-0.98, FDR=0.052), MMP3, Stromelysin-1 (log2FC=-0.58, FDR=0.097), MMP9, Matrix Metalloproteinase-9 (log2FC=1.15, FDR=0.097), TIE1, Tyrosine-protein kinase receptor-1 (log2FC= 1.0047, FDR=0.097) and GDF15, Growth Differentiation Factor 15 (log2FC= 1.30, FDR=0.099). After adjustment for multiplicity of the tests, no statistically significant associations were found between gene expression and clinical variables (*e.g.* tumor size, stage…). The most enriched KEGG pathways were: Estrogen signaling (3 genes out of 133, FDR=0.00088), Vascular smooth muscle contraction (3/119, FDR= 0.00088), cGMP-PKG signaling (3/160, FDR=0.00088), Proteoglycans in cancer (3/195, FDR= 0.00093), Cortisol synthesis and secretion (2/63, FDR=0.0041), Leukocyte transendothelial migration (2/112, FDR= 0.0061), TNF signaling (2/108, FDR=0.0061), IL-17 signaling (2/92, FDR=0.0061) and Calcium signaling (2/179, FDR=0.0078).
**Conclusions** Our preliminary results indicate that altered expression of genes related to inflammation and antigen presentation, adhesion and migration are involved in trastuzumab resistance, highlighting the role of the immune system and of the tumor microenvironment in this particular subtype of BC. For HER2+ BC with extremely poor prognosis, we aim to validate these results, reproducing the genetic landscape of unfavorable prognostic factors, in order to identify new therapeutic targets and gene signatures, able to identify Trastuzumab resistance mechanisms.

| **Table 1. Patient characteristics** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Global** | | **Cases** | | **Controls** | | ***P*** |
| | **(42)** | | **(18)** | | **(24)** | | |
| | **N** % | | | | | | |
| **Tumor Size** | | | | | | | |
| T1-T2 | 43 | 79.63 | 16 | 59.26 | 27 | 100.00 | **<0.001** |
| T3-T4 | 11 | 40.74 | 11 | 40.74 | 0 | 0.00 | |
| **Stage** | | | | | | | |
| 1 | 8 | 21.05 | 1 | 5.88 | 7 | 33.33 | **0.004** |
| 2 | 16 | 42.11 | 5 | 29.41 | 11 | 52.38 | |
| 3 | 14 | 36.84 | 11 | 64.71 | 3 | 14.29 | |
| Unknown | 4 | | 1 | | 3 | | |
| **Lymph Node Status** | | | | | | | |
| pN negative | 17 | 41.46 | 3 | 17.65 | 14 | 58.33 | **0.012** |
| pN positive | 24 | 58.54 | 14 | 82.35 | 10 | 41.67 | |
| Unknown | 1 | | 1 | | 0 | | |
| **ER** | | | | | | | |
| <1% | 11 | 26.19 | 5 | 27.78 | 6 | 25.00 | 0.839 |
| ≥1% | 31 | 73.81 | 13 | 72.22 | 18 | 75.00 | |
| **PR** | | | | | | | |
| <1% | 17 | 41.46 | 8 | 47.06 | 9 | 37.50 | 0.54 |
| ≥1% | 24 | 58.54 | 9 | 52.94 | 15 | 62.50 | |
| Unknown | 1 | | - | | 1 | | |
| **Ki67** | | | | | | | |
| <20% | 14 | 33.33 | 5 | 27.78 | 9 | 37.50 | 0.508 |
| ≥20% | 28 | 66.67 | 13 | 72.22 | 15 | 62.50 | |
| **Adjuvant Chemotherapy** | | | | | | | |
| Anthracyclines + taxanes | 22 | 52.38 | 7 | 38.89 | 15 | 62.50 | **0.025** |
| Taxanes | 5 | 11.90 | 3 | 16.67 | 2 | 8.33 | |
| Anthracyclines | 10 | 23.81 | 3 | 16.67 | 7 | 29.17 | |
| Other | 5 | 11.90 | 5 | 27.78 | 0 | 0.00 | |

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# Achieving a pathologically negative axilla after neoadjuvant chemotherapy for breast cancer is associated with presenting tumor size and subtype

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**Introduction:** Axillary pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) confers higher overall and recurrence-free survival, compared to residual axillary disease. Recent findings suggest that pCR in the breast (ypT0) post-NAC is associated with a pathologically negative axilla (ypN0) in patients (pts) presenting with lower stage HER2+ and triple negative breast cancer (TNBC). Additional studies are needed to understand how clinical T (cT) and N (cN) staging are associated with ypN0 in other tumor subtypes, including hormone-receptor (HR) positive tumors. The ability to reliably predict axillary pathologic response post-NAC may allow identification of a subset of pts for whom axillary staging may be safely omitted. We hypothesize that tumor subtype and lower clinical stage at presentation are associated with ypN0.
**Methods:** A single institution cancer registry was retrospectively reviewed for pts receiving NAC followed by surgery from January 2010-June 2018. Fisher's exact tests were used to compared proportion of breast and axillary pCR by tumor subtype (TNBC, HR+/HER2-, HR+/HER2+ and HR-/HER2+). Univariable logistic regression determined factors associated with ypN0. Multivariable logistic regression determined the association between ypN0 and tumor subtype adjusting for factors that retained significance on univariable analysis. Sensitivity analyses determined how cN status affected ypN status by tumor subtype.
**Results:** Of the 1348 pts who received NAC followed by surgery, median age was 54 (IQR 44-63); 59% (n=738) were postmenopausal. Proportion of tumor subtypes were: 15% (n=197) TNBC, 12% (n=155) HR+/HER2-, 48% (n=653) HR+/HER2+, and 25% (n=343) HR-/HER2+. Tumor size at diagnosis was: 1% (n=18) T0, 20% (n=272) T1, 53% (n=713) T2, 17% (n=230) T3 and 9% (n=111) T4. Clinical nodal staging at diagnosis was: 52% cN0 (n=695), 41% cN1 (n=550), 5% cN2 (n=61), and 3% cN3 (n=43). TNBC and HER2+ subtypes were associated with the highest rate of breast pCR and ypN0. On univariable analyses of the cN positive pts, younger age at diagnosis, non-postmenopausal status, oral contraceptive use, alcohol consumption, cT stage, cN stage and tumor subtype were significantly associated with ypN0 (Table1A). In the adjusted model, postmenopausal status, cT, and tumor subtype were associated with ypN0. Lower cT and HR- subtypes had significantly higher odds of ypN0 (Table 1B). In sensitivity analyses, cN2/cN3 was associated with lower odds of ypN0 compared to cN0/cN1 disease in TNBC (OR0.11 95%CI 0.03,0.40, p=0.001), HR-/HER2+ disease (OR0.42, 95%CI 0.22,0.77, p=0.005), and HR+/HER2+ (OR0.26 95%CI 0.11,0.61 p=0.002), but not in HR+/HER2- disease (OR1.17, 95%CI 0.25,5.57, p=0.838).
**Conclusion:** HR- and low cT stage at diagnosis are associated with ypN0 in this large cohort. Younger age, pre-menopausal status and cN stage may be important considerations in future investigations aimed at defining the subset of patients most likely to achieve ypN0 and ultimately to be considered for de-escalation of axillary staging post NAC.

| A.**Univariable logistic regression analysis** | | | |
|---|---|---|---|
| **Variable** | **Odds Ratio** | **95% Confidence Interval** | **p value** |
| Age at diagnosis | 0.99 | 0.98, 0.99 | <0.001 |
| Race | | | |
| White | 1.06 | 0.70, 1.60 | 0.777 |
| Black | 0.60 | 0.17, 2.08 | 0.421 |
| Asian | 1.20 | 0.36, 4.00 | 0.768 |
| Postmenopausal | 0.76 | 0.60, 0.96 | 0.023 |
| BMI | 1.00 | 0.99. 1.00 | 0.424 |
| Oral contraceptive use | 1.25 | 0.95, 1.63 | 0.114 |
| Alcohol consumption | 1.60 | 1.05, 2.44 | 0.027 |
| Tobacco use | 1.13 | 0.99, 1.29 | 0.064 |
| Family history of cancer | 1.25 | 0.92, 1.68 | 0.148 |
| Grade | | | |
| 1 | 2.17 | 0.75, 6.25 | 0.153 |
| 2 | 0.95 | 0.45, 2.01 | 0.891 |
| 3 | 1.70 | 0.81, 3.59 | 0.163 |
| Histology | | | |
| IDC | 1.45 | 1.10, 1.89 | 0.007 |
| ILC | 0.37 | 0.23, 0.60 | <0.001 |
| Mixed | 0.95 | 0.68, 1.32 | 0.764 |
| Other | 0.44 | 0.18, 1.08 | 0.073 |
| Clinical T stage | | | |
| 1 | 1.37 | 0.47, 3.98 | 0.569 |
| 2 | 0.76 | 0.27, 2.16 | 0.605 |
| 3 | 0.35 | 0.12, 1.02 | 0.055 |
| 4 | 0.15 | 0.05, 0.45 | 0.001 |
| Clinical N stage | | | |
| 1 | 0.14 | 0.11, 0.18 | <0.001 |
| 2 | 0.13 | 0.07, 0.23 | <0.001 |
| 3 | 0.11 | 0.06, 0.21 | <0.001 |
| Tumor subtype | | | |
| TNBC | 1.59 | 1.00, 2.53 | 0.049 |
| HR+/ HER2 - | 0.55 | 0.35, 0.87 | 0.010 |
| HR+/ HER2+ | 0.69 | 0.47, 1.00 | 0.049 |

| | | | |
|---|---|---|---|
| HR-/ HER2 + | 1.64 | 1.09, 2.46 | 0.019 |
| B.**Multivariable logistic regression analysis** | | | |
| Age at diagnosis | 0.98 | 0.97, 0.99 | <0.001 |
| Alcohol use | 1.19 | 0.74, 1.93 | 0.476 |
| Histology | | | |
| IDC | 1.15 | 0.82, 1.61 | 0.414 |
| ILC | 0.57 | 0.32, 1.01 | 0.053 |
| Mixed | 1.08 | 0.71, 1.63 | 0.721 |
| Other | 0.79 | 0.28, 2.22 | 0.660 |
| Clinical T stage | | | |
| 1 | 1.19 | 0.39, 3.58 | 0.761 |
| 2 | 0.74 | 0.25, 2.16 | 0.585 |
| 3 | 0.51 | 0.17, 1.54 | 0.235 |
| 4 | 0.29 | 0.09, 0.91 | 0.034 |
| Clinical N stage | | | |
| 1 | 0.13 | 0.10, 0.18 | <0.001 |
| 2 | 0.14 | 0.08, 0.26 | <0.001 |
| 3 | 0.10 | 0.05, 0.20 | <0.001 |
| Tumor subtype | | | |
| TNBC | 1.44 | 0.84, 2.47 | 0.181 |
| HR+/ HER2 - | 0.54 | 0.31, 0.94 | 0.028 |
| HR+/ HER2+ | 0.60 | 0.39, 0.93 | 0.024 |
| HR-/ HER2 + | 1.70 | 1.05, 2.73 | 0.030 |

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Health-related quality of life (HRQOL) outcomes in arandomized controlled trial of yoga in breast and gynecological cancer survivors with chemotherapy-induced peripheral neuropathy

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**Background:** Yoga is a meditative movement therapy that improves body conditioning, flexibility, and balance through mind-body awareness. We conducted a two-armed pilot randomized wait-list controlled trial in breast and gynecological (GYN) cancer survivors with persistent moderate to severe chemotherapy-induced peripheral neuropathy (CIPN) and found that yoga significantly reduced CIPN pain. Here we report on the HRQOL results.
**Patients and Methods:** We randomized breast and GYN cancer survivors with persistent moderate to severe CIPN to eight weeks of yoga or usual care (UC). The HRQOL endpoints were Hospital Anxiety and Depression Score (HADS), Treatment Expectancy Scale (TES), Brief Fatigue Inventory (BFI), and Insomnia Severity Index (ISI). We estimated and compared the mean changes from baseline to weeks 8 and 12 along with 95% confidence intervals (CIs) between arms using linear mixed models.
**Results:** From February 2018 to May 2019, we enrolled and randomized 41 female cancer survivors (93% breast, 7% GYN; mean (SD) age 61.7 (10.2) years; 56% white/non-Hispanic, 20% African American, 12% Asian, 12% other) to yoga (N=21) and UC (N=20) arms. The HADS anxiety score significantly reduced in the yoga arm compared to usual care at weeks 8 and 12. At baseline, the mean (95% CI) HADS anxiety score was 9.23 (7.42, 11.04) in the yoga arm, and 5.05 (3.19, 6.91) in the UC arm ($p$=0.002). At week 8, the mean (95% CI) HADS anxiety score decreased by -1.91 (-3.07, -0.76) points in the yoga arm, and by -0.02 (-1.10, 1.06) points in the UC arm ($p$=0.019). At week 12, in the yoga arm, the mean HADS anxiety score was 7.50 (5.62, 9.39), and a decrease of 1.73 (-2.88, -0.57) points; in the UC arm, the mean was 5.81 (3.94, 7.69) with an increase of 0.76 (-0.32, 1.84) points ($p$=0.002). There was no difference in HADS depression, BFI, and ISI scores between yoga and UC arms at baseline, week 8, and week 12. The TES at baseline was 14.9 (3.27) in the yoga arm, which was significantly higher than in the UC arm 14.9 (SD 3.27) vs. 12.7 (SD: 2.58), $p$= 0.019. The TES was not associated with HADS anxiety reduction, and HADS anxiety reduction was not associated with CIPN pain reduction.
**Conclusions:** Our trial showed that a yoga intervention may be useful to reduce anxiety in patients with CIPN. We previously found that a yoga intervention reduced CIPN pain. CIPN pain reduction was not associated with anxiety reduction or TES. Future studies are needed to confirm our findings and to explore the mechanism of yoga in CIPN pain reduction.

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# Comparison of metastatic genomic profile in patients ≤45 years and patients >45 years with triple-negative breast cancer

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**Background:** Metastatic triple negative breast cancer (mTNBC) is often associated with aggressive biology, particularly in younger women. We hypothesized that the tumor genomic profile might vary based on age. The primary objective of this study was to compare the genomic profile, utilizing plasma-based targeted sequencing of common cancer related genes, in patients ≤45 years and >45 years with mTNBC. The age cut-off of ≤ 45 was selected based on prior literature in TNBC using a similar cut-off for younger age stratification (Dolle, 2009).

**Methods:** A retrospective review of patients with mTNBC who had cell-free DNA (cfDNA) analysis (next generation sequencing, Guardant360®, 73 gene panel) collected at an academic institution after mTNBC diagnosis as part of clinical care from 1/2016-10/2019 was conducted. Patient age, demographics, and genotyping results were collected. Clinical and genomic characteristics were compared for patients ≤45 and >45 using the Wilcoxon rank-sum test (continuous variables) and Pearson's chi-squared test (categorical variables). **Results:**Of 74 patients with mTNBC and cfDNA results available, 17 were ≤45 years (median age 39 at mTNBC diagnosis), and 57 were > 45 years (median age 58). In comparing patients ≤45 years with those > 45 years, similar rates of de novo disease (≤45: 24%, >45: 9%, p=0.10), visceral disease (≤45: 65%, >45: 67%, p=0.88), and median number of prior lines of chemotherapy (≤45: 2, > 45: 1, p=0.49) were observed. The percentage of patients with more than 1 detectable mutation (≤45: 94%, >45: 93%, p=0.87), and median number of detected mutations (≤45: 5, >45: 4, p=0.67) was similar between groups. However, the median mutant allele fraction (MAF; maximum) was significantly higher in patients ≤45 (≤45: median 29.8%; >45: median 4.6%, p=0.006), and this finding remained significant after correcting for number of prior therapies. Table 1 depicts the mutation spectrum. While *TP53* mutations were commonly seen in both cohorts, the median *TP53* MAF was significantly higher in patients ≤45 years (≤45: 29.8%, >45: 4.0%, p=0.015). *PTEN* mutations were found in a portion of patients >45, but not identified in those ≤45 years. Amplifications in *MYC, BRAF, PI3KCA, AR, CDK6, EGFR, MET, KIT,* and *CCND2* were seen more often in those ≤45 years, although these findings did not reach statistical significance. Survival outcomes will be presented at the meeting.

**Conclusions:**Patients with mTNBC diagnosed at ≤45 years had a significantly higher cfDNA MAF than those >45, likely reflecting higher detectable tumor genomic burden. Mutations often associated with aggressive biology such as *MYC, MET*, and *EGFR* were more commonly found in patients ≤45, but the small sample size and limited statistical power makes it difficult to draw strong conclusions about differences in individual genes in this study. Further research with a larger multi-center cohort is ongoing to validate these findings.

Table 1.

| **Mutation** | Age ≤45 | Age >45 | p-value |
|---|---|---|---|
| *TP53* | 76% | 75% | 0.93 |
| *AR* | 18% | 7% | 0.19 |
| *BRCA1* | 18% | 12% | 0.57 |
| *APC* | 12% | 9% | 0.71 |
| *NF1* | 12% | 7% | 0.53 |
| *ERBB2* | 12% | 11% | 0.89 |
| *BRCA2* | 6% | 9% | 0.70 |
| *PTEN* | 0% | 11% | 0.16 |
| **Amplification** | | | |
| *MYC* | 29% | 19% | 0.37 |
| *CCNE1* | 29% | 21% | 0.47 |
| *BRAF* | 29% | 14% | 0.14 |
| *PI3KCA* | 29% | 12% | 0.093 |
| *AR* | 24% | 7% | 0.054 |
| *CDK6* | 24% | 12% | 0.25 |
| *EGFR* | 24% | 12% | 0.25 |
| *MET* | 24% | 11% | 0.17 |
| *KIT* | 18% | 7% | 0.19 |
| *FGFR1* | 18% | 21% | 0.76 |
| *CCND2* | 18% | 5% | 0.10 |
| *PDGFRA* | 12% | 7% | 0.53 |
| *RAF1* | 12% | 7% | 0.53 |
| *KRAS* | 12% | 11% | 0.89 |
| *CCND1* | 6% | 7% | 0.87 |

**Publication Number:** PS2-19

Circulating tumor cell (CTC) enumeration in a phase II trial of pazopanib in addition to endocrine therapy in patients with hormone resistant advanced breast cancer (ABC)

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**Background:** CTCs are detectable in approximately 50% of pts with metastatic breast cancer, and elevated CTC levels are an independent negative prognostic factor. CTCs have been shown to play a valuable role in predicting outcomes in pts with ABC treated with chemotherapy or endocrine therapy. This phase II trial was conducted to evaluate the clinical benefit (CB) of pazopanib, a VEGF receptor tyrosine kinase inhibitor (TKI) combined with nonsteroidal aromatase inhibitors (NSAIs) in pts with ABC resistant to NSAIs. As an exploratory analysis, we hypothesized that CTC levels might be correlated with response to pazopanib plus endocrine therapy.
**Methods:** Eligibility included postmenopausal women with hormone receptor positive (HR+) ABC and progressive disease after at least one month of NSAIs. Treatment was pazopanib 800 mg/day plus either letrozole or anastrozole. The primary endpoint was clinical benefit rate at 12 weeks (CBR12, wks). Secondary endpoints included progression free survival (PFS), safety, and the impact of pazopanib and NSAI on CTCs. A CBR of 20% was considered a clinically meaningful comparison to the expected CBR of <5% with continued NSAIs after PD. Blood samples were collected for CTC analysis at baseline, then every 4 wks while on treatment. The presence of CTCs was assessed using the FDA-cleared CellSearch System; CTCs were defined as EPCAM-positive, CD45-negative nucleated cells. Samples with 5 CTCs per 7.5 mLs of blood were considered CTC-positive.
**Results:** 32 pts were enrolled; 28 are evaluable for study endpoints. The median age was 58 years (range: 41-77). Pts were heavily pre-treated, with a median of 2 prior hormone therapies (range 1-6) and 1 prior chemotherapy (range 0-8). 8 pts (28.6%) stopped treatment due to adverse events, and 6 pts progressed before wk 12. CBR12 was 46.4% (12 SD, 1 PR), and CBR24 was 25% (5 SD, 2 PR). Safety has been presented (ASCO 2020). Median PFS was 20 wks, and median PFS for pts with CBR12 was 24 wks. Five (22%) of 23 pts with CTC data were CTC-positive (5 CTC/7.5 mL). There was no significant association between CBR12 and CTC status at baseline, or between CBR12 and change in CTC status (baseline to 4 wks after initiation of treatment). 7 pts had non-CBR12 and CTC data; 4 pts (n=4/7; 57%) were CTC positive at either baseline, week 4 or both. 11 pts had CBR12 and CTC data; all patients were CTC negative at baseline and remained negative at 4 wks. 7 pts had PFS >6 months (24, 32, 36, 36, 48, 184 and 274 wks), and 6 had CTC data: all were CTC-negative at baseline and 4 wks, then remained negative at 12 wks. Based on baseline values only, CTC-positive pts had a shorter median PFS compared to CTC-negative pts, but the difference was not statistically significant (11 wks vs 14 wks, p=0.18). Persistently CTC negative patients had significantly longer PFS compared to patients who were CTC positive at any time during study treatment (36 wks vs 11 wks, p=0.01).
**Conclusions:** The addition of pazopanib to NSAIs resulted in a CBR12 of 46.4%, and a CBR24 of 25% in pts with heavily pre-treated ABC resistant to NSAIs. These results support clinical efficacy of antiangiogenic TKI in HR+ ABC and suggest benefit in hormone resistant disease. Consistently negative CTCs correlated with response and response duration. PFS was significantly longer in patients who were consistently CTC negative, further defining the prognostic role of CTCs in HR+ ABC. (NCT01466972)

**Publication Number:** PS8-19

High rates of *BRCA*1 and *BRCA*2 variants of uncertain significance (VUS) among Jordanian breast cancer patients

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**Background:** Contrary to pathogenic *BRCA* mutations, recommendations for management of Variants of Uncertain Significance (VUS) is not clear and focus more on clinical factors, personal and family history of cancer; breast and ovarian in particular. Genetic variants that may or may not have clinical consequence can be confusing and anxiety-provoking to patients and physicians, alike. No data exist on Arab patients with VUS mutations. In this study we search for the frequency of VUS among high risk breast cancer patients tested for *BRCA* mutations and study risk-reduction interventions related to such findings. **Methods:** We utilized an institutional database started January 2015 for all patients with breast cancer tested for *BRCA* mutations as per the National Comprehensive Cancer Network (NCCN) guidelines, including those with early onset cancers, triple-negative disease and positive family history. We also reviewed surgical interventions patients had in relation to their breast cancer and VUS mutation identification. **RESULTS:** Between January 2015 and May 2020, a total of 1181 patients were tested for *BRCA*1 and *BRCA*2 mutations as per the NCCN guidelines. Pathogenic mutations were detected in 134 (11.3%) patients, while 109 (9.2%) others had VUS; 79 (72.5%) were in *BRCA*2. At time of testing, all VUS patients had breast cancer; 7 (6.4%) with metastatic disease. Median age (range) was 39 (25-66) years with 63 (57.8%) were 40 years or younger at diagnosis. Twelve (11.0%) had triple negative disease while 14 (13.1%) others had bilateral or two or more unilateral primary breast cancers. Family history of breast, ovarian or pancreatic cancers, in at least one close relative, was identified in 52 (47.7 %) patients. Among 101 patients with nonmetastatic disease, 48 (48.0%) had breast conserving surgery (BCS) while only 5 (5.0%) had bilateral mastectomies, all were due to bilateral disease and not prophylactic. VUS diagnosis was known prior to initial surgery in 33 (32.7%) patients; 11 (33.3%) of them had lumpectomy only. Since we started genetic testing 5 years ago, there is a slight decline in VUS rate but none of the VUS reported mutations so far were reclassified. **Conclusions**: Despite significant decline in VUS rates reported in the western societies, our rate continues to be high and alarming. Our knowledge of VUS had not significantly impacted on therapeutic or prophylactic surgical decisions. Given the relatively high rate of second breast cancers among such patients, management should be dictated by their personal or family history. A regional (Arab) VUS registry and comprehensive genetic counseling to ensure appropriate follow up and understanding by affected patients, are highly needed.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS7-19

Pre/perimenopausal (preMeno) women receiving palbociclib (PAL) for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) in a real-world setting: Treatment patterns from POLARIS

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**Background:** POLARIS is an ongoing, prospective, real world, noninterventional study in patients (pts) with HR+/HER2– ABC receiving PAL. This interim report describes real-world PAL use in preMeno pts. **Methods:** POLARIS has a targeted enrollment of 1500 pts from ~110 sites in the United States and Canada. Using patient data collected from medical charts and physician surveys, baseline demographics, clinical characteristics, and treatment patterns were analyzed descriptively in self-reported preMeno pts with ABC. **Results:** At the data cutoff of May 20, 2020, 1208 pts were enrolled; 134 (11.1%) from 61 sites were preMeno, of whom 14.2% completed ≥6 months of PAL treatment. Among 134 preMeno pts (74.6%) who received first-line (1L) therapy, 69.0% received PAL+letrozole (LET) or anastrozole, 28.0% PAL+fulvestrant, and 3.0% PAL+exemestane. Median disease-free interval was 39.3 (range: 0 to 236) months; median treatment-free interval was 14.8 (-3 to 134) months. Of 34 pts (25.4%) who received PAL as second or later line (≥2L), 23.8% previously received hormonal therapy, 28.6% chemotherapy, and 14.3% both. The majority of pts (96.27%) initiated PAL at 125 mg regardless of line of therapy (**Table**). During the first PAL treatment cycle, 2.9% of all preMeno pts, 1% of 1L pts, and 8.8% of ≥2L pts had a dose reduction; 8.2%, 9%, and 5.9%, respectively, had an interruption. Dose reductions/interruptions peaked in cycle 2 (11.9%/15.7%); 56.67% of these modifications were due to adverse events. **Conclusions:** PAL is routinely prescribed in clinical practice for preMeno women with HR+/HER2- ABC. The majority of preMeno pts in this real-world dataset received PAL+LET as 1L ABC treatment; PAL was primarily initiated at the recommended dose (125 mg) and was well tolerated with few dose modifications required. **Clinical trial identification:** Pfizer (NCT03280303)

**Table.**

| **Characteristic** | **First-Line Pre/Perimenopausal Patients (n=100)** | **Second or Later Line Pre/Perimenopausal Patients (n=34)** | **Pre/Perimenopausal Patients (N=134)** |
|---|---|---|---|
| Age at study enrollment, y | | | |
| Median (range) | 44 (22-61) | 42.5 (27-58) | 44 (22-61) |
| Distribution, n (%) | | | |
| <40 | 32 (32.0) | 12 (35.3) | 44 (32.8) |
| 40–50 | 45 (45.0) | 17 (50.0) | 62 (46.3) |
| 51–69 | 23 (23.0) | 5 (14.7) | 28 (20.9) |
| Race, n (%) | | | |
| White | 73 (73.0) | 26 (76.5) | 99 (73.9) |
| Black or African American | 16 (16.0) | 4 (11.8) | 20 (14.9) |
| Asian | 1 (1.0) | 1 (2.9) | 2 (1.5) |
| Native Hawaiian or other Pacific Islander | 2 (2.0) | 0 (0.0) | 2 (1.5) |
| American Indian or Alaska Native | 1 (1.0) | 0 (0.0) | 1 (0.7) |
| Other | 3 (3.0) | 2 (5.9) | 5 (3.7) |
| Not reported because of confidentiality regulations | 4 (4.0) | 1 (2.9) | 5 (3.7) |
| Hispanic/Latino ethnicity, n (%) | 10 (10.0) | 3 (8.8) | 13 (9.7) |
| Disease status, n (%) | | | |
| Visceral | 35 (35.0) | 13 (38.2) | 48 (35.8) |
| Nonvisceral | 61 (61.0) | 17 (50.0) | 78 (58.2) |
| Not reported | 4 (4.0) | 4 (11.8) | 8 (6.0) |
| Bone metastases at mBC diagnosis, among patients with metastatic (stage IV) disease at study enrollment, n (%) | | | |
| Bone only | 40 (40) | 8 (23.5) | 48 (35.8) |
| Bone plus other metastases | 32 (32) | 13 (38.2) | 45 (33.6) |
| Disposition of patient ABC/mBC diagnosis at study at study enrollment, n (%) | | | |
| Recurrent from earlier stage (Stage 0-III) | 72 (72.0) | 18 (52.9) | 90 (67.2) |
| De novo (Newly diagnosed Stage IV at enrollment) | 26 (26.0) | 15 (44.1) | 41 (30.6) |
| Not reported | 2 (2.0) | 1 (2.9) | 3 (2.2) |
| ECOG performance status at study enrollment (N, %) | | | |
| 0 | 41 (41) | 15 (44.1) | 56 (41.8) |
| 1 | 26 (26) | 7 (20.6) | 33 (24.6) |
| 2 | 8 (8) | 3 (8.8) | 11 (8.2) |
| 3 | 2 (2) | 0 (0) | 2 (1.5) |
| Not reported | 23 (23) | 9 (26.5) | 32 (23.9) |
| Starting dose, first cycle of PAL treatment n (%) | | | |
| 125 mg | 96 (96.0) | 33 (97.1) | 129 (96.3) |
| 100 mg | 2 (2.0) | 1 (2.9) | 3 (2.2) |
| 75 mg | 2 (2.0) | 0 (0.0) | 2 (1.5) |
| Reason for first cycle starting dose <125 mg, n (%) | | | |
| Patient preference | 0 (0.0) | 1 (100) | 1 (25.0) |

| | | | |
|---|---|---|---|
| Other | 3 (100) | 0 (0.0) | 3 (75.0) |

**Publication Number:** OT-07-01

Guardant360® related clinical outcomes in patients who share medical records-breast cancer (GRECO-B)

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**Background:** Cell free circulating tumor DNA (ctDNA) is a proven viable alternative to tissue molecular profiling with high sensitivity, specificity, and positive predictive value. However, there is limited data on the overall outcomes of patients following ctDNA testing. Guardant360® Related Clinical Outcomes in Patients who Share Medical Records - Breast Cancer (GRECO-Breast) is a novel, patient-centric approach to evaluate clinical data and outcomes. This real-world prospective observational study intends to assess the health outcomes of patients with advanced breast cancer who have undergone Guardant360 ctDNA testing by consenting patients through siteless methodologies to share their medical records and imaging studies documenting their clinical history.
**Trial design:** This is an observational study to be conducted in the United States. Patients with a diagnosis of breast cancer and a completed Guardant360 test will consent to share their medical records. Patients will be recruited by telephone or email to determine interest in the study. Should patients be interested in contributing to this study, they will be asked to consent via an electronic signature platform (e-signature) and electronic informed consent form (e-consent). Enrolled participants will be required to sign an electronic medical records release form for data review and verification by the study team. A healthcare information management organization will abstract participant demographics, cancer-related therapies, and clinical outcomes directly from source data for final analysis.
**Eligibility criteria:** Prospective participants will be adults (age 18+) with a diagnosis of breast cancer with a completed Guardant360 test who consent to be enrolled in the study.
**Endpoints:** *Primary endpoint*: To measure event free survival (EFS, composite endpoint of overall survival, progression events, and subjects lost to follow-up) stratified by treatment and genomic biomarker. *Secondary endpoints*: 1) Assess the rate of biomarker discovery compared to tissue genotyping results, when available; 2) Time to Next Treatment (TTNT); 3) Real-world Time to Tumor Progression (rwTTP); defined and documented either clinically or radiologically 4) Real-world Overall Survival (rwOS); defined as either clinically recorded death or secondary validated sources; 5) Record completeness of data and data quality.
**Statistical methods:** Descriptive statistics will be used to characterize the patient population. These will include frequency distributions, cross tabulations, and summary measures such as means, standard deviations, and ranges. Graphical displays will be employed, where appropriate, such as box plots, scatter plots, and survival curves for time-to-event endpoints.
**Present accrual and target accrual:** GRECO-Breast opened for enrollment in June 2020 with a goal of enrolling up to 300 participants.
**Contact information:** For more information, please visit: https://clinicaltrials.gov/ct2/show/NCT04436393

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**Publication Number:** PS1-20

# Pathologic lymph lode status of patients with T1 HER2-positive breast cancer who did not receive neoadjuvant chemotherapy using the national cancer database

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**Purpose:** HER2 directed neoadjuvant therapies for locally advanced HER2-positive breast cancer have improved complete pathologic response and event-free survival. For T1 breast cancer, lymph node status often determines whether neoadjuvant treatment is indicated. The aim of this study was to identify patient and tumor characteristics using the National Cancer Database.**Methods:** A retrospective review of patents diagnosed with T1 clinically node negative (cT1N0) HER2-positive breast cancers was performed using the American College of Surgeons National Cancer Database (ACS NCDB) from 2004-2016. Exclusion criteria included age <18 years and neoadjuvant treatment. Primary outcome was lymph node status. Additional variables included: age, tumor size, tumor location, histology, grade, lymphovascular invasion (LVI), grade, and estrogen receptor (ER) and progesterone receptor (PR) status. Chi-Square tests were performed to evaluate the relationship between these variables and lymph node positive disease.
**Results:** A total of 57,366 T1 HER2-positive patients were identified with 8,994 patients (15.68%) having positive lymph nodes. Characteristics associated with lymph node involvement included age ($p<0.001$), tumor location ($p<0.001$), lymphovascular involvement ($p<0.001$), ER positivity ($p=0.021$), and PR positivity ($p<0.001$). There was a significant difference in tumor size when comparing lymph node positive and negative disease (19.06 mm vs. 13.11 mm, $p<0.001$). **Conclusion:** Age, tumor location, LVI, ER positivity, PR positivity, and larger tumor size are associated with lymph node involvement in cT1N0 HER2-positive breast cancers. Future research includes determining best practices to identify which patients in this population would benefit from neoadjuvant chemotherapy.

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**Publication Number:** PS17-19

# Intrathecal (IT) delivery of Her2/Her3-pulsed dendritic cell vaccine (DC1) eradicates tumor growth in breast cancer (BC) xenograft model with leptomeningeal disease (LMD)

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**BACKGROUND:** Approx. 5% of BC patients develop LMD. Currently there are no effective treatments for BC-associated BM/LMD. Systemic therapies are not very effective and an IT administration is an alternative. We have shown there is a loss of the anti-HER2/HER3 CD4 Th1 immune response in BC patients. In clinical trials class II HER2 peptide-pulsed Type I polarized dendritic cell vaccine (HER2-DC1) partially restored anti-HER2 Th1 immune responses with pathologic CRs in HER2+ BC pts. In this study, we examined the IT delivery of HER2/HER3- DC1 in immunocompetent BC-LMD models. **METHODS:** Luciferase-labeled HER2+ TUBO BC cells were administered IT in BALB/c mice and developed LMD. We developed a murine Ommaya Reservoir (MOR). The MOR allows the IT therapy administration directly into CSF. BC-LMD bearing mice were treated with HER2- and HER3-DC1s IT. **RESULTS AND DISCUSSION:** BM-LMD mice were randomized into: 1) Systemic HER2-DC1 2) IT HER2-DC1 3) Alternating IT HER2-/HER3-DC1. The median survival (MS) of control mice was 10 days and systemically treated mice was 19 days. IT HER2-DC1 animals survived significantly longer than both control & systemic treated groups [MS: 63 days; $p<0.0001$; and overall survival (OS): 44%]. Interestingly, mice treated with IT alternating HER2- & HER3-DC1 had the best OS (78%). Surviving animals ultimately became disease free and these mice were immune to subsequent IT tumor re-challenge. Immune cell infiltration/cytokine responses are described. **CONCLUSIONS:** IT alternating HER2/HER3 pulsed DC1 can eradicate BC-LMD in preclinical models with lasting CD4 Th1 immunity suggesting promise for testing this therapy in BC patients with LMD.

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**Publication Number:** PS16-19

# Hotspot p53 mutations correlate with increased expression of stem cell markers in triple-negative breast cancer

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p53 mutations occur in 80% of triple-negative breast cancer (TNBC) cases. Several types of p53 mutations have been reported, among which gain of function mutations have been associated with increased cancer stem cells, chemotherapy resistance, and disease relapse in several malignancies. Particularly, hotspot p53 mutations (mutations at amino acid location 157, 175, 248, 249, 273 predict worse overall survival in some cancer types. We have previously reported that Ganglioside GD2, a cell surface glycosphingolipid, identifies breast cancer stem cells and promotes tumorigenesis. We have also reported that GD3 synthase, a key enzyme which catalyzes the rate-limiting step of the GD2 biosynthesis pathway, is significantly upregulated in breast tumors with p53 mutations. Here, we hypothesize that mutant p53 promotes stemness in TNBC cells by regulating GD3 synthase and GD2 expression. To identify specific p53 mutations that contribute to TNBC stemness, we stratified TNBC cell lines (N=18) based on p53 mutation status including mutation type, location, and domain affected. We measured GD2 and GD3 synthase expression in the available TNBC cell lines by flow cytometry and RT-PCR, respectively. We found that GD3 synthase expression is significantly upregulated in TNBC cell lines with p53 hotspot mutations compared to cell lines with other p53 mutations (Median relative expression 0.0114 compared to 0.0003, p=0.005). Similarly, we found that GD2 expression is significantly higher in TNBC cell lines with hotspot mutations compared to non-hotspot counterparts (Median $GD2^+$ cells 15.2% compared to 0.97%, p= 0.013) Additionally, GD2 and GD3 synthase are upregulated in basal-type TNBC cell lines and TCGA patient samples compared to other TNBC molecular subtypes. Interestingly, we also found that GD2 expression is not always directly correlated with GD3S expression, suggesting that GD2 synthase expression is also a key factor in the regulation of GD2 expression. To examine the effect of mutant p53 protein levels on TNBC stemness, we measured p53 expression in all the available TNBC cell lines by western blot, and found that p53 protein levels do not correlate with GD2 or GD3S expression. To validate these findings, we analyzed RPPA data from the MD Anderson Cancer Cell Lines Project and found similar results. These data suggest that it is the type of p53 mutation, but not the amount of p53 protein in the cells that determines GD2 and GD3 synthase expression in TNBC cells. For instance, p53 hotspot mutations involving amino acid position 248 have been shown to be strongly associated with increased cancer stemness. We found that cell lines with p53 mutations at this specific location have significantly higher GD3 synthase expression compared to other mutant p53 forms. We are currently examining the direct role of mutant p53 in the regulation of GD3S expression by stabilizing mutant p53 using MDM2 inhibitors as well as stable knockdown of p53 gene in multiple TNBC cell lines to establish a clear link between mutant p53 and stem cell marker expression in TNBC cell lines.

In conclusion, stem cell markers are highly expressed in p53 mutant TNBC cell lines compared to wild type p53 counterparts. Specifically, cell lines with hotspot p53 mutations significantly correlate with increased TNBC stemness. The type of p53 mutation, rather than level of its expression correlates with stem cell marker expression in TNBC cells.

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**Publication Number:** PS5-20

# Protein interactome dysregulation analysis reveals putative therapeutic targets for BCI(H/I)-low breast cancers patients

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**Background:** Hormone receptor-positive (HR+) breast cancer (BC) is a disease of late recurrence. HR+ BC patients who are disease free after five years of adjuvant hormonal therapy, have an ongoing risk of disease recurrence and death for at least 15 years from diagnosis. Multiple trials have demonstrated consistent absolute benefits with extending adjuvant endocrine therapy to 10 years in HR+ patients. In several extended endocrine therapy trials, we have shown that HR+ patients with BCI(HoxB13/IL17BR) [BCI(H/I)]-high biomarker expression benefit from extended endocrine therapy, while those with low BCI(H/I)-low expression do not benefit from such therapy. Currently, there are limited therapeutic options for BCI(H/I)-low patients who are at high risk for late disease recurrence. Previous cell line-based, global scale protein-protein interaction (PPI) dysregulation mapping studies have identified therapeutic pathways within cellular circuits carrying the perturbed protein-protein interaction. To identify exploitable therapeutic vulnerabilities in BCI(H/I)-low BC patients, we performed comparative multiplexed quantitative mass spectrometry-based interactome dysregulation analysis of BCI(H/I)-low with BCI(H/I)-high BC samples and correlated interactome perturbations with drug responses. **Methods:** 21 BCI(H/I)-high and 23 BCI(H/I)-low frozen tumor samples from ER+ BC patients were identified in the MGH BC tissue repository, and proteomes were mapped using TMT-11 reagents, and the Synchronous Precursor Selection supported MS2/MS3 method on an Orbitrap Fusion and an Orbitrap Lumos. Dysregulations of PPIs were mapped through using bivariate outlier testing on each identified protein pair based on mapping Mahalanobis distances. . Protein identifiers (IDs) were converted to their appropriate gene IDs and gene set enrichment analysis (GSEA) was performed. Using previously established PPI data from 41 human breast cancer cell lines, we performed comparative PPI dysregulation GSEA and leading edge GSEA of the BCI(H/I)-high and -low samples. To identify therapeutic target candidates for BCI(H/I)-low patients, tumor interactome dysregulations were correlated with drug response dysregulations determined in drug screen of 195 cancer therapeutics against 41 breast cancer cell lines. **Results:** Across 44 samples, we have quantified more than 11,608 proteins with an average of 7,890 proteins per sample. Protein concentration co-regulation analysis resulted in identifying more than 11,908 protein-protein associations ($\rho > 0.65$, FDRq $< 0.0001$). PPI dysregulation analysis revealed an average of more than 1596 dysregulated PPIs per tumor sample. GSEA of the 21 BCI(H/I)-high proteome samples revealed a positive association with the Bowie tamoxifen response, and the α- and γ-interferon response C2 gene sets, while the 23 BCI-H/I-Low samples revealed a positive association ($p=0.03$, FDRq=0.052) with the hedgehog signaling and the early estrogen Hallmark gene sets. Protein-protein interaction GSEA identified 85 significant gene sets ($p < 0.016$, FDRq $< 0.25$) that were more frequently dysregulated in the BCI-H/I-low samples as compared with the BCI(H/I)-high samples. Dysregulated pathways in BCI-H/I-low samples included cell cycle regulation, anaphase promoting complex-mediated degradation of mitotic proteins, and ERK and RAS signaling. Correlation of the BCI(H/I)-low interactome perturbations with cell line model drug responses to a library of 195 therapeutics revealed a significant correlation with PI3K inhibitor drug response. **Conclusion:** Quantitative mass spectrometry-based protein-protein interaction dysregulation identified the PI3K- pathway as a putative exploitable therapeutic vulnerability in BCI(H/I)-low HR+ BC patients at risk for late disease recurrence.

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Rapid beside diagnosis of breast core needle biopsies using stimulated raman histology

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Image-guided core needle biopsy plays a central role in the diagnosis and management of a wide range of breast lesions. After collection, tissue cylinders are transported from a biopsy suite to a pathology laboratory for analysis. The existing workflow for microscopic diagnosis of tissue specimens precludes the option of using histologic data to inform clinical decision-making at the time of biopsy. Here, we introduce stimulated Raman histology (SRH), a rapid label-free optical imaging method that enables microscopic imaging of unprocessed breast biopsy specimens in the biopsy suite within minutes of sample collection. SRH has been thoroughly validated for use in the detection and diagnosis of brain tumors but its use has not been validated in breast lesions. In our study, we collected core needle biopsy specimens and allocated a 2mm portion of the tissue sample for SRH imaging. Each specimen was imaged with SRH and subsequently fixed in formalin, embedded, stained and sectioned in a conventional manner. A board-certified breast pathologist first analyzed the diagnostic features of the imaged specimens with SRH and then with conventional H&E-stained sections. In a pilot series of six patients, we found that SRH could differentiate between lesions that can mimic cancer such as a radial scar from neoplastic ones like invasive ductal carcinoma. SRH also demonstrated histologic differences between a benign tumor like a fibroadenoma and a malignant tumor like an invasive ductal carcinoma. We also observed diagnostic differences amongst benign processes such as radial scar and pseudoangiomatous stromal hyperplasia. Importantly, we showed that SRH is non-consumptive and the imaged tissue can be used for downstream histologic and immunohistochemical analysis. Our data provide proof of concept that SRH can reveal the diagnostic features of tissue collected in breast core needle biopsies, supporting further validation of this technology. Ultimately, we envision the use of SRH to create new, efficient workflows for managing patients with breast lesions, especially those in which fine needle aspiration is of limited value, and where rapid diagnosis of tissue biopsies could streamline care and increase patient satisfaction.

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Prognostic value of baseline circulating tumor cells (CTCs) enumerations is for stage III and stage IV breast cancer

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**Introduction:** Prognosis of metastatic breast cancer (MBC) is initially predicted by the cancer's characteristics based on AJCC TNM system, including the size of the cancer tumor, invasion into nearby tissue, lymph nodes and other parts of the body beyond the breast. Although additional information including hormone-receptor status, HER2 status, and possibly Oncotype DX score contributed to improve prognostic evaluation, predicting clinical outcomes and treatment benefit for MBC is still a challenge in clinic because of the clinical and biologically heterogeneous condition. We recently reported that CTCs enumeration can classify MBC in two distinct prognostic groups independently of clinical and molecular characteristics (Crit Rev Oncol Hematol. 2019). Moreover, our group reported that CTCs is associated with HER2 expression in MBC which may indicate more aggressive tumor (2019 AACR #1919). Here we compared CTCs enumeration of Stage III and Stage IV, which would be helpful to evaluate the MBC metastasis capability and treatment in clinic. **Methods:** The study included 38 specimens prospectively collected under IRB-approved protocol from 38 patients with Stage III MBC, and 254 specimens from 254 patients with stage IV MBC who received standard systemic treatments based on disease subtypes at NMH (2016-2020). Duplicate whole blood samples (7.5ml/each) were collected in EDTA tubes from these patients who were longitudinally characterized for CTCs before therapy (baseline). CTCs enrichment and enumeration were performed in FDA approved semi-automated fluorescence CELLTRACKS ANALYZERII® System (Menarini) by using CELLSEARCH® CXC Kit contains antibodies targeting the Epithelial Cell Adhesion Molecule (EpCAM) antigen for capturing CTCs, anti-CK-PE which is specific for the intracellular protein cytokeratin in epithelial cells, DAPI for staining the cell nucleus, anti-CD45-APC is specific for leukocytes (2019 ASCO #1036). The CTCs were classified based on morphology and correct phenotype as $CK^+$, $DAPI^+$ and $CD45^-$. Kruskal-Wallis test was used for statistics. **Results:** Patients were classified as Luminal, HER2 positive and TNBC disease subtypes in 46.6%, 46.7% and 6.7% respectively in Stage III patients, and 54%, 18% and 28% respectively in Stage IV patients. The patients at age above 50 were 26.% in Stage III group and 68% in Stage IV group respectively. IBC patients represented 61.5% and 33.5% of Stage III and Stage IV patients respectively. Metastasis in liver, lung and bone were diagnosed in 40.7%, 40.2% and 62.8% in Stage IV patients. CTC negative (<5 CTCs) and positive (≥5CTCs) patients were identified in 32/38 (84.22%, group 1) and 6/38 (15.78%, group 2) respectively in Stage III patients, and 149/254 (59%, Stage IV $_{indolent}$ ) and 105/254 (41%, Stage IV $_{aggressive}$ ) respectively in Stage IV patients. Patients in Group 1 have a significantly less recurrence probability than patients in Group 2 (p=0.015). Correspondingly, patients with Stage IV $_{indolent}$ also had significantly longer survival than patients with Stage $_{aggressive}$ disease (p=0.0021). When comparing the all population, Group 1 patients still have the highest survival probability (p=0.00057) within 47 months follow-up survey. More interesting, there was no any CTC-clusters found in all Stage III patients when there were 28 out of 254 stage IV patients (11.02%) were detected with CTC-clusters, who had the worst prognosis in compared to either Stage IV patients without CTC-clusters or Stage III patients (p=0.00035). **Conclusions:** In this study, we showed that enumeration of baseline CTC and CTC-clusters correlated with worse prognosis even the patients were pathologically diagnosed for the same stage, which provided an additional measure to predict disease recurrence after systemic therapies especially for Stage III MBC patients.

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# Neoadjuvant (neoadj) and adjuvant (adj) treatment patterns in HER2-positive early breast cancer (EBC): Analysis of US real-world oncology data

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**OBJECTIVES**
Over the last decade, new treatment options have transformed the standard of care for patients (pts) with HER2-positive EBC and the treatment landscape continues to evolve. The primary objectives of our study were (1) to describe and compare the demographic and clinical characteristics of pts with HER2-positive EBC who received neoadj or adj treatment, (2) to describe the common neoadj and adj regimens according to hormone receptor (HR) status, and (3) to describe trends in neoadj treatment use from 2011 to 2019 in a US real-world setting.
**METHODS**
Unstructured and structured electronic health record-derived data were analyzed from the US Flatiron Health de-identified database (2011-2020), a longitudinal database of >2.4 million pts with cancer in >280 clinics, largely from community-based practices. Eligible pts had HER2-positive EBC (diagnosis: Jan 1, 2011-Jul 31, 2019; follow-up: until Feb 29, 2020). Systemic or oral anti-neoplastic treatments with initiation either prior to (neoadj) or within 6 months (adj) of the first primary surgery date were included. Adj treatment also required at least 6 months of follow-up and was captured for up to 1 year after initiation of adj therapy.
**RESULTS**
Pts with HER2-positive EBC treated in the neoadj setting, versus those in the adj setting alone, were more likely to be younger, pre-menopausal, have HR-negative disease, clinical stage II or III stage disease (refer to footnote in Table 1), have received treatment at an academic center, and were ~2 times as likely to have bilateral mastectomies (Table 1). Conversely, race/ethnicity as well as tumor grade, histology and laterality did not differ by neoadj versus adj treatment. The most common therapies are presented in Table 1. There was an upward trend in the annual percentage of pts diagnosed with HER2-positive EBC who initiated neoadj treatment starting in 2011 (<20% of pts) and peaking in 2017 (~50% of pts). Most pts (78%) who received neoadj therapy were treated with a taxane-based chemotherapy regimen and a dual blockade of HER2 with trastuzumab plus pertuzumab (HP). A minority of neoadj pts (11%) received an anthracycline-based regimen plus HER2-targeted therapy. As expected, most pts received HER2-targeted therapy alone with HP post-surgery. The most common chemotherapy for adj-only pts included a taxane-based regimen combined with H (+/- P). Hormonal therapy was mostly administered post-surgery (adj-continuation: 61%; adj-only: 78%) with low use in the neoadj setting (9%). When evaluating pts by HR status, pts with HR-positive EBC more commonly received hormonal and 'other' therapy; adj-only pts with HR-negative disease more commonly received HER2-targeted therapies with taxanes (83% v 54%), irrespective of the additional use of platinum-based chemotherapy (64% v 38%) or anthracyclines (15% v 8%).
**CONCLUSIONS**
Neoadj therapy use has increased, which is in line with changes in the standard anti-HER2 therapies that have occurred since 2013. Despite considerable variation, neoadj pts are mostly treated with dual HER2 blockade and chemotherapy, with a preference for taxane-based regimens.

Table 1. Summary of key demographics and clinical characteristics

| **Characteristic*** | **Neoadj (n = 394)** | **Adj (n = 696)** |
|---|---|---|
| **Age at diagnosis, mean (IQR)** | 55 (46, 64) | 61 (51, 69) |
| **Race / ethnicity** | | |
| - Non-Hispanic white | 237 (60) | 433 (62) |
| - Other | 134 (34) | 218 (31) |
| - Unknown | 23 (6) | 45 (7) |
| **Menopausal status** | | |
| - Postmenopausal | 219 (56) | 495 (71) |
| **ECOG PS** | | |
| - 0 | 203 (52) | 277 (40) |
| - 1 | 52 (13) | 86 (12) |
| - 2+ | 7 (2) | 13 (2) |
| - Unknown | 132 (34) | 320 (46) |
| **Combined clinical stage?** | | |
| - Clinical stage I | 30 (8) | 364 (52) |
| - Clinical stage II | 167 (42) | 216 (31) |
| - Clinical stage III | 104 (26) | 57 (8) |
| - Unknown | 93 (24) | 59 (9) |
| **Type of surgery** | | |
| - Lumpectomy | 155 (41) | 435 (63) |
| - Mastectomy | 225 (59) | 261 (37) |
| - Unknown | 14 (4) | 0 |
| **Year of Diagnosis** | | |
| - 2011-12 | 45 (11) | 180 (26) |
| - 2013-14 | 109 (28) | 209 (30) |
| - 2015-16 | 98 (25) | 170 (24) |
| - 2017-19 | 142 (36) | 137 (20) |
| **Practice type (EHR format)** | | |
| - Community | 348 (88) | 659 (95) |
| - Academic | 46 (12) | 37 (5) |
| **ER-positive and/or PR-positive** | 280 (71) | 557 (80) |
| **Most common treatment regimens, n (%)?** | | |
| | **Pts with HER2-positive EBC, with available treatment data** | |
| **Neoadj** | **n = 280** | |
| - TCH / TCHP | 43 (15) / 176 (63) | |

| | |
|---|---|
| - ACT + H/HP? | 14 (5) / 18 (6) |
| - Any hormonal therapy | 25 (9) |
| **Adj continuation** | **n = 266** |
| - H / HP only | 171 (64) / 38 (14) |
| - Any hormonal therapy | 163 (61) |
| - T (H / HP) + other? | 35 (13) |
| **Adj-only** | **n = 642** |
| - Any hormonal therapy | 500 (78) |
| - TCH / TCHP | 223 (35) / 43 (7) |
| - T (H / HP) + other? | 106 (17) |

*$P$ <0.05 (t-test) when comparing pts in the neoadj and adj treatment groups for the clinical characteristics listed (with the exception of race / ethnicity where no major differences were noted). ?Clinical stage prior to the start of systemic treatment, which is close to the time of diagnosis for neoadj pts and after the time of surgery for adj pts. ?'Other' therapies accounted for 5% of regimens. ?The majority of anthracycline use was a TCH / HP regimen. ?'Other' treatments include CD20 monoclonal antibody, CDK 4/6 inhibitors, antimetabolites (e.g., gemcitabine) and clinical trial study drugs (not specifically listed/known). A, anthracycline; adj, adjuvant; C, a platinum-based compound; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHR, electronic health record; ER, estrogen receptor; H, trastuzumab; IQR, interquartile range; neoadj, neoadjuvant; P, pertuzumab; PR, progesterone receptor; pts, patients, T, taxane.

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# The PREDICT registry: A prospective registry to evaluate the effect of a predictive assay on treatment decisions in patients with DCIS following breast conserving therapy

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**Background.** The benefits of adjuvant radiation therapy (RT) in patients with ductal carcinoma in situ (DCIS) treated with breast conserving surgery (BCS) remains controversial. Although there is level-I evidence supporting the role of RT in reducing the risk of local recurrence, the absolute benefit is variable. Current guidelines generally recommend RT for all patients having BCS, but it is important to develop prognostic and predictive tools to better assess risk and understand the impact such a tool would have on treatment decisions. The DCISionRT Test (PreludeDx, Laguna Hills, CA) is a biologic signature that provides a validated score for assessing 10-year risk of recurrence and RT benefit using individual tumor biology as assessed by clinical and pathologic biomarkers.**Methods.** This is a prospective cohort study for patients diagnosed with DCIS of the breast. Treating physicians complete a treatment recommendation survey before and after receiving DCISionRT test results. Test results, treatment recommendations, patient preferences and clinico-pathologic features are stored in a de-identified registry for participating institutions from a variety of geographic regions across the US. The study will also collect 5- and 10-year recurrence and survival data. The study includes females over age 25 who are candidates for BCS and eligible for RT and/or systemic treatment with sufficient tissue to generate test results. Subjects must not have been previously treated for DCIS or have previous or current invasive or micro-invasive breast cancer. The primary endpoints are changes in treatment recommendations for surgical, radiation and hormonal therapy. Secondary endpoints are identification of key drivers for treatment recommendations, including age, size, grade, necrosis, hormone receptor status and other clinico-pathologic factors. Changes in treatment recommendations will be assessed using McNemar's test with an alpha level of 0.05. Differences in recurrence-free and overall survival will be evaluated by Kaplan-Meier survival analysis using the log-rank test and/or the Cox Proportional Hazards model. A planned early interim analysis based on the first 200 patients has been recently completed and reported. **Results.** As of July 6, 2020, 1,000 patients have been accrued from 49 institutions. Twenty additional institutions are currently in the process of joining the study. We are planning to enroll up to 2,500 patients from up to 100 institutions.

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**Publication Number:** PS13-20

# Bringing diarrhea under CONTROL: Dose escalation reduces neratinib-associated diarrhea and improves tolerability in HER2-positive early-stage breast cancer

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**Background:** Neratinib (NERLYNX®), an irreversible pan-HER tyrosine kinase inhibitor, is used for the extended adjuvant treatment of patients with early-stage HER2-positive (HER2+) breast cancer following adjuvant trastuzumab-based therapy and for patients with HER2+ metastatic breast cancer in the 3rd-line setting. Diarrhea, particularly in the first 1-2 months, is the main tolerability concern with neratinib and is common in the absence of proactive management. In the ExteNET trial, where no mandatory prophylaxis was used, the rate of grade 3 diarrhea was 40%, 34% of patients experienced at least 1 dose hold, and 17% of patients discontinued due to diarrhea. The CONTROL trial previously showed that pre-emptive antidiarrheal prophylaxis (loperamide alone or in combination with budesonide or colestipol) or dose escalation (DE) reduced the rate, severity, and duration of neratinib-associated grade ≥3 diarrhea compared with ExteNET. Currently, antidiarrheal prophylaxis is initiated with the first dose of neratinib and used during the first 2 cycles of treatment (US PI). Updated findings from two DE cohorts in CONTROL are reported.
**Methods:** CONTROL is an international, multi-cohort, open-label, phase 2 study. Patients ≥18 years with stage I-IIIc HER2+ breast cancer were treated with neratinib (240 mg/day for 1 year) after trastuzumab-based adjuvant therapy. Patients were enrolled sequentially into separate cohorts including 2 dose-escalation cohorts: DE1 (neratinib 120 mg/day on days 1-7, 160 mg/day on days 8-14, then 240 mg/day to day 365) + loperamide as needed (PRN); and DE2 (neratinib 160 mg/day on days 1-14, 200 mg/day on days 15-28, then 240 mg/day to day 365) + loperamide PRN. Adverse events were graded per NCI-CTCAE v4.0. Primary endpoint: incidence of grade ≥3 diarrhea. Data cut-off: May 1, 2020.
**Results:** Complete data for DE1 (60 patients) and interim data for the ongoing DE2 (60 patients) are presented. All patients in DE1 were off study and 40 (66.7%) of patients remained on treatment in the ongoing DE2. The median treatment duration for DE1 was 12.0 months (IQR 11.1-12.0) and for DE2 was 3.7 months (IQR 1.6-9.1). Overall, 48% and 57% of DE1 and DE2 patients, respectively, had prior pertuzumab; 0% and 3%, respectively, had prior T-DM1. The majority of patients in both DE1 and DE2 dose-escalated to 240 mg on planned schedule. The incidence of grade ≥3 diarrhea was 13.3% in DE1 and 20.0% in DE2. The median cumulative duration of grade ≥3 diarrhea over the entire 12-month treatment period was 3 days (range 1-6 days) for DE1 and 2 days (range 1-7 days) for DE2. In both DE1 and DE2, 7 patients (11.7%) had at least one dose hold while on study (none during escalation phase in DE1 and 4 during escalation phase in DE2). In both DE1 and DE2, 2 (3.3%) patients discontinued neratinib because of diarrhea (1 during escalation phase in each cohort). Updated data for the DE2 cohort will be presented.

| | **Neratinib dose escalation scheme 1 (n=60)** | **Neratinib dose escalation scheme 2 (n=60)** |
|---|---|---|
| **On neratinib treatment, %** | 0 | 66.7 |
| **Median duration of treatment, months** | 12.0 | 3.7 |
| **Diarrhea, %** | | |
| Grade 1 | 40.0 | 41.7 |
| Grade 2 | 45.0 | 33.3 |
| Grade 3 | 13.3 | 20.0 |
| Grade 4 | 0 | 0 |
| **Discontinuation rate due to diarrhea, %** | 3.3 | 3.3 |
| **At least one dose hold due to diarrhea, %** | 11.7 | 11.7 |

**Conclusions:** Adoption of neratinib DE reduced the incidence, severity, and duration of neratinib-associated diarrhea in CONTROL compared with ExteNET. DE1 was associated with low rates of dose holds and diarrhea-related discontinuations compared with all previously mandated prophylaxis strategies investigated in CONTROL and with ExteNET. Together these results show improved tolerability of neratinib with DE and suggest that DE combined with loperamide PRN may allow patients to stay on neratinib for the recommended period of time.

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# Frequency and spectrum of double*PIK3CA*somatic mutations in metastatic breast cancer patients

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**Background:** *PIK3CA* is the most frequently mutated oncogene in breast cancer (BC). These mutations are considered drivers, indeed, several novel PI3K inhibitors are under evaluation in clinical trials. Recently, alpelisib, a PI3Kα inhibitor, combined with hormonotherapy has improved progression-free survival in mutated advanced luminal BC. As a result, alpelisib has been FDA-approved for this setting.
In some tumors, double PIK3CA mutations in cis demonstrated increasing oncogenicity and sensitivity to PI3Kα inhibitors compared to those tumors with single-hotspot mutations. We aim at assessing the proportion and distribution of *PIK3CA* double mutations of a monocentric genomic screening program to select patients for trials with experimental targeted agents.
**Methods:** We assessed *PIK3CA* mutation in a cohort of 345 consecutive metastatic BC patients diagnosed at Hospital Clínico València-INCLIVA from Jan-13 to Apr-20. Molecular screening of hotspot mutations was performed in primary (36.2%, 125/345) and metastatic tissue (63.8%, 220/345), with either MassArray or Next-Generation Sequencing. Hotspots were selected according to public published databases. To be considered mutant, tumors needed to harbor at least 5% of mutant alleles. Our cohort is enriched in luminal BC, according to clinical trials developing PI3K inhibitors.
**Results**: Patients with *PIK3CA* mutations represented 34.8% (120/345) of the whole cohort. The distribution of BC subtypes was: 80.5% Luminal, 12.0% HER2, and 7.5% triple-negative. The most frequent metastatic site was liver (32.8%) followed by nodes (21.4%), and bone (11.4%).
We detected 27 different hotspots, of which three comprised 73% of all *PIK3CA* mutations: H1047R (32%), E545K (27%), and E542K (14%). Others hotspots were: E545D (4%), H1047L (3%), M1043I (2%), N345K (2%), C420R (1%), E545A (1%), R88Q (1%). Furthermore, 12% *PIK3CA* mutations were unique (<1%): R38C, R93Q, R93W, P104R, G106V, E110K, K111E, R115Q, V344G, N345D, N345S, E418K, P539R, E542Q, E453Q, M1043V, and H1047L.
In our series, 19 patients (15.8%) of all mutant tumors presented a double *PIK3CA* mutation. In almost all double-*PIK3CA* mutated tumors (89%, 17/19), one of the hotspots was either a helical or kinase domain (E542, E545, and H1047). Interestingly, E545D was never detected among tumors with a single-mutations.
**Conclusions:** In our cohort, a wide spectrum of *PIK3CA* mutations was found in patients with metastatic breast cancer, suggesting the clinical relevance of molecular screening. Double *PIK3CA* mutations were identified in 15.8% of mutant tumors and maybe related to higher sensitivity to PI3K inhibitors. E545D mutation was always associated with a second mutation suggesting a different biological behavior.

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# The 21-gene recurrence score in early non-ductal breast cancer: A national cancer database analysis

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**Background**: The Oncotype DX 21-gene expression assay (ODX) is prognostic for recurrence and predictive of chemotherapy benefit in early estrogen receptor-positive (ER+) HER2-negative (HER2-) breast cancer (BCA). Invasive ductal carcinoma (IDC) comprises approximately 80% of BCA. Invasive lobular carcinoma (ILC) is a subtype of BCA with distinct pathologic features, and often has low to intermediate ODX Recurrence Score (RS). We evaluated differences in clinicopathologic characteristics, RS and chemotherapy benefit between IDC, ILC, and carcinomas of mixed histologies (ductal + lobular (DLC), ductal + other (DOC), and lobular + other (LOC)) in the National Cancer Database (NCDB). **Methods**: Female patients (pts) diagnosed between 1/1/2010 and 1/1/2014 with ER+ HER2- BCA, measuring up to 5 cm, with 0-3 involved axillary lymph nodes (LN), treated with definitive surgery as first treatment, and with numeric ODX recurrence score (RS) available were identified from the 2005-2016 NCDB database. Associations between categorical variables were examined using the chi-square test. The Cox proportional hazards model was used to examine the difference in overall survival between histology subtypes while controlling for age, race/ethnicity, RS, tumor size, grade, LN involvement and treatment. **Results**: 77,472 pts met inclusion criteria, 62,395 (83.8%) node negative (N0) and 12,077 (16.2%) node positive (N+). 57,615 pts (77.4%) had IDC; 8693 (11.7%) ILC; 5393 (7.2%) DLC; 2457 (3.3%) DOC; and 312 (0.4%) LOC. DOC and LOC were more common in Black than White pts ($p<0.0001$). IDC was associated with smaller tumor size and high grade disease. ILC was associated with larger tumor size, and was least likely to be high grade ($p<0.0001$). IDC was most likely to have high RS $\geq$26. Presence of lobular histology (ILC, DLC and LOC) was associated with lower incidence of RS $\geq$26. ILC was least likely to have both low RS (0-10) and high RS ($p<0.0001$). Pts with IDC were more likely to receive adjuvant chemotherapy (27.4%) than pts with other BCA types (ILC 19.3%; DLC 21.9%; DOC 20.5%; LOC 19.2%, $p<0.0001$). Overall survival (OS) for IDC, ILC and DOC were similar. DLC was associated with improved OS compared with IDC (HR 0.82, $p=0.02$). Receipt of adjuvant chemotherapy was associated with improved OS in IDC (HR=0.76, $p<0.0001$) but not in ILC (HR=0.99, $p=0.93$), DLC (HR=1.04, $p=0.86$), DOC (HR=0.87, $p=0.71$), or LOC (HR=2.91, $p=0.10$). **Conclusion**: Lobular and mixed BCA histologies have distinct clinicopathologic features compared with IDC, and are less likely to have high RS. OS is similar for early IDC and ILC. Chemotherapy benefit was not seen in ILC or mixed BCA histologies.

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Bc mps a novel breast cancer microphysiological system

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Breast cancer (BC) is among the most commonly diagnosed cancers in women and is the leading cause of malignant death in U.S. women. The triple negative breast cancer (TNBC) subtype is more aggressive and has a poorer prognosis compared to other subtypes. Few treatments exist for TNBC, partially due to limitations of current preclinical models. Current approaches to drug development in TNBC rely on simple, *in vitro* models. However, TNBCs are marked by cellular heterogeneity and complex interactions with the tumor microenvironment. Preclinical data from models that do not capture this complexity have yielded poor translational results. Patient derived xenografts (PDX), human tumors transplanted and grown in mice, are a newer, better model of TNBC. However, there are barriers when using mouse models: mice stroma can take over the PDX tumors, using immunocompromised mice can prevent immune responses and site-specific interaction, and mice are expensive. To overcome these barriers, a translational microphysiological system (MPS) was developed that is capable of maintaining the primary, human breast microenvironment *in vitro*. By seeding these MPS with breast cancer cell lines or tumor explants, we produce breast cancer MPS (BC-MPS).Here, we demonstrate BC-MPS' stability ex vivo; the models remain healthy and viable for at least 2 weeks. This allows for long term studies on breast cancer and human breast tissue interactions. Different BC cell lines have been studied in the system. Initial comparisons between TNBC and ER+ cell lines showed a more aggressive remodeling of the human breast tissue (HBT) ECM by MDA-231 compared to MCF7. These cell lines have remained viable up to 14 days within the system. To examine the ability of BC-MPS to support PDX explant viability ex vivo, the TNBC PDX models 4QAN and 4IC were excised and seeded alone or in the BC-MPS system. After 6 days of incubation, viability was assessed by flow cytometry. Live/dead staining demonstrated that the 4QAN and the4IC PDX tumor explants have better viability in the BC-MPS model compared to being cultured in only media.After demonstrating the model's capabilities of supporting PDX tumor viability, assays were performed to test experimental capabilities of BC-MPS. In addition to tumor architectural changes, cells in the system were treated with paclitaxel, and their response was monitored by luciferase imaging, demonstrating that BC-MPS can be used for drugstudies. BC-MPS is a promising new translational microphysiological system that facilitates studying long term interactions between real human breast tissue and cancer cells as well as the native tumor environment in HBT. The BC-MPS system's ability to support the growth of established cell lines as well as PDXs has been demonstrated. Future studies will focus on developing the model for drug discovery studies.

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Prospective observational study of chemotherapy-induced alopecia after sequential FEC+taxane and the effects of age in breast cancer patients

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***BACKGROUND:*** Chemotherapy-induced alopecia (CIA) is a common and quite distressing adverse effects of chemotherapy. CIA, which can occurr not only in the scalp but also in the eyebrows, eyelashes, and pubic hair, has been known to be a transient condition. However, the degree, pattern, phenotype and processes of CIA are not fully known. CIA might be influenced by many factors, such as the specific chemotherapy regimen, drug doses, the patient's age, and hormonal statuses. There are few detailed observational studies of CIA or of the impact of age on CIA. We performed a prospective observational study to investigate the prevalence and degree of CIA, including CIA of eyebrows, eyelashes, and body, and we examined patient's recovery from CIA, focusing on age-depending effects. ***METHODS:*** We analyzed 68 female Japanese patients with breast cancer (median age 53 years, range 29-76 yrs) who received perioperative adjuvant chemotherapy with fluorouracil/epirubicin/cyclophosphamide (FEC) and taxane. A questionnaire was administered at the point of chemotherapy completion and 6 and 12 months after chemotherapy completion. The data collected by the questionnaire were as follows: the degree of alopecia, including the eyebrows, eyelashes, and body (pubic, leg, and axillary hair), the onset of alopecia, the onset of hair regrowth, and changes in hair characteristics (color, texture, thickness, structure). ***RESULTS:*** CIA occurred in all patients, with severe hair loss irrespective of age. CIA occurred mainly in the scalp but also in the eyebrows, eyelashes, and body for most of the patients. There were significant associations between the patient's age and the onset of hair regrowth in the eyebrows, eyelashes, and body. The onset of eyebrows, eyelash, and body hair growth were significantly shorter in the premenopausal patients. Any hair changes (e.g., thinned diameter, softer texture, curlier structure) were reported by 85.3% of the patients. The changes in hair diameter were significantly more often 'thinner' in the menopausal group compared to the premenopausal group, but the changes in texture, structure, and color were not significantly different between these groups. ***CONCLUSIONS:*** Our results revealed the clinical process of CIA in early breast cancer patients who received standard chemotherapy. Severe CIA occurred in all 68 patients who received FEC and taxane chemotherapy. The present findings provide the first data demonstrating that age was not associated with the degree or incidence of hair loss, but age affected the recovery from CIA. These findings are important for the provision of more accurate information to patients who may undergo chemotherapy, and our data will contribute to the optimal treatment for CIA.

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# Radiation therapy (RT) induced toxicity in advanced breast cancer (ABC) patients treated with CDK4/6 inhibitors (CDK4/6is)

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**Background:** For patients with ABC being treated with CDK4/6is palliative (RT may still be necessary to metastatic sites that are symptomatic or at risk for complications. Although preclinical data suggests synergy between CDK4/6is and RT, clinical data regarding the safety of this combination are conflicting, with some reports of increased toxicity in the radiation field. Our aim was to review the practice regarding holding CDK4/6is during RT and subsequent clinical outcomes at the cancer centre with the largest volume of ABC patients in Canada. **Methods:** Chart review was completed for 313 ER positive and Her2 ABC pts treated with CDK4/6is at the Sunnybrook Health Sciences Centre from 2016 to 2020. All patients who received RT during the course of treatment with CDK4/6is were included in this analysis. Greater than expected toxicity events were defined as higher than grade 1 non-hematological toxicity as per Common Terminology Criteria for Adverse Events during RT or in the 30 days post RT. Descriptive statistics were used for demographics and treatment outcomes. **Results:** Fifty patients received RT to 74 different sites during treatment with CDK4/6is (46 palbociclib and 4 ribociclib). Median age was 56 (41-88) years. Most frequent RT sites were: bone (n=51), brain (n=7), lung (n=4), breast (n=4) and liver (n=3). CDK4/6is were held during RT of 55 sites (37 patients), starting a median of 7 (0-43) days prior to first fraction of RT and restarted a median of 7 (0-71) days after completing the RT. A CDK4/6i was administered concomitantly with RT to 19 sites (15 patients). No greater than expected toxicity was observed in patients for whom the CDK4/6i was held during RT. Among patients who received concomitant treatment, we observed 4 non-hematological adverse events (21%) in organs included in the field of radiation. In combination with palbociclib we observed grade 3 colitis after 30 Gy to hip/pelvis bones, grade 2 esophagitis after 30 Gy to C1-C4 vertebrae and grade 2 enteritis after 30 Gy to the upper femur. In combination with ribociclib one patient developed grade 3 hepatitis after 20Gy to T10-L2 vertebrae. **Conclusions:** This retrospective observational study of 50 patients with advanced ER positive Her2 negative BC treated with CDK4/6is who received palliative RT demonstrated a high rate of radiation toxicity (21%) in those patients for whom the CDK4/6i was given concurrently. Quality improvement work in this area, including practice guidelines, is warranted.

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Targeting the RNA-binding protein HuR to overcome chemoresistance in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) has a much lower 5-year relative survival rate (77%) than the overall breast cancer (91%). Chemotherapy remains the primary choice for the treatment of TNBC. However, patients often develop resistance to conventional chemotherapy after long-term exposure to the chemo-drugs, resulting in poorer prognosis and higher tumor reoccurrence compared to other subtypes of breast cancer. Therefore, understanding and overcoming drug resistance is critical for the successful treatment of TNBC. The Hu antigen R (HuR) or ELAVL1 (embryonic lethal, abnormal vision, Drosophila-like protein 1) plays an important role in chemotherapy resistance. The RNA-binding protein HuR is a posttranscriptional regulator, which can stabilize target mRNAs by binding to U- or AU-rich elements (ARE) mainly in 3' untranslated region (UTR) of mRNAs and upregulate the translation of them. The encoded proteins are implicated in multiple cancer hallmarks, including chemoresistance. The overexpression of HuR, especially accumulated cytoplasmic expression, has been identified to be related to chemoresistance in many types of cancer. We hypothesize that inhibition of HuR function by disrupting its interaction with mRNAs can accelerate the decay of mRNAs and thus reduce the translation of proteins responsible for chemoresistance.Recently, we reported a small molecule HuR inhibitor, KH-3, which potently inhibit HuR function by disrupting the HuR-mRNA interaction. KH-3 can effectively suppress the growth and invasion of TNBC cells in vitro and in vivo. In this study, we aim to verify that HuR is a target for overcoming chemoresistance and evaluate that KH-3 as a HuR functional inhibitor can enhance the efficacy of chemotherapy for TNBC cells. To determine whether HuR inhibition can overcome acquired chemotherapy resistance of TNBCs, we generated MDA-MB-231 sub-cell lines with acquired
resistance against docetaxel or doxorubicin. Our results show that inhibition of HuR by KH-3 could synergize chemotherapy for TNBC in vitro and in vivo. More interestingly, KH-3 treatment could re-sensitize resistant TNBC cells to chemo-drugs, indicating that HuR inhibition can overcome acquired chemoresistance. In the study of mechanism of actions, several pathways and HuR direct target mRNAs are found to be involved in acquired docetaxel and doxorubicin resistance. The detailed molecular mechanisms of how KH-3 sensitizes TNBC to chemotherapy is currently under investigation. This study provides a new strategy to overcome chemotherapy resistance and improve the overall survival rate of patients with TNBC.

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# Molecular fluorescence-guided surgery using Beva800 for the assessment of tumor margins during breast conserving surgery of patients with primary breast cancer (MARGIN-II)

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**Introduction:**The goal of breast conserving surgery (BCS) for early breast cancer (EBC) is to remove the tumor and a surrounding rim of normal tissue, while preserving as much of the normal breast tissue as possible. Incomplete resections are associated with higher rates of surgical re-excision. Repeat surgeries are not only a burden to patients physically but also psychologically and can delay recommended adjuvant therapies. Accurate determination of tumor margins during surgery is therefore critical for successful outcome. Breast cancer tissue produces significantly higher amounts of VEGF-A than healthy tissue. VEGF-A stimulates tumor angiogenesis and is therefore an excellent target for molecular imaging techniques. The fluorescence imaging agent bevacizumab-IRDye800CW (Beva800) is a conjugate of bevacizumab (a humanized antibody targeting human VEGF) and IRDye800CW (a near-infrared fluorescence dye) which binds specifically to VEGF-A. Beva800 provides a potentially highly efficacious approach to imaging specimen and cavity margins during BCS. Herein we present a phase II study that combined Beva800 with the SurgVision Explorer Air camera for intraoperative margin assessment during BCS for EBC.**Methods:**MARGIN II is a multicenter open-label single arm prospective clinical trial aimed at evaluating Beva800 for assessment of tumor margins in women with EBC scheduled for BCS. The study was a within-patient comparison of positive tumor margin rates using BCS standard of care compared to intraoperative assessment with 4.5 mg Beva800 and fluorescence imaging with the SurgVision Explorer Air camera. Patients undergoing neoadjuvant chemotherapy were excluded. All patients received a single intra-venous bolus injection of 4.5 mg of Beva800 three days before surgery. The fluorescent signal was visualized during surgery using NIR fluorescence imaging (700-1000 nm). This wavelength window typically has very low tissue auto-fluorescence (filtering out background noise) and greater tissue penetration depth due to reduced haemoglobin absorption. Standard of care assessment was defined as visual inspection, palpation and, in cases of pre-operative wire marking, specimen sonography or mammography. Beva800 efficacy was determined as the number of patients in which a pathology-confirmed positive margin was identified by fluorescence guided surgery using Beva800 but not by standard of care BCS. The results per patient were divided into two clusters: results after standard of care BCS and results after fluorescence guided surgery, according to their margin status at pathology. The need for re-operation because of involved margins within 30 days after the first BCS and the safety of 4.5 mg Beva800 was assessed.**Results:**The recruitment goal of 40 patients in 5 centers has almost been reached and results of the final analysis will be presented at the meeting.**Conclusion:**Molecular fluorescence-guided surgery using Beva800 has the potential to change the practice of breast conserving surgery by avoiding unnecessary re-operations. This would lead to fewer interventions, a reduced burden on patients through repeat surgery and reduced delay of adjuvant therapies.

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Low levels of interleukin-6 at baseline were significantly associated with improved overall survival of patients treated with eribulin for locally advanced or metastatic breast cancer

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(Background)Eribulin, a non-taxane inhibitor of microtubule dynamics, is a unique chemotherapy agent for locally advanced or metastatic breast cancer (MBC). The treatment has been demonstrated to extend overall survival (OS) without extending progression-free survival (PFS). This effect seems to result from the suppression of epithelial-mesenchymal transition (EMT) and improvement of the hypoxic microenvironment by vascular normalization induced by eribulin, directly or indirectly. In a previous study, we identified that high absolute lymphocyte count (ALC) at the baseline was significantly associated with longer OS in the eribulin group, but not in the treatment of physician's choice (TPC) group, in the phase III EMBRACE trial (Miyoshi et al., Breast Cancer, 2020). These results strongly suggest an association between eribulin efficacy and immune response. Therefore, we focused on serum levels of immune and inflammatory cytokines,which are expected to have greater utility as a predictive factor for eribulin than ALC. Interleukin (IL) 6, an inflammatory cytokine associated with cancerprogression, and soluble interleukin-2 receptor (sIL-2R), a receptor of IL-2 released from various immune cells including T cells, B cells, and natural killer cells, were selected for the investigation. (Patients and methods)A total of 44 patients treated with eribulin for MBC were recruited for the study. We examined the predictive values of IL-6 and sIL-2R in addition to the neutrophil-to-lymphocyte ratio (NLR) and ALC at baseline. The cutoff values of NLR and ALC were set at 3.0 and 1500/μL, respectively. We used the normal ranges of IL-6 (4.0 pg/mL) and sIL-2R (474 U/mL) as cutoff values. (Results)The OS of patients with low NLR (n=28) and high ALC (n=17) were significantly longer than that of patients with high NLR (n=16, p=0.0287) and low ALC (n=27, p=0.0234). There were no significant associations between PFS and NLR or ALC (p=0.0852 and p=0.2231, respectively). Patients with normal IL-6 levels (n=17) had significantly longer PFS (p=0.0023) and OS (p=0.0013) than those with elevated IL-6 levels (n=27). Regarding sIL-2R, patients with normal sIL-2R levels (n=18) had longer OS (p=0.0483) than those with elevated sIL-2R levels (n=26), but their PFS was similar (p=0.2435). Multivariate analysis showed that IL-6 levels were only significantly associated with OS (hazard ratio, 0.093; 95% confidence interval, 0.012-0.720; p=0.0106). There was no significant association between IL-6 levels and NLR or ALC. (Conclusion and discussion)Patients treated with eribulin demonstrated a significantly longer OS if their baseline IL-6 levels were within the normal range. This predictive efficacy for eribulin was more accurate than that of NLR or ALC. As there was no significant association between IL-6 levels and NLR or ALC, IL-6 appears to predict whether the tumor microenvironment is favorable or unfavorable for eribulin treatment, mediated through different mechanisms. Therefore, IL-6 levels may be useful for selecting patients who will benefit from the administration of eribulin in terms of improved OS.

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# Identification of a novel two-microRNA signature for recurrence prediction in HER2 positive breast cancer

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**Background:** HER2+ breast cancer (BC) is a heterogeneous disease. Despite the novel targeted therapies against HER2, 20% of patients relapse. In this context, the identification of prognostic and predictor biomarkers is needed.MicroRNAs are involved in BC development and prognosis. We aim at assessing the prognostic significance of two micro-RNAs (named as A and B) in HER2+ BC tissue, to propose signature to predict relapse in this setting of patients.**Methods:** This study was conducted in a cohort of 46 non-consecutive HER2+ BC patients diagnosed at Hospital Clínico València-INCLIVA. All BC patients received standard treatment for localized disease. RNA was isolated from formalin-fixed paraffin-embedded primary tumor and retro-transcribed to cDNA. MicroRNA expression levels were measured by real-time qPCR and results were normalized according to the expression of housekeeping mir-16 miRNA.Non-parametric Mann-Whitney U test was used to ascertain the statistical significance of differences in miRNA expression levels between disease-free and relapse. Receiver operator characteristics (ROC) curves were constructed and AUC, accuracy, specificity and sensitivity, were calculated as a biomarker performance parameter. The best cutoff value was established based on the highest value obtained in ROC curve analysis according to the maximization of the sum of sensitivity and specificity. Kaplan-Meier curves were plotted for disease-free survival (DFS) based on the best cutoff value. As both microRNA showed high correlation (r=0.85), a genetic signature was developed using Principal Component Analysis (PCA) and extracting the first component. MicroRNA targeted genes were downloaded from miRTarBase (release 7.0). Cytoscape (v3.8.0) and ClueGo (v2.5.6) and were used to perform functional enrichment analysis with the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database. To select significant terms/pathways, p-values were adjusted by the Benjamni-Hochberg method ($p<0.05$). **Results:** The expression of both microRNA-A and B was higher in the primary tumor of those patients who relapsed after treatment compared to those free of disease (p= 0.003 and 0.0002, respectively). ROC curves demonstrated that microRNA-A and B might discriminate those HER2+ BC patients who relapse. MicroRNA-A predicts relapse with an AUC 0.740, sensitivity of 0.810, specificity of 0.583 and accuracy of 0.689, and microRNA-B presented an AUC 0.821, sensitivity of 0.810, specificity of 0.750, and accuracy of 0.778. The survival analysis showed that microRNA-A and B strongly predicted shorter DFS (p= 0.014 and 0.0012, respectively).Two-microRNA signature combining (PCA1= 99.4% absorbed variance) microRNA-A and microRNA-B expression levels had high performance in discriminating relapsed from non-relapsed HER2+ BC patients (AUC 0.748, accuracy 0.689, sensitivity 1, specificity 0.417). Signature predicted DFS (p= 0.009). Functional enrichment analysis returned 55 significant pathways. Of these, important pathways related to tumorigenesis and response to treatment were enriched. Interestingly, P53 pathway, apoptosis, and cell cycle were in the top 5 enriched pathways. **Conclusions:** We demonstrated the value of microRNA A and B as potential prognostic biomarkers. High expression was related to poor prognosis in over cohort of HER2+ BC patients. Both microRNAs were able to strongly discriminate patients who will relapse and predict shorter DFS. Moreover, our signature was able to predict the outcome, suggesting a potential prognostic role at diagnosis. Both microRNAs are related to important biological pathways associated to BC progression. Further investigations to optimize the micro-RNA signature are on-going.

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# Retrospective analysis of time to progression intracranially in HER2+ breast cancerpatients with brain metastases who receive treatment with radiation

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Human epidermal growth factor receptor 2 (HER2) positive (+) breast cancer is a disease with distinct clinicopathological features. Survival for women with HER2+ disease has increased with the development of novel systemic therapeutic agents, however the brain is increasingly reported as the first site of relapse. As patients with HER2-positive breast cancer live longer, CNS progression after radiation therapy and / or surgery is an emerging clinical challenge. The average progression free interval intracranially is unknown for women who receive radiation for brain metastases while on modern HER2 targeted therapy. Multiple novel systemic agents are under investigation for the treatment of HER2 positive breast cancer metastatic to the brain. In order to establish a historical control for early phase clinical trials, understanding this time to progression is critical. In our retrospective chart review, we sought to determine the time to progression intracranially for women with HER2+ breast cancer who receive CNS radiation and/or surgery while on modern HER2 targeted systemic therapy. We present preliminary results from our review of 48 patients with HER2+ breast cancer with brain metastases treated at two academic referral centers between 2010-2017. 36 of these patients received some form of local therapy for brain metastases. Mean age at the time of diagnosis with primary breast cancer was 52, with a mean age of 55 at the time of diagnosis of brain metastases. The minority of patients (n=16) were stage IV at the time of their initial diagnosis. Standard of care systemic treatment was given in 43/48 cases. Mean length of time from the diagnosis of the primary breast cancer to the diagnosis of brain metastases was 34.6 months, including 3 patients diagnosed at initial presentation and at the other extreme, 2 patients diagnosed 9 years after their primary diagnosis of cancer. Of the patients who received treatment for brain metastases and for whom data was available (n=33), mean time from first treatment for brain metastases to first brain recurrence was 8.24 months (range: 1 to 24 months). 7 patients (21%) recurred within 3 months. In 9 patients mortality data was available. Mean time from treatment to death was 20 months (range 1 - 58 months). For patients who underwent surgery alone as primary treatment, mean time until first recurrence was 7.1 months (n=14), compared with a mean of 7.8 months for patients who received WBRT (n=26). Patients who received both surgery and radiation as a primary treatment had a mean time from first treatment to recurrence of 11.5 months (n=4). Only 34% of patients changed systemic treatment after the diagnosis of brain metastases. 5 patients had brain metastases as their only site of measurable disease. Only 1 of these patients had a change in systemic treatment after the diagnosis of brain metastases. These results suggest that the time from initial local treatment for brain metastases to recurrence is devastatingly short. Future clinical trials in metastatic HER2+ breast cancer should consider the impact novel therapeutics have on brain metastases in addition to overall and progression free survival. These data provide a historical reference for evaluating the impact of novel therapies on HER2-postive brain metastases.

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# A dose escalation study of the novel oral SERD-ZN-c5 in women with ER-positive, HER2-negative advanced/metastatic breast cancer

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**Background:** ZN-c5 is an orally bioavailable selective estrogen receptor degrader (SERD) that binds potently to the estrogen receptors alpha and beta. It shows improved activity over fulvestrant in human tumor xenograft models and activity in tumor models that are resistant to tamoxifen. This is a Phase 1/2, open-label, multicenter, dose-escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), and clinical activity of ZN-c5 in subjects with advanced/metastatic estrogen receptor (ER) positive/ human epidermal growth factor receptor (HER2) negative breast cancer, both as monotherapy and in combination with palbociclib. The results from the ongoing monotherapy dose escalation are reported. **Methods**: Single agent ZN-c5 is being evaluated at sequentially escalating doses starting at 50 mg/day, administered orally, once daily (QD). The endpoints are to determine a maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D), preliminary clinical activity and to characterize the PK profile. Subjects must be intolerant to or have breast cancer refractory to established therapies and to have received up to 2 prior lines of chemotherapy for the treatment of advanced breast cancer. Subjects must have a documented prior response to endocrine therapy for advanced/metastatic disease (SD, PR, or CR) lasting > 6 months or disease recurrence after at least 24 months of adjuvant endocrine treatment. **Results:** A total of 15 female subjects (median age 57 years, range 51 - 89 years) were enrolled across 5 cohorts (3 subjects/dose level). The dose levels were 50, 75, 100, 150, and 300 mg/day. The subjects had a median of 4 prior therapies for advanced/metastatic disease, with a median of 3 prior hormonal-based therapies and a median of 1 prior chemotherapy. Eleven of 15 subjects (73%) received prior fulvestrant. The cut off-date for this analysis was 30 June 2020. There was no increase in incidence or severity of TEAEs with increase in dose level. The most frequent TEAEs reported in > 1 subject were nausea (33%), arthralgia, cough, musculoskeletal pain and vomiting (20% each), alanine aminotransferase increased, anemia, back pain, blood alkaline phosphatase increased, breast pain, diarrhea, fatigue, gamma-glutamyl transferase increased, headache, hypophosphatemia, myalgia and skin mass (13% each). Grade 3 events were COVID-19, hypercalcemia, arthralgia, back pain musculoskeletal chest pain, pain in extremity and hypertension, none were deemed related to ZN-c5. Grade 4 events were not reported. No bradycardia was observed. A single subject reported a Grade 1 visual field defect, not deemed related to ZN-c5. No DLTs were reported. ZN-c5 demonstrated a best response of stable disease (SD) in 10/15 subjects (66.5%), while progression of disease (PD) was reported in 5/15 subjects (33.5%). The clinical benefit rate (CBR, SD ≥ 24 weeks) was 40%. In addition, the progression free survival (PFS) was a median of 3.8 months (95% [CI], 1.6 to 6.3). The preliminary PK was characterized by fast absorption with median $T_{max}$ values of 1 - 2 hrs. The exposures were approximately dose-proportional at the dose levels of 50 - 100 mg and less than dose-proportional between 100 - 300 mg. No ZN-c5 accumulation after 15 days of QD dosing was observed. The estimated mean elimination half-lives ranged between 11 - 18 hrs. **Conclusion:** This monotherapy dose escalation study demonstrates that ZN-c5 is very well-tolerated and has promising clinical activity in patients with ER+/HER2-negative advanced breast cancer who have disease that progressed on standard therapies. The trial with ZN-c5 in monotherapy and with palbociclib is ongoing and the RP2D has not been determined yet.

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Response to a modified whole tumor cell targeted immunotherapy in patients with advanced breast cancer correlates with tumor grade

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**Background:** SV-BR-1-GM is a GM-CSF transfected breast cancer cell line, exceptional for having antigen-presenting capability and expressing both HLA I and II. The parent cell line, SV-BR-1, was derived from a patient with grade II (moderately differentiated) breast cancer. We report molecular characterization of SV-BR-1-GM, noting it retains features of a grade II tumor, and report enhanced disease control in patients with grade I or II breast cancer.**Methods:** SV-BR-1 and SV-BR-1-GM were characterized molecularly using RNAseq and proteomic analyses. We treated 23 evaluable patients with recurrent and/or metastatic breast cancer refractory to standard therapy. The SV-BR-1-GM regimen included cyclophosphamide 300 $mg/m^2$ 2-3d prior to intradermal injection of SV-BR-1-GM (20-40x$10^6$ cells divided into 4 sites) and IFNα into the inoculation sites (10,000 IU/site) about 48 and 96 hours subsequently. Cycles were q2 weeks x3 then qmo x 3 (clinical trial NCT03066947). Eleven patients were treated with the above regimen in combination with a PD-1 inhibitor (pembrolizumab or INCMGA00012) (clinical trial NCT03328026). Disease response was evaluated radiographically q3 mo and as clinically indicated. **Results:** To estimate the tumor grade represented by the SV-BR-1-GM cell line, we developed a score we refer to as Relative Molecular Grade (RMG). SV-BR-1-GM is most similar to the MDA-MB-468 cell line (RMG of 52.1), which was classified as Basal A phenotype. Basal A cancers are less aggressive than Basal B but more aggressive than Luminal, suggesting that SV-BR-1-GM may have retained features of a grade II breast cancer. We also noted that SV-BR-1-GM expresses both Class I (HLA-A, B & C) and Class II (HLA-DR and -DP) molecules, and that the HLA-DR expression is enhanced by treatment with IFNγ. SV-BR-1-GM expressed 31 genes which are overexpressed in breast cancer, 8 cancer-testis antigens and 3 genes expressed in breast tissue. In 30 patients treated with the SV-BR-1-GM regimen (19 with the SV-BR-1-GM regimen alone, 4 who began on the SV-BR-1-GM regimen and transitioned to combination with a PD-1i, and 7 with combination therapy alone) there were 7 with grade II breast cancer and 1 with grade I breast cancer (Table). These patients were heavily pre-treated with an average of 10 prior regimens. While only one patient with grade III cancer showed disease control, 75% of the patients with grade I or II tumors showed disease control. Patients remained on study for up to 259 days.**Conclusions:** SV-BR-1-GM appears to retain characteristics of a moderately differentiated breast cancer, expresses multiple potential tumor antigens, and can elicit disease control especially in patients with grade I and II breast cancer.

Table

| | Patients with Grade I/II Tumors | | |
|---|---|---|---|
| Characteristic | SV-BR-1-GM Regimen Alone(n=6) | SV-BR-1-GM Regimen + PD-1i(n=3) | All Patients(n=8) |
| Age | 64 ± 7 | 67 ± 4 | 65 ± 7 |
| Mean Prior Systemic Regimens | 6 (range 1-20) | 15 (range 14-15) | 10 (range 1-20) |
| % ER/PR + | 80% | 100% | 86% |
| % Her2/neu + | 0% | 33% | 14% |
| % Triple Negative | 20% | 0% | 14% |
| Delayed-type Hypersensitivity | 83% | 100% | 88% |
| Disease Control Rate* | 67% | 100% | 75% |
| Days on Study (Range) | 94 (32-181) | 189 (133-259) | 141 (32-259) |

•Includes CR, PR, SD (including minor responses and mixed responses)

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# Identification of pathogenic mutations in otherwise unaffected patients through the CARE program

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**Introduction** Approximately one out of eight women are diagnosed with breast cancer in their lifetime. Women are recommended to begin annual mammograms at age 40 unless they are high-risk risk for breast cancer based on risk algorithms or positive germline mutations. Unfortunately, genetic testing and risk counseling are often not offered until a cancer diagnosis is already made. It is estimated that 5-10% of the general population has genetic predisposition to cancer. **Purpose** We established the Comprehensive Assessment, Risk & Education (CARE) Program at our mammogram center. Offered in partnership with Ambry Genetics, the CARE Program's goal is to facilitate unaffected women in obtaining genetic testing and risk-counseling who otherwise may not have access to these services. **Methods** Patients undergoing a screening mammogram were given a tablet with a preprogrammed Progeny questionnaire. This questionnaire included questions on the patient's gynecological history and family history. It calculates a Tyrer-Cuzick risk score and assesses National Comprehensive Cancer Network (NCCN) genetic testing criteria. Patients qualifying for genetic testing received pretest counseling by video and were offered genetic testing the same day as their mammogram appointment. Our genetic counselors performed follow-up counseling for patients receiving positive test results. Patients testing negative or inconclusive received a letter generated by Ambry. Our CARE program began on June 7$^{th}$, 2019, and data was assessed through July 6$^{th}$, 2020. **Results** 1,065 women met NCCN criteria for genetic testing. Of those women, 464 (43.6%) proceeded with testing, 387 (36.3%) declined testing and 214 (20.1%) were not able to obtain day-of genetic testing due to operational/personnel limitations. Of those who submitted tests, 403 (86.9%) completed testing and 61 tests were cancelled due to out of pocket costs or patient preference. Of the 403 patients who completed testing, 262 (65%) tested negative, 105 (26%) tested inconclusive and 35 (8.7%) tested positive. Positive test results were found in 15 genes (Table 1). **Clinical Impact** Over 13 months, we identified 35 patients at increased risk for cancer based on positive genetic test results. Based on these results, 6 (17%) patients were offered prophylactic surgeries, 16 (45.7%) were offered breast MRIs and enrollment in our high-risk breast clinic, 14 (40%) were offered increased colonoscopies and 9 (25.7%) were offered pancreatic screening based on family history. All patients were offered family variant testing. **Conclusion** Our experience integrating a screening questionnaire into our mammogram clinic shows that 44% of patients meeting NCCN criteria agree to do day of testing. Of those completing testing, 9% tested positive. This result is consistent with the national expected positive rate. Our CARE Program offers unaffected patients an opportunity to be tested in a comfortable low stress setting through the mammography suite. These patients and their families will now benefit from cancer prevention options that may not have been offered to them had they not been pre-emptively screened by our program.

Table1. Positive test results for 35 patients.

| Mutation | Number of patients identified (%) |
|---|---|
| CHEK2 | 9(25.7) |
| MUTYH | 5(14.2) |
| HOXB13 | 4(11.4) |
| ATM | 3(8.6) |
| APC | 2(5.7) |
| BARD1 | 2(5.7) |
| PALB2 | 2(5.7) |
| BRCA2 | 1(2.9) |
| BRIP1 | 1(2.9) |
| MRE11A | 1(2.9) |
| MSH2 | 1(2.9) |
| MSH6 | 1(2.9) |
| RAD50 | 1(2.9) |
| RAD51D | 1(2.9) |
| TP53 | 1(2.9) |

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# High expression of MicroRNA-223 indicates better prognosis in triple negative breast cancer

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**Background:** MicroRNAs (miRNAs) can influence many biological processes and also show promise as biomarkers for cancer. Few researches have focused on the expression of microRNA-223 (miR-223) and its precise role in breast cancer (BC). We aimed to examine the expression level of miR-223 and further explored the prognostic value in BC.**Methods:** Tissue microarray-based miRNA detection in situ hybridization with LNA probe was used to detect miR-223 expression in 450 BC tissue. Overall survival (OS) and disease-free survival (DFS) were compared between two groups using the Kaplan-Meier method and Cox regression model.**Results:** Better OS and DFS were observed in the high-miR-223 expression patients compared to those of low expression patients (P < 0.0001 and P = 0.017, respectively), especially in the triple-negative breast cancer (TNBC) subtype (P = 0.046and P < 0.001, respectively). Combined with the univariate and multivariate Cox regression analysis, TNM stage (p = 0.008), molecular subtype (p =0.049) and miR-223 (p < 0.001) were independently linked to OS and DFS. External validation was performed in METABRIC and TCGA database via online webtool and consistent with the data above.**Conclusions:** This study provided evidence that high-miR-223 expression at diagnosis was associated with better DFS and OS for BC, especially for the TNBC subtype. miR-223 is a valid and independent prognostic biomarker in BC.

**Table Univariate and multivariate survival analysis for disease-free survival**

| | **Univariate** | | | **Multivariate** | | |
|---|---|---|---|---|---|---|
| **Variable** | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| **Age** | | | 0.594 | | | |
| ≤40 vs >60 | 1.351 | 0.626-2.914 | 0.444 | | | |
| 40-60 vs >60 | 0.994 | 0.548-1.803 | 0.984 | | | |
| **Menopausal status** | | | | | | |
| pre vs post | 0.737 | 0.487-1.113 | 0.147 | | | |
| **Differentiation** | | | | | | |
| II vs III | 0.730 | 0.457-1.164 | 0.186 | | | |
| **TNM stage** | | | 0.008 | | | **0.008** |
| II vs I | 1.421 | 0.860-2.346 | 0.170 | 1.485 | 0.887-2.485 | 0.132 |
| III vs I | 2.758 | 1.446-5.259 | 0.002 | 2.858 | 1.469-5.563 | 0.002 |
| **Molecular subtype** | | | 0.194 | | | **0.049** |
| Luminal B vs Luminal A | 1.106 | 0.580-2.107 | 0.760 | 0.813 | 0.415-1.593 | 0.546 |
| HER2+ vs Luminal A | 0.986 | 0.497-1.956 | 0.967 | 0.701 | 0.337-1.458 | 0.342 |
| Triple-negative vs Luminal A | 1.626 | 0.930-2.843 | 0.088 | 1.493 | 0.849-2.626 | 0.164 |
| **MicroRNA-223** | | | | | | |
| low vs high | 3.960 | 2.201-7.126 | <0.001 | 3.789 | 2.098-6.843 | **<0.001** |

Abbreviations: CI, confidence interval; HR, hazard ratio.

The covariates in the Cox model were all categorical variables, and the adjusted *p* value and HR were derived from the model.

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# Characterization of the immune microenvironment in ductal carcinoma *in situ* of the breast

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*Background* Ductal carcinoma *in situ* (DCIS) is considered a low-risk disease of the breast. Current increases in its incidence have resulted in many women either being under- or over-treated due to our limited findings on independent prognostic and predictive biomarkers. The Van Nuys Prognostic Index, based on tumor size, margin status, grade and age, is one tool used in treatment decisions. Patients with a low score show no significant benefit from radiotherapy, in contrast to those with an intermediate score, while patients with high scores should be considered for mastectomy. In contrast, for invasive ductal carcinoma (IDC) of the breast there is a strong consensus for the prognostic and predictive value of tumor infiltrating lymphocytes (TIL). As very little is known about TIL in DCIS, the goal of this study is to fully characterize the immune infiltrate and compare it to IDC, examine differences in the balance between effector and regulatory subpopulations and potentially discover new biomarkers for risk stratification.
*Material and Methods* Fourteen patients were prospectively enrolled at the St. Luc hospital in Brussels, including 4 pure DCIS, 5 mixt DCIS and IDC, and 5 normal breast tissues. Formalin-fixed paraffin-embedded sections were stained with three fluorescent multiplex immunohistochemistry (mIHC) panels that combined antibodies to CD45, CD4, CD8, CD20, FOXP3, CD68, GZMB, PD-1, Ki67 and cytokeratin. InForm® Tissue Finder™ software and PhenoptrReports (Akoya Biosciences®) were employed for TIL quantification and spatial distribution. Freshly resected DCIS tissues were used to isolate tumor-infiltrating CD4 and CD8 T cells for single cell RNAseq analysis to determine the T cell clonotypes present (A. Devaux's poster)
*Results* Our analyses reveal the DCIS stroma has a significant immune infiltrate dominated by $CD4^+$ helper T cells and B cells (140 and 115 cells/$mm^2$, respectively) followed by $CD8^+$ cytotoxic T cells (72 cells/$mm^2$), regulatory T cells (Treg) (27 cells/$mm^2$) and to a lesser extent macrophages (23 cells/$mm^2$). The immune pattern in DCIS is similar to IDC except there are fewer macrophages in the tumor areas and Treg increase in the stroma. Tumor areas are generally less infiltrated than the stroma but some DCIS cells are in direct contact with T cells and macrophages. Spatial distribution analysis within a radius of 30 µm confirms that Treg are in close proximity to the DCIS cells and in the proximity of $CD4^+$ helper and $CD8^+$ cytotoxic T cells. Moreover, proliferating $GZMB^+$ cells, mainly $CD8^+$ cytotoxic T cells, were observed in direct contact with DCIS cells. Only one patient out of 4 had $PD1^+$ TIL in the stroma. A comparison of pure and mixt DCIS reveals lower stromal infiltration by T and B cells in the former, which is also associated with an increase in macrophages. Finally, the abundance of stromal TIL was frequently organized in tertiary lymphoid structures (TLS), composed by a B cell follicle surrounded by a T cell zone containing both $CD4^+$ helper and $CD8^+$ cytotoxic T cells. TLS were characterized by the presence of proliferating B cells and $PD1^{high}$ T follicular helper cells. $FOXP3^+$ and $GZMB^+$ cells were also observed in the T cell zone.
*Conclusions* Examination of the immune infiltrate in DCIS shows an abundance of helper T cells, B cells and active cytotoxic T cells in association with stromal TLS. These observations reveal an active tumor immune microenvironment in DCIS and suggest that the immune response plays an active role in DCIS pathogenesis.

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Patient reported outcomes of newly diagnosed women with breast cancer enrolled in a digital health coaching program

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**Background**: With breast cancer (BC) treatment primarily managed in the ambulatory setting opportunities exist to provide support services to individuals that enhance their ability to manage side effects of treatment and their overall health outcomes. The aim of this randomized control trial was to evaluate the effect of a digital health coaching program on patient reported outcomes (PROs) and experience of women with BC undergoing chemotherapy treatment in the ambulatory setting.
**Methods**: Women newly diagnosed with BC were randomized to receive either a 3-month digital health coaching intervention or standard of care support services provided by the treating hospital. PROs were captured at baseline and monthly for 3 months. The primary objective compared Patient Reported Outcomes Measurement Information System (PROMIS) Global Health Scale scores between arms at the 3-month assessment. Secondary objectives evaluated the PROMIS physical and mental subscales, and the MD Anderson Symptom Inventory (MDASI) for differences between arms and over time. Summary statistics were used to describe demographic and baseline clinical characteristics by arm. Linear mixed effects models were used to assess PROMIS and MDASI over time. Statistical analysis were performed using Stata/MP v15.0.
**Results**: A total of 210 subjects were randomized to the control arm and 208 to the digital health coaching intervention. A significant time (Table 1) but not intervention effect was observed.
The mean (SD) of the PROMIS physical health t-score for the control arm was 43.9 (4.7) and 44.1 (4.3) for the intervention arm (p = 0.699). The mean (SD) of the PROMIS mental health t-score for the control arm was 45.3 (5.4) and 45.1 (5.0) for the intervention arm (p = 0.742). The mean (SD) of MDASI severity score for the control arm was 2.4 (1.6) and was 2.5 (1.8) for the intervention arm (p = 0.715). The mean (SD) of the MDASI interference for the control arm was 2.6 (2.3) and was 2.8 (2.3) for the intervention arm (p = 0.633).
Of 208 individuals randomized to the intervention, the majority (n=195; 94%) preferred engagement by phone, email and text. Participants averaged 9.17 calls with a mean duration of 13.04 minutes per call, 12.3 outbound texts to and 3.8 inbound texts from the participant, and a 47% email open rate over the course of 12-weeks.
**Conclusions**: Study results suggest that while digital health coaching did not produce a statistically significant improvement in PRO over the course of the first 3 months of treatment, it did result in engagement that could be leveraged during and potentially beyond primary treatment for women with BC. PRO scores reflected minimal symptom burden and high global health at baseline before the start of treatment, which predictably declined over the course of treatment. Results informed the development of a currently enrolling expansion trial for individuals with diverse treatment types to evaluate which population receives the greatest
benefit. Given the need for increasing engagement using telehealth solutions, the optimization of digital health coaching for individuals with BC is timely and increasingly relevant to promote optimal health self-efficacy and PROs.
Table 1. Linear Mixed Models of PROMIS and MDASI Scores Over Time

| **PROMIS** | **Effect** | **Beta** | **95% LB** | **95% UB** | **p-value** |
|---|---|---|---|---|---|
| Physical | Time | | | | **<0.001** |
| | 30 | -0.88 | -1.50 | -0.26 | **0.006** |
| | 60 | -0.74 | -1.39 | 0.09 | **0.026** |
| | 90 | -1.88 | -2.53 | -1.22 | **<0.001** |
| | Intervention | 0.12 | -0.73 | 0.98 | 0.980 |
| Mental | Time | | | | **<0.001** |
| | 30 | -3.53 | -4.22 | -2.85 | **<0.001** |
| | 60 | -3.94 | -4.66 | -3.22 | **<0.001** |
| | 90 | -4.64 | -5.36 | -3.92 | **<0.001** |
| | Intervention | -0.25 | -1.13 | 0.63 | 0.583 |
| **MDASI** | **Effect** | **Beta** | **95% LB** | **95% UB** | **p-value** |
| Severity | Time | | | | **<0.001** |
| | 30 | 1.17 | 0.99 | 1.35 | **<0.001** |
| | 60 | 0.99 | 0.81 | 1.18 | **<0.001** |
| | 90 | 1.26 | 1.06 | 1.45 | **<0.001** |
| | Intervention | -0.08 | -0.33 | 0.16 | 0.499 |
| Interference | Time | | | | **<0.001** |
| | 30 | 1.32 | 1.08 | 1.58 | **<0.001** |
| | 60 | 1.19 | 0.92 | 1.46 | **<0.001** |
| | 90 | 1.56 | 1.29 | 1.83 | **<0.001** |
| | Intervention | -0.09 | -0.42 | 0.24 | 0.587 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS16-21

# Apc control of taxane resistance in breast cancer

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Adenomatous Polyposis Coli (APC) is a multi-domain tumor suppressor with multiple binding partners, including β-catenin, axin, and microtubules. APC is lost in many epithelial cancers, including up to 70% of sporadic breast cancers, with a tendency towards triple negative breast cancers (TNBCs). We previously demonstrated that APC knockdown in the human TNBC cell line, MDA-MB-157, resulted in resistance to Paclitaxel (PTX), a chemotherapeutic agent of the Taxane family that inhibits mitotic progression. Further studies have confirmed this finding in the MDA-MB-231 cells with CRISPR-mediated APC knockout. To understand the mechanism(s) by which APC controls response to PTX, we have taken two approaches. We first performed an unbiased analysis of transcriptomic changes downstream of APC loss to identify potential therapeutic targets to overcome PTX resistance. In this, a group of transcripts involved in regulation of the cell cycle were identified, including LBH, GLI1, RGS4, and NUPR1. These results have been validated by qRT-PCR and western blot, leading to studies in the laboratory to investigate their specific effects on the response to PTX in breast cancer. Along with the broad exploration studies, molecular studies have focused on whether APC controls expression of cell cycle proteins, leading to PTX resistance. While we observed changes in multiple cell cycle proteins, our focus was on the G2/M transition, given that both PTX and APC impact microtubule dynamics and the G2/M phase of the cell cycle. We examined the effect of APC loss on expression of G2/M proteins, identifying a significant upregulation of CDK1 in $APC^{KD}$ cells. Despite no changes in phosphorylation status of CDK1, we found that Cyclin B1 and CDK1 are only complexed in the $APC^{KD}$ cells, suggesting increased activation. Further studies showed that while the majority of CDK1 and Cyclin B1 are localized to the cytoplasm, there is a small amount in the nucleus. Based on these findings, we sought to investigate whether PTX sensitivity would be altered in response to CDK1 inhibitor, RO-3306. We have shown that PTX resistant $APC^{KD}$ cells are more sensitive (IC50 = 25.5uM) to RO-3306 compared the parental control (IC50 = 78uM). Future studies will use combination and sequential treatments to monitor PTX response *in vitro* and *in vivo*. Combined, these studies are elucidating the mechanisms by which loss of APC controls sensitivity to PTX in TNBC, with the long-term goal of designing treatment regimens to improve patient health and survival.

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Comparison of risk assessment in primary ER+, HER2- Breast Cancer in a real-world data set: Classical pathological parameters vs. 12-gene molecular assay (EndoPredict)

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Background: Risk assessment on molecular level is becoming more common in modern pathology to determine the recurrence risk for patients diagnosed with estrogen receptor positive (ER+), HER2 negative (HER2-) breast cancer (BC). The gene expression test EndoPredict (EP) was trained and validated to predict a 10-year risk of distant recurrence to support therapy decision regarding endocrine therapy alone or in combination with chemotherapy. The EP test provides the 12-gene molecular score (12-gene MS) and the EPclin-Score (EPclin) combining the molecular score with tumor size and nodal status. In this project we investigated the correlation of 12-gene MS and EPclin scores with classical pathological markers like tumor grading and proliferation. Methods: Retrospectively, we investigated EP test results in a total of 1652 patients tested in clinical routine from 2017 to 2020 at the Institute of Pathology, Charité University Hospital, Berlin. Consecutive cases with valid EP test result and available tumor grading and proliferation (Ki67) status were included in the dataset. 12-gene MS and EPclin were classified as low or high risk based on validated cutoff values at 5 and 3.32867, respectively. Ki67 cut-offs were set according to St. Gallen guidelines at 20% for binary classification (Bustreo et al., 2016) and Federal Joint Committee (G-BA) guidelines, using 10% and 30% for three classes (low, intermediate, high). Results: In our dataset with 1652 cases, 1242 (75.2%) cases were detected as 12-gene MS high risk and 1026 (62.1%) as EPclin high risk score. Mean Ki67 expression was 17.5% (95%CI 16.9 - 17.9). As expected we found a strong association between risk scores and clinical parameter with p-values ≤ 0.001: In the Ki67 binary low group (N=1203, Ki67≤20%) 695 (57.8%) patients had a EPclin high risk score while in the Ki67 binary high expression group (>20%) still 118 (26.3%) patients had a EPclin low risk score. Similar results were found using three Ki67 classes: In the Ki67 low (N=557, <10%) group 299 (53.7%) patients had EPclin high results and in the Ki67 high (N=101, >30%) group, 28 (27.7%) patients were classified as EPclin low (p<0.001). Regarding tumor grading we observed a correlation between poorly differentiated breast cancer (G3) and a higher EPclin risk score. Nevertheless, in Grade 1 tumors (N=140) 57.9% of patients had a EPclin high risk score (p=0.001). In comparison, in 25% (N=46) of G3 cases EPclin risk score was low. Similar results were seen using 12-gene-MS, not shown here. Conclusions: In this study we could show that EP risk scores are distributed differently among Ki67 expression groups, especially in Ki67 low (<10%) and high (>30%) tumors with a substantial proportion of patients with EPclin high risk results in Ki67 low tumors and vice versa. Our research group is currently collecting a long time follow up of all patients.

**Publication Number:** PS1-22

# The oncological safety of lipofilling after breast cancer surgery: A meta-analysis

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***INTRODUCTION*** Autologous fat grafting (AFG) for the purpose of breast reconstruction presents difficulties during follow-up radiological exams and the oncological potential of grafted fat is uncertain. Coleman et al in 2007 confirmed that, provided a rigorous protocol is respected, the fatty tissue could be transferred under good conditions and would not interfere with mammographic follow-up, although the issue remains controversial about the oncological safety. This study aims to analyze the oncological safety of lipofilling through a meta-analysis of the current literature. ***METHODS*** We conducted a meta-analysis to evaluate the oncological safety of AFG after breast cancer (BC) surgery. We reviewed the literature published until 07/05/2020. The outcomes were overall survival (OS), disease free-survival (DFS) and local recurrence (LR). We included RCTs, cohort studies, case-control studies that evaluated women with BC diagnosis who undergone surgery followed by reconstruction with AFG. This review was performed in accordance with the PRISMA guidelines and we searched the electronic databases of Medline, EMBASE and LILACS, using the MeSH terms for AFG and BC. There was no language restriction. Methodological quality was assessed using the Downs and Black instrument and evidence quality by GRADE. We synthesized data using the inverse variance method on the log-HR scale for time-to-event outcomes using RevMan. We assessed the presence of statistical heterogeneity using the $Chi^2$ statistic and we investigated its extension by the use of $I^2$ statistic. ***RESULTS*** We identified 624 references. Of these, 16 studies fulfilled our eligibility criteria and were included. Funnel plot analysis revealed no publication bias. There were 8667 patients included and their mean age was 49 years. The breast surgery indications were invasive breast carcinoma (66.1%), carcinoma *in situ* (18.4%) and prophylactic reasons (15,5%). Ten out of 16 studies described the technique used to perform the AFG as Coleman's. In 9 out 16 studies there was no difference in adjuvant treatment between groups, two studies do not mention if there was any difference and in 4 studies there were different adjuvant treatments in control and intervention arms. Quality assessment resulted in 11 studies being considered 'good', 4 studies were considered 'fair' and 1 study was considered poor. The HR could be extracted from four studies and an increase of OS for lipofilling group was detected with high heterogeneity (HR 0.47, 95% CI 0.32 to 0.7, p=0.0002, 2331 patients, $I^2$= 84%, high certainty evidence). Funnel plot analysis indicated a high risk of publication bias from one study, Krastev et al, which included 587 patients. The analysis excluding this article found no difference in OS between lipofilling group and control and publication bias was not detected (HR 0.9, 95% CI 0.53 to 1.54, p=0.71, 1744 patients, $I^2$= 58%, high certainty evidence). The HR for DFS could be extracted from six studies and no difference was found between lipofilling group and control (HR 1.01, 95% CI 0.73 to 1.38, p=0.96, 2755 patients, $I^2$= 0%, high certainty evidence). The HR for LR could be extracted from ten studies and no difference was found between lipofilling group and control (HR 0.86, 95% CI 0.66 to 1.12, p=0.43,6839 patients, $I^2$= 1%, moderate certainty evidence). Funnel plot analysis indicated a publication bias from one study (Petit et al) that included only DCIS tumors. The analysis excluding this article did not demonstrate difference in results. (HR 0.8, 95% CI 0.61 to 1.05, p=0.94, 6662 patients, $I^2$= 0%, moderate certainty evidence) ***CONCLUSION*** Based on published data, AFG is a safe technique of breast reconstruction for patients that undergone BC surgery. According to our findings, AFG did not affect OS, DFS or LR. These data have moderate to high certainty and additional studies probably will not change the current evidence.

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Tak1 signaling regulates p53 through a mechanism involving ribosomal stress

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Triple-negative breast cancer (TNBC) is among the most aggressive forms of breast cancer with limited therapeutic options. TAK1 is implicated in aggressive behavior of TNBC, while means are not fully understood. Here, we report that pharmacological blockade of TAK1 signaling hampered ribosome biogenesis (RBG) by reducing expression of RBG regulators such as RRS1, while not changing expression of ribosomal core proteins. Importantly, TAK1 blockade upregulated expression of p53 target genes in cell lines carrying wild type (wt) *TP53* but not in p53-mutant cells. By examining involvement of the ribosomal stress response, we found that p53 activation by blockade of TAK1 was prevented by depletion of ribosomal protein RPL11. Further, siRNA-mediated depletion of TAK1 or RELA resulted in activation of p53 signaling and this response was dependent on RPL11. Knockdown of RRS1 disrupted nucleolar organization and resulted in activation of p53. Genomic TCGA data showed that TNBCs express high levels of ribosome biogenesis regulators, and elevated RRS1 levels correlate with unfavorable prognosis. Cytotoxicity data showed that TNBC cell lines are more sensitive to TAK1 inhibitor compared to luminal and $HER2^{+}$ cell lines. Together, the data indicate that TAK1 regulates p53 activation by controlling ribosome biogenesis factors, and the TAK1-ribosome axis is a potential therapeutic target in TNBC.

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# Identifying efficacy of targeted HER2 antibodies in sensitization of HER2 positive breast cancer to fractionated radiation

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**Introduction:** Tumor hypoxia contributes to intra-tumoral heterogeneity and decreases efficacy of cytotoxic therapy. Fractionated radiation therapy has emerged as an alternative to single dose radiation, and is a component of standard-of-care therapy for patients with unresectable human epidermal growth factor receptor 2 (HER2+) breast cancer. Because radiation therapy is dependent on tissue oxygenation, therapies that increase oxygenation could radio-sensitize tumors. The goal of this study is to investigate if molecular imaging with [$^{18}$F]-fluoromisonidazole (FMISO)-PET can quantify anti-HER2 therapy-induced changes in tumor oxygenation and utilize imaging metrics to enhance the effectiveness of fractionated radiation. Improving treatment synergy in HER2+ breast cancer has potential to increase therapeutic effectiveness without increasing cytotoxic therapy.

**Methods:** For *in vitro* studies, HER2+ breast cancer cells (BT474, SKBR3, MDA-MB-361 and MDA-MB-453) were treated with various sequencing of combination trastuzumab (1 µg/mL) and fractionated radiation (6/3 Gy) and assessed for cell death. HER2+ cancer cells (BT474 and MDA-MB-361) were also treated with combination trastuzumab and fractionated radiation and analyzed for DNA double strand breaks (DSB) through flow cytometry. For *in vivo* studies, HER2+ cell line (BT474 and MDA-MB-361) and HER2+ patient derived xenograft (BCM 3472) tumors were engrafted into mice and treated with trastuzumab (4 mg/kg) on days 0 and 3 and fractionated radiation (6/3 Gy) on days 1, 2 and 3 (or single agent control). [$^{18}$F]-FMISO-PET imaging was conducted on day 0, 3 and 7. At the imaging endpoint, tumors were either extracted for biological validation or continued to measure tumor size changes for longitudinal assessment of response. Bliss test of independence and a non-parametric T-test was used to assess for treatment synergy and significance, respectively.

**Results:** *In vitro* cell death assay revealed single agent trastuzumab or fractionated radiation treated groups exhibited 15.2% ± 6.5% or 53.6% ± 9% cell death respectively, while trastuzumab prior to fractionated radiation groups exhibited 72.5% ± 2.5% cell death ($p = 0.01$) on day 7 in MDA-MB-361 cells. Flow cytometry analysis showed MDA-MB-361 cells treated with trastuzumab prior to fractionated radiation exhibited 62.4% ± 8.7% DSB, which significantly increased from single agent trastuzumab (0.74% ± 0.39%) or fractionated radiation groups (37.3% ± 7.3%) ($p = 0.01$). *In vivo*, MDA-MB-361 tumors treated with trastuzumab and fractionated radiation had a [$^{18}$F]-FMISO $SUV_{mean}$ of 0.20 ± 0.09, while tumors treated with fractionated radiation had a [$^{18}$F]-FMISO $SUV_{mean}$ of 0.31 ± 0.06 on day 7 ($p = 0.05$). MDA-MB-361 tumors treated with trastuzumab and fractionated radiation experienced a 26.1% ± 16.8% decrease in tumor volume, while tumors treated with single agent fractionated radiation experienced a 10.4% ± 2.8% decrease in tumor volume from day 0 to day 7 ($p = 0.11$). 30 days after start of therapy, MDA-MB-361 tumors treated with single agent fractionated radiation had a tumor volume of 471.8 ± 120 $mm^3$, whereas tumors treated with combination trastuzumab and fractionated radiation had a tumor volume of 116 ± 38 $mm^3$ ($p < 0.01$). Bliss test of independence confirmed *in vivo* treatment synergy of trastuzumab and fractionated radiation starting 14 days after start of therapy.

**Conclusion:** HER2+ breast cancer treated with trastuzumab prior to fractionated radiation synergistically increases efficacy of radiotherapy *in vitro* and *in vivo*. [$^{18}$F]-FMISO-PET imaging has potential to identify *in vivo* response to combination therapies and better understand changes in the tumor microenvironment to guide combination therapy.

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# Predicting cardiac dysfunction in breast cancer patients undergoing aromatase inhibitor treatment using biomechanical model-based elasticity imaging

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**Introduction** Premenopausal women with intermediate-high risk HR+ breast cancer often receive near-complete estrogen deprivation with ovarian function suppression concurrent with an AI. Hypoestrogenemia is associated with cardiotoxicity, but the cardiovascular impact of this newer breast cancer treatment is largely unknown. With increases in survival rates and younger women being diagnosed, methods to monitor and predict cardiac damage due to OFS+AI therapy are needed. Left ventricle (LV) ejection fraction is currently used for monitoring cancer treatment-related cardiovascular degradation, and can detect major heart defects, but is insensitive to subclinical left ventricle function. Emerging methods include T1 mapping and estimation of myocardial strain to indicate fibrosis. We propose an extension of these methods by estimating cardiac tissue elasticity using LV wall deformation to drive a biomechanical model. Elasticity is a more functional and direct measurement of tissue response based on structural mechanics driven by patient-specific cardiac magnetic resonance imaging (CMR) data. Elasticity measurements may serve as a predictive biomarker of early AI-induced cardiac changes.**Methods**This study is a retrospective initial proof-of-concept correlative imaging study to an existing clinical study for the use of CMR to detect cardiovascular damage (ESPRIT). Two cohorts of premenopausal breast cancer patients either: (1) undergoing OFS+AI for HR+ breast cancer or (2) triple negative breast cancer (TNBC) patients that have already received chemotherapy, were imaged twice, 3-6 months apart using CINE CMR. TNBC patients serve as the control, with no expectation of further cancer treatment-related cardiac damage. Time steps during passive ventricular diastole were visually selected from CINE CMRs. Each slice was non-rigidly registered to estimate LV deformation during passive filling. Deformation was simulated on a finite element mesh of the LV based on linear elastic transverse isotropic mechanical equilibrium. Using an inverse problem formulation, simulated deformation was compared to model-calculated deformation to estimate the spatial tissue longitudinal and transverse elasticity. Elasticity maps of the LV at initial and final points are compared to determine regional stiffening of the LV wall, to be used as early biomarkers for LV fibrosis. **Results**In this initial investigation, elasticity maps were analyzed for four patients (n=2 from each cohort). Passive LV tissue stiffening was observed in each AI patient, with 100% and 25% relative increases observed for longitudinal elasticity and 50% increases for transverse elasticity in the basal inferior region, and mid anterior region of the LV in each patient, respectively. No increases in stiffness of the LV were observed for TNBC patients. Ejection fraction remained consistent for all patients. **Conclusion**In this proof-of-concept study, we demonstrate that elasticity maps indicate local stiffening of the LV using a biomechanical model-based elasticity imaging method that could be used to indicate cardiac dysfunction in breast cancer patients receiving AIs. Spatial elasticity mapping allows direct observation of structural mechanics to reveal specific areas of LV stiffening. Moving beyond traditional strain imaging, our method yields a functional measure of tissue stiffness to directly indicate cardiac fibrosis. This study demonstrates the use of biomechanical models to interpret CMR and provides potential for use of more advanced constitutive models. Our non-invasive biomechanical model-based elasticity imaging method shows significant promise to indicate early cardiac function deterioration, critical for premenopausal women undergoing extended cancer therapies.

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First-line treatment of hormone receptor positive metastatic breast cancer (MBC) in everyday practice: Results from the Austrian AGMT_MBC-Registry

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**Background:** International guidelines recommend endocrine-based first-line therapy [ET] in hormone receptor-positive, HER2-negative (HR+/HER2- or luminal) metastatic breast cancer (MBC), nowadays in combination with a CDK4/6 inhibitor. Several real-word data suggest, however, that in daily practice up to 40% of patients with luminal MBC receive chemotherapy in first-line. To clarify the treatment landscape in an Austrian population of HR+/HER2- MBC patients, we analyzed the data from the MBC registry of the Austrian Study Group for Medical Tumor Therapy (AGMT-MBC-Registry). In addition, we investigated the influence of different treatment strategies on overall survival (OS). **Methods:** The AGMT-MBC-Registry is an ongoing multicenter registry for MBC patients in Austria. Only patients with HR+/HER2- MBC with available ER and HER2 status and sufficient outcome data were included in this analysis. Unadjusted, univariate survival probabilities of PFS and OS were calculated by the Kaplan-Meier method and compared by the log-rank test, multivariate hazard ratios (HR) were estimated by Cox regression models. A multivariate analysis including the following parameters was performed for first-line PFS and OS: age (continuous, as interaction with menopausal status), menopausal status (pre- vs postmenopausal vs unknown,), DFS (*de novo*metastatic vs < 24 months vs ≥ 24 months), (neo)adjuvant chemotherapy (yes vs no), grading (1+2 vs 3 vs unknown), visceral disease (yes vs no) and number of metastatic sites (1 vs 2-3 vs ≥4), first-line treatment (ET+CDK4/6i vs ET vs chemotherapy +/- bevacizumab +/- ET). **Results:** As of 24/06/2020, 1904 patients were included in the AGMT-MBC-Registry. Out of 1633 evaluable patients, 931 (57.01%) had HR+/HER2- disease and had received at least one treatment line for metastatic disease. In first-line, 577 (62.0%) patients received endocrine-based therapy (356 [61.7%] ET, 172 [29.8%] ET+CDK4/6i, 49 [8.5%] ET+Targeted other), and 354 (38.0%) received chemotherapy. The proportion of chemotherapy treated patients was slightly higher in pre- vs. postmenopausal women (41/94=43.6% vs. 222/664=33.4%) but decreased significantly over time (<2010: 60.3%; 2010-2015: 44.8%; >2015: 19.7%). In multivariate analysis, both ET and ET+CDK4/6i were significantly associated with longer first-line PFS and OS compared to chemotherapy (Table 1).

| **Adjusted analysis** | **ET vs. chemotherapy** | **ET+CDK4/6i vs. chemotherapy** |
|---|---|---|
| **1st-line PFS** | **HR 0.63**; 95%CI 0.52-0.77; P<0.001 | **HR 0.19**; 95%CI 0.13-0.29; P<0.001 |
| **OS** | **HR 0.59**; 95%CI 0.49-0.72; P<0.001 | **HR 0.35**; 95%CI 0.23-0.51, P<0.001 |

The most frequently used drugs across all treatment-lines were aromatase inhibitors (77.9%), fulvestrant (53.9%; 39.8% in first-line and 36.3% in second-line), tamoxifen (17.2%), CDK4/6 inhibitors (40.0%; 48.9% in first-line and 21.8% in second-line), everolimus (18.9%; 30.7% in second-line and 69.3% in ≥ third-line), taxanes (41.6%), capecitabine (35.0%), anthracyclines (28.6%), vinorelbine (17.0%) and eribulin (12.6%). **Conclusion:** In our registry, first-line chemotherapy for luminal MBC was significantly associated with an inferior PFS and OS compared to endocrine-based therapy. Because of the retrospective design of the study, biases influencing these results cannot be fully excluded, however, our data suggest that first-line chemotherapy should be avoided in luminal MBC.

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# Use of a novel convolutional neural network (CNN)-based mammographic evaluation to assess response to adjuvant endocrine therapy

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**Background:** The standard of care for early-stage hormone receptor (HR)-positive breast cancer is 5-10 years of adjuvant endocrine therapy (ET), which is associated with a 50-60% relative risk reduction in breast cancer recurrence. However, patients remain at risk of recurrence up to 20 years after diagnosis, and there is a need for biomarkers of response to ET. While decrease in mammographic density (MD) is associated with improved disease-free survival (DFS), measurement is subject to variability in radiologists' interpretations. We developed a novel, fully-automated convolutional neural network (CNN)-based mammographic evaluation that is a more accurate, independent predictor of breast cancer risk than MD. We evaluated the role of the CNN model as a pharmacodynamic biomarker of response to adjuvant ET among women with early-stage HR-positive breast cancer.
**Methods:** We conducted a retrospective cohort study among women with HR-positive, stage I-III unilateral breast cancer diagnosed at Columbia University Irving Medical Center (CUIMC) in New York, NY, from 2007-2017, who received adjuvant ET and had at least two contralateral mammograms (baseline and on ET) in our electronic health record (EHR). Demographics, clinical characteristics, breast cancer treatment (surgery, radiation, systemic therapy), type of ET (aromatase inhibitor [AI], tamoxifen, or both), and breast cancer relapse (distant, local, new breast primary) were extracted from the EHR and New York Presbyterian Hospital (NYPH) Tumor Registry. We performed CNN analysis of contralateral mammograms at baseline (within 1 year of diagnosis and prior to ET) and at 1- and 2-year (y) follow-up on ET. The primary endpoint was change in CNN risk score, expressed as a continuous variable (range, 0-1.00). Paired *t*-tests were used to assess for differences in CNN scores between baseline and 1y and 2y follow-up. Logistic regression was used to evaluate if CNN scores at baseline and change from baseline were associated with relapse, with adjustment for known prognostic factors.
**Results:** Of 2,559 women diagnosed with stage I-III HR-positive breast cancer at CUIMC from 2007-2017, 465 had serial mammograms available for CNN analysis. Mean age at diagnosis was 61.2y (SD, 12.2y), and 38.1% of women were non-Hispanic white, 12.5% non-Hispanic black, 39.8% Hispanic, and 9.7% other/unknown. At initial diagnosis, 62.2% had stage I tumors, 74.4% received lumpectomy, and 41.7% received chemotherapy. There were 28 (6.0%) breast cancer relapses (15 distant, 10 local, 3 new primary). Women who had relapsed were more likely to be obese (p=0.009), have higher tumor stage (p<0.001) and grade (p=0.022), higher Ki67% (p=0.003), and have received chemotherapy (p=0.036). While baseline CNN risk scores were higher among women who had relapsed compared to those who did not (0.295 vs 0.269), this difference was not statistically significant (p=0.197). Among all women, mean CNN scores were 0.271 (SD, 0.101) at baseline, 0.216 (SD, 0.073) at 1y, and 0.208 (SD, 0.072) at 2y; changes in scores from baseline to 1y and 2y were significant (p<0.001), consistent across subgroups. However, in multivariable logistic regression, there was no significant association between change in CNN score from baseline to 1y and 2y and breast cancer relapse.
**Conclusions:** We demonstrated a significant change in CNN risk scores from baseline to short-term follow-up among women with early-stage breast cancer who received adjuvant ET. Women who relapsed had higher baseline CNN risk scores, but this was not significant. Due to the small number of relapses, change in CNN risk scores was not associated with breast cancer recurrence. The CNN risk model will be evaluated prospectively in adjuvant clinical trials, to further evaluate its role as a predictor of breast cancer relapse and response to adjuvant ET.

**Publication Number:** PS8-21

The impact of exogenous estrogen exposure on the characteristics of estrogen receptor (ER) positive, early-stage breast cancer (EBC)

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*Background*: Oral contraceptives (OC) and hormone replacement therapy (HRT) are well-established risk factors for ER positive breast cancer. Infertility is associated with an increased breast cancer risk and there is conflicting data on the influence of fertility treatments on breast cancer risk. The impact of exogenous estrogen exposure on breast cancer characteristics is not well described. *Methods*: A single center retrospective cohort study comprising all women with ER positive, human epidermal growth factor receptor 2 (HER2) negative, EBC whose tumors were sent to OncotypeDX analysis and were treated in our institute between 2005 and 2012. Data on exogenous estrogen exposure were collected including: OC and HRT use and prior fertility treatments. The impact of these exposures was assessed on pre-specified histopathological features including: tumor size, nodal status, ER and progesterone receptor (PR) staining, grade, Oncotype recurrence score (RS), ki67, lymphovascular and perineural invasion. *Results*: A total of 620 women were included, 79% (Num) were postmenopausal. Prior exposure to OC, HRT and fertility treatments was documented in 19% (103), 30% (136) and 11% (62), respectively. OC use was associated with smaller (≤1cm) tumors (30% vs. 20%, p=0.023) and were less likely to have grade 3 disease (10% vs. 19%, p=0.049). No other associations were found between exogenous estrogen exposures and tumor characteristics (Table).
*Conclusions*: Use of OC may be associated with breast cancer with a distinct features compared to women with luminal breast cancer without history of OC use. Large scale studies are needed to better characterize these findings.

| Fertility treatment | | | HRT ≥ 2 years | | | HRT | | | OC | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P | No (%) | Yes(%) | P | No(%) | Yes (%) | P | No (%) | Yes (%) | P | No(%) | Yes(%) | |
| 0.172 | 225425 | 216515 | 0.700 | 235522 | 205724 | 0.700 | 225523 | 245620 | 0.023 | 205723 | 304426 | T≤1 cm 1<T≤2 T>2 cm |
| 0.859 | 17 | 18 | 0.098 | 15 | 20 | 0.098 | 15 | 21 | 0.667 | 18 | 15 | Node positive |
| 0.064 | 79138 | 89110 | 0.299 | 82126 | 76159 | 0.299 | 82135 | 77159 | 0.207 | 79148 | 8795 | IDC ILC Other |
| 0.167 | 186418 | 147313 | 0.500 | 166718 | 166419 | 0.500 | 166717 | 176221 | 0.049 | 186319 | 187310 | Grade 1 23 |
| 0.189 | 22078 | 32968 | 0.708 | 11781 | 12277 | 0.708 | 11781 | 22178 | 0.739 | 22277 | 32275 | ER intensity≤1 1<ER<=2 ER>2 |
| 0.112 | 14 | 7 | 0.671 | 16 | 15 | 0.671 | 16 | 14 | 0.103 | 14 | 8 | PR Negative |
| 1.000 | 5 | 3 | 0.455 | 5 | 2 | 0.455 | 5 | 3 | 0.282 | 5 | 2 | PNI present |
| 0.772 | 6 | 7 | 0.351 | 7 | 8 | 0.351 | 5 | 7 | 0.056 | 10 | 5 | LVI present |
| 0.186 | 20 | 29 | 0.362 | 22 | 19 | 0.362 | 23 | 18 | 0.528 | 22 | 18 | Ki67 >20% |
| 0.859 | 17 | 18 | 0.787 | 18 | 16 | 0.787 | 17 | 18 | 0.570 | 18 | 16 | Oncotype RS>25 |

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Comparing an operation to monitoring, with or without endocrine therapy (COMET): A prospective randomized trial for low-risk DCIS (AFT-25)

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**Background:** Approximately 50,000 women in the U.S. are diagnosed with ductal carcinoma *in situ* (DCIS) annually. Without treatment, it is estimated that 20-30% of DCIS will lead to invasive breast cancer. Currently, more than 97% of women undergo surgery, with many also undergoing radiation. An alternative to surgery for low-risk DCIS is active monitoring (AM), an approach in which regularly scheduled mammography and physical exams are used to monitor breast changes and determine if, or when, surgery is needed. **Trial design:** COMET, a multicenter phase III prospective randomized trial, opened in the U.S. in June 2017 (clinicaltrials.gov reference: NCT02926911). The hypothesis is that management of low-risk DCIS using an AM approach does not yield inferior invasive breast cancer and/or quality of life outcomes compared to surgery. **Eligibility criteria:** Patients with a new diagnosis of unilateral, bilateral, unifocal, multifocal, or multicentric DCIS, or atypia verging on DCIS are eligible. Patients must be ≥40 years of age, have no contraindication for surgery, and pathologic confirmation of grade I/II DCIS. DCIS must be ER and/or PR≥ 10% and HER2-negative without invasion, diagnosed within 120 days of registration. Breast tissue, blood and imaging are collected at trial entry and if invasive cancer subsequently occurs, and are stored in central repositories. **Specific aims:** The primary aim is to assess whether the 2-yr ipsilateral invasive breast cancer rate for AM is non-inferior to surgery. Secondary aims include comparison of 2-, 5-, and 10-yr mastectomy rate, contralateral invasive breast cancer rate, overall survival and invasive breast cancer-specific survival, as well as 5- and 10-yr ipsilateral invasive breast cancer rate between groups. Patient reported outcomes (PRO) using validated tools are critical secondary endpoints, and will enable comparison of health-related quality of life and psychosocial outcomes between surgery and AM groups at prespecified time points over a period of 5 years. **Statistical methods:** An accrual goal of 1200 was estimated using a 2-group test of noninferiority of proportions, with the 2-yr invasive breast cancer rate in the surgery group assumed to be 0.10, including accounting for upstaging. The projected drop-out rate is 25%, for a total of 900 patients treated per allocation arm. The non-inferiority boundary was set at 0.05. Based on a 1-sided un-pooled z-test, with alpha=0.05, a sample size of n=446 per group will have 80% power to detect the specified noninferiority margin. Intention-to-treat analysis of the 2-yr invasive breast cancer rate will be conducted using all patients as randomized, and will be completed using Kaplan-Meier estimates, stratified by group, combined with Greenwood's confidence interval. Several sensitivity analyses (per protocol, as-treated, and instrumental variable) are also planned to account for loss of follow-up, rejection of randomization allocation and withdrawals. **Present and target accrual:** Trial accrual as of 7/1/20 is 540 randomized patients from 84 activated Alliance for Clinical Trials in Oncology sites. Despite logistical challenges posed by the COVID-19 crisis, patients continue to be recruited to the COMET trial. Over 80% of patients have sample sets/images stored in the tissue and image repositories. This trial will provide definitive clinical, quality of life and biomarker evidence regarding the trade-offs of surgery vs AM in patients with low-risk DCIS. **Support:** CER-1503-29572; https://acknowledgments.alliancefound.org
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# Cardiac function in patients receiving trastuzumab for HER2+ metastatic breast cancer with left ventricular ejection fraction<50% at baseline

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**Research objectives and rationale** Trastuzumab greatly enhances the efficacy of treatment in HER2+ metastatic breast cancer (MBC). Due to its potential to induce cardiomyopathy, however, trastuzumab is contraindicated in patients with baseline left ventricular ejection fraction (LVEF) <50%, although this criterion is sometimes waived. We investigated the effect of trastuzumab on the cardiac function in a real-world cohort of patients with HER2+ MBC with a reduced baseline LVEF, i.e. baseline LVEF <50%. **Methods** We collected data on patients with HER2+ MBC who received at least one cycle of trastuzumab-based treatment between 2000 and 2014 in eight Dutch hospitals. Eligible patients had baseline LVEF 40-50%. Data were retrospectively collected from medical files using case record forms. Primary endpoint was severe cardiotoxicity defined as LVEF <40%. We also investigated whether severe cardiotoxicity was reversible. Reversibility was defined as any LVEF increase to a value <5% below baseline value and irreversibility as any absolute LVEF increase <10% from lowest value to >5% below baseline. Exploratory, we compared the incidence of severe cardiotoxicity in patients with and without cardioprotective medication at start trastuzumab. **Results** Of the 758 patients identified with HER2+ MBC, 41 patients were included with a LVEF <50% at start of trastuzumab treatment. The median LVEF at start was 46% with an interquartile range (IQR) of 42-48%. The median duration of trastuzumab treatment was 14 months (IQR 8-32 months). During this period, 16 patients (39%) developed severe cardiotoxicity. The median time to severe cardiotoxicity was 7 months (IQR 4-10 months). Severe cardiotoxicity was reversible in 6 patients (43%), partly reversible in 4 patients (29%) and irreversible in 4 patients (29%). Two patients were lost-to-follow-up. Of the 6 patients with reversible severe cardiotoxicity, trastuzumab treatment was continued in 2 patients (33%), interrupted <6 months in 1 patient (17%) and discontinued in 3 patients (50%). Of the 4 patients with irreversible severe cardiotoxicity, trastuzumab treatment was interrupted in 1 patient (25%) and discontinued in the other 3 patients (75%). In total, 12 patients (29%) received cardioprotective medications, i.e. beta-blocker (n=4), ACE inhibitor (n=4) or both (n=4), at start of trastuzumab treatment. In patients who received cardioprotective medications at start trastuzumab severe cardiotoxicity was less often observed compared to patients who did not received cardioprotective medications at start of trastuzumab (17% vs 48%, p=0.059, Table). **Conclusion** In our cohort of patients with HER2+ MBC, trastuzumab could be safely administered in 61% without developing severe cardiotoxicity despite an impaired LVEF at the start of trastuzumab treatment. Severe cardiotoxicity was (partly) reversible in about two thirds of the cases. Risks and benefits of trastuzumab use in this vulnerable population must be balanced carefully. The use of cardioprotective medications at start of trastuzumab treatment might reduce the risk of developing severe cardiotoxicity.

Clinical characteristics of patients with and without cardioprotective medication from start trastuz

| | **All patients** (n=41) | **Patients with cardioprotective medication from start trastuzumab** (n=12) | **Patients without cardioprotective medication fromStart trastuzumab** (n=29) | **P-value** |
|---|---|---|---|---|
| Severe cardiotoxicity[a], n (%) | 16 (39) | 2 (17) | 14 (48) | 0.059 |
| Time to cardiotoxicity, months [IQR] | 7 [3 - 12] | 6 [not reached - 8] | 8 [4 - 11] | 0.515 |
| Reversibility[b], n (%)<br>No<br>Partial<br>Yes | 4 (29)<br>4 (29)<br>6 (43) | 1 (8)<br>0 (0)<br>0 (0) | 3 (10)<br>4 (14)<br>6 (21) | 0.260 |
| Trastuzumab treatment , n (%)<br>Continued<br>Interrupted<br>Discontinued | 27 (66)<br>6 (15)<br>8 (20) | 7 (58)<br>2 (17)<br>3 (25) | 20 (69)<br>4 (14)<br>5 (17) | 0.796 |
| LVEF, median % (IQR)<br>Baseline<br>Nadir<br>Highest<br>Difference nadir and highest | 46 [42 - 48]<br>42 [33 - 45]<br>53 [50 - 57]<br>13 [9 - 20] | 47 [44 - 49]<br>43 [40 - 47]<br>52 [50 - 57]<br>11 [7 - 19] | 46 [43 - 48]<br>40 [32 - 45]<br>53 [49 - 58]<br>13 [10 - 21] | 0.177<br>0.322<br>0.761<br>0.464 |
| Cardiac symptoms, n (%) | 16 (39) | 4 (33) | 12 (41) | 0.515 |

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Pulsed electric field exposure (PEFE) applied in breast cancer: A potential normothermic clinical cancer therapy

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**Background:** Current and existing ablation for cancer treatment such as laser, RF and MW, all induce local high temperatures. The hyperthermia generated by these techniques lead to burns, pain and unwanted side effects in patients. Consequently, we aimed to develop a normothermic pulsed electric field exposure (PEFE) treatment that when applied in cancer treatments can effectively induce cell death and tumour degeneration without associated physical consequences. **Method:** The pulsed electric field exposure (PEFE) was generated with a carrier signal at 5.8GHz, then transmitted by a pointed open-ended coaxial cable**.** Breast cancer cells were treated with PEFE and assessed for their viability, apoptosis and other biological responses, together with the intracellular signalling events by using protein kinase array and related technologies. Breast cancer cells were also assessed for their ultrastructure changes by electron microscopy. *In vivo* experimentation was used to determine efficacy using human breast cancer tumour models in which *tumours* were treated with short PEFE pulses. The temperature at the area of treatment was monitored to ensure normothermic conditions. Tumour size were checked every 3 days for 36 days duration following different treatment protocols, followed by histological and biochemical analyses of the tumour and surrounding tissues. **Results:** MDA-MB-231 cancer cells were subject to PEFE, which induced no temperature change. Cells react to different pulse regimes and is related to cell type and aggressiveness. The treated cells became apoptotic after 4 hrs and this continued for at least 24 h after exposure with a 70% death rate. The apoptotic changes were confirmed by both immunofluorescent based and electron microscopy based methods. Protein kinase array (Kinexus$^{tm}$) revealed that PEFE exposure resulted in marked signature changes in the intracellular signalling event leading to apoptosis, including (BCL2, the CHK family, EGFR and ERK). In the *in vivo* trial, tumours were allowed to reach approximately 0.5 $cm^3$ before treatment with PEFE with multiple conditions, which all resulted in a significant reduction of tumour volume after one week ($p<0.01$ vs control). Three weeks after the PEFE treatment, most tumours were found to have disappeared with no detectable scarring and detectable side effects. Histological and biochemical analyses revealed the concurrent changes in both Caspase3 and BCL2 in PEFE treated tumours. **Conclusion:** Normothermic PEFE can induce cancer cell death *in vitro* and marked tumour reduction *in vivo*. Compared to existing thermal ablation techniques, PEFE does not induce high temperatures locally and therefor there is no influence on surrounding normal tissue. This technique has potential in minimally invasive surgery in cancer therapy for those unable to undergo general surgery or receive current chemo- or radiotherapies.

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# Refining loco-regional therapy for inflammatory breast cancer protocol in progress

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Background: Inflammatory breast cancer (IBC) is the most aggressive locally advanced breast cancer subtype. It is associated with loco-regional recurrence rates of 12-25%, and neoadjuvant chemotherapy (NAC) followed by modified radical mastectomy and comprehensive chest wall and regional nodal radiotherapy remain the standard of care. As has been demonstrated in non-IBC, achievement of pathologic complete response (pCR) has been shown to be associated with improved loco-regional control, recurrence-free and overall survival. Advances in NAC for IBC have resulted in improved pCR rates in both the breast and the axilla, with overall axillary pCR rates of approximately 30%, reaching as high as 67% in patients with HER2-positive disease receiving HER2-directed therapy. Hypothesis: Sentinel lymph node biopsy (SLNB) may be feasible in IBC patients who experience a good clinical and pathologic response in the axilla to NAC. Primary Objective: To evaluate the sentinel lymph node (SLN) identification rate in stage III IBC patients who experience cN0 status at completion of NAC. Secondary Objective: To assess the incidence of lymphedema following standard local-regional therapy for IBC. Methods and Study procedures: In this feasibility study, 50 patients with cT4dN0-2M0 IBC will be enrolled in order to evaluate 40 patients whose axillary nodal status becomes cN0 upon completion of NAC. All patients will undergo a research breast biopsy and lymphoscintigram pre and post NAC to evaluate lymphatic drainage patterns and patency of breast and axillary lymphatics. Post NAC lymphoscintigraphy will be appropriately timed for pre-operative SLN mapping and all patients will undergo SLNB using dual tracers (Tc99 Sulfur colloid and blue dye) with immediate axillary lymph node dissection (ALND), at the time of mastectomy. The patient-reported Lymphedema Symptom Intensity and Distress Survey (LSIDS-A) will be collected at 6 timepoints. Patients will be followed for 2 years post-surgery for oncologic outcomes. Correlatives: We plan to evaluate genetic and phenotypic heterogeneity in IBC and to assess markers of angiogenesis and lymph-angiogenesis associated with IBC, as well as to explore immunologic aspects of the tumor microenvironment and their association with pCR. Statistics: The identification rate will be calculated as number of patients in whom SLNs were successfully identified over the number of patients with cN0 disease after NAC in whom SLN mapping was attempted. Using a Simon two-stage design ($\alpha$=.10, $\beta$=.10), a SLN identification rate of ≥90% would result in considering this procedure feasible whereas an identification rate of ≤75% (null hypothesis) would lead to the conclusion that it is not feasible. In the first stage, if greater than 18 of 25 patients have SLNs identified, then a total of 40 patients will be enrolled. If fewer than 33 of 40 patients have SLN identified, then the null hypothesis is rejected.

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# Timelines to initiate an adjuvant phase III trial across the globe: A sub-analysis of the APHINITY trial

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**Background:**Previous analysis of an adjuvant breast cancer trial (NCT00490139) suggested that geographical location and income affected the time required to set up a clinical trial, being significantly longer in South American and upper-middle income economies, potentially affecting access of innovative therapies in these locations. Understanding that this can be a dynamic process, we performed a similar analysis for the recent global phase III APHINITY trial (NCT01358877), which investigated the addition of pertuzumab to chemotherapy and trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer.
**Methods:**Time to regulatory authority (RA) submission to approval, time to ethics committee/institutional review board (EC/IRB) approval, time from study approval by EC/IRB to first randomized patient, and time from first to last randomized patient were collected prospectively. Analyses were conducted by grouping countries either by geographical region or economic income classification as per 2019 World Bank criteria. Descriptive statistics of medians and ranges were calculated for the different timelines evaluated. Differences between geographical regions and economic income classification groups were calculated using one-way analysis of variance (ANOVA) following data normalization on square roots of the time to local RA. Geographical regions represented by only one participating country were not included in the ANOVA calculations.
**Results:**APHINITY randomized 4805 patients between November 2011 and August 2013. Of the 42 participating countries, 41 had data available regarding all relevant timelines. Of those, 21 (51.2%) were located in Europe, 9 (21.9%) in the East Asia-Pacific region, 8 (19.5%) in Latin America and Caribbean, 2 (4.8%) in North America, and 1 (2.4%) in Sub-Saharan Africa. Twenty-seven (65.8%) of the participating countries had high, 11 (26.8%) upper-middle, and 3 (7.3%) had lower-middle income economies.
Except for time from first patient to last patient randomized, there was wide variation in timelines within geographical region and across economic income classification. For example, the median time from EC/IRB approval to first recruited patient across all geographical regions was 118 days, but the range was wide (13– 463 days). There was, however, no statistical difference between the time to RA according to geographical region (p=0.47) although there was a trend to longer time to RA in upper-middle income economies compared to the others (p=0.07).
**Conclusion**
Our results did not demonstrate a significantly longer time for trial activation in Latin American & Caribbean countries and upper-middle income economies compared to other groups in the APHINITY trial. When compared to a previous report, this may reflect collective work from collaborative research groups, pharmaceutical industry sponsors and regulatory authorities across the globe and is to be welcomed. Variability in timelines within geographical regions and income classifications may exist and should be further investigated.
Table 1: Timelines in the activation process of APHINITY across geographical region and economic income classification.

| | Time to RA (days)* | Time to EC/IRB (days) | Time from EC/IRB approval to first patient (days) | Time from first patient to last patient randomized (months) |
|---|---|---|---|---|
| Europe and Central Asia | 56 (4-135) | 67 (22-164) | 109 (13-257) | 17.6 (13.2-21.7) |
| North America | 31 (30-32) | 73 (19-126) | 126 (86-165) | 17.6 (13.8-21.5) |
| East Asia and Pacific | 53 (15-372) | 67 (31-421) | 108 (56-147) | 18 (8.7-19.9) |
| Latin America and Caribbean | 51 (15-276) | 43 (19-273) | 232 (98-463) | 14.6 (6.5-17.5) |
| Middle East and North Africa | - | 141 (141-141) | 92 (92-92) | 13.9 (13.9-13.9) |
| Sub-Saharan Africa | 103 (103-103) | 14 (14-14) | 185 (185-185) | 18.2 (18.2-18.2) |
| Overall | 53 (4-372) | 56 (14-421) | 118 (13-463) | 17 (6.5-21.7) |
| High income | 45 (4-276) | 60 (19-273) | 98 (13-257) | 18.2 (11.9-21.7) |
| Upper middle income | 92 (15-372) | 54 (14-421) | 185 (73-463) | 14.2 (6.5-18.2) |
| Lower middle income | 55 (32-111) | 33 (32-78) | 201 (147-209) | 15.1 (13.5-17.4) |
| Overall | 53 (4-372) | 56 (14-421) | 118 (13-463) | 17 (6.5-21.7) |

Data are medians (range)*The protocol was not submitted to a country regulatory authority for Israel. The corresponding timelines for Israel cannot be calculated.EC/IRB = ethics committee/institutional review board; RA = regulatory approval

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# Analysis of the clinical applicability of modified residual cancer burden system in evaluating the pathological response of breast cancer after neoadjuvant treatment

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**Objective:** To study the related factors affecting the residual cancer burden (RCB) after neoadjuvant therapy for breast cancer, and to modify the residual cancer burden system for patients after neoadjuvant therapy. To analyze the modified residual cancer burden system in predicting prognosis in patients with different molecular types. **Methods:** A retrospective analysis was conducted on 1274 patients who were diagnosed with invasive carcinoma of the breast by preoperative coarse needle aspiration pathology from January 2009 to December 2017, and who underwent surgical resection after neoadjuvant therapy. Follow-up was 1186. From 2009 to 2016, 837 patients were randomly assigned to the training set, and combined with HER2 expression before neoadjuvant therapy for revised residual cancer burden system (HER2-RCB). In 2017, 349 patients formed a verification set, which was used to verify the effectiveness of the analytical model. In this study, SPSS21.00 was used for statistical analysis, Spearman was used for correlation analysis, Hosmer-lemeshow test constructed model calibration degree, ROC curve was used to evaluate the efficiency comparison, Kaplan-Meier and Cox were used for survival analysis, $P<0.05$ was statistically significant. **Results:** All patients in this study were female, with an average age of 50±8.7 years (24-86 years). Spearman correlation analysis showed that RCB classification was positively correlated with ER, PR expression, clinical stage, and age before neoadjuvant therapy ($P<0.05$), and negatively correlated with KI67, HER2 expression before neoadjuvant therapy, postoperative vascular tumor thrombus and lymph node metastasis ($P<0.05$). In the training set and validation set groups, the HER2-RCB classification has a good and consistent calibration between the predicted value of the patient's overall survival (OS) and disease-free survival (DFS) risk and the actual observed value. Sexuality is high ($P>0.05$), and the prognostic risk stratification of patients is higher than RCB classification (AUC=0.782, 0.699; 0.819, 0.719). According to the molecular types of breast cancer, and compared with other molecular typing, the differences that the RCB classification predicts the OS of patients with HER2 over-expression and Luminal B HER2 positive breast cancer were statistically significant ($P<0.05$), but there was no statistically significant difference in DFS ($P>0.05$), while the differences that the HER2-RCB classification predicts OS and DFS in patients with HER2 over-expression, and Luminal B HER2-positive breast cancer were statistically significant ($P<0.05$). **Conclusions:** HER2-RCB classification is more accurate than RCB classification in predicting prognosis, and the prediction of recurrence and metastasis risk in patients with HER2 over-expression and Luminal B HER2 positive breast cancer is better than RCB classification. It is suggested that HER2-RCB classification has better clinical applicability.**Key words:** Neoadjuvant therapy, Residual cancer burden, Pathologic complete response, Human epidermal growth factor receptor 2, Molecular type

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# First-line treatment trends in metastatic breast cancer before and at the early stage of the COVID-19 pandemic in the United States

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**BACKGROUND:** As of June 2020, more than 2.5 million cases of COVID-19 and over 125,000 deaths related to COVID-19 have been confirmed in the United States (US). A strained healthcare system, quarantine orders, and national social distancing guidelines have forced healthcare providers to adopt new protocols to safely interact with and manage treatment for oncology patients. Recommendations put forth by the COVID-19 Pandemic Breast Cancer Consortium suggest some patients be considered for dose or schedule adjustments to ongoing treatment to reduce the risk of side effects and frequency of healthcare visits while deferring invasive procedures and initiating treatments with less need for monitoring or risk of side effects. The objective of this study was to understand whether patients with metastatic breast cancer (mBC) are experiencing changes in treatment during the pandemic in routine clinical practice in the US.
**METHODS:** A retrospective cohort of patients, aged 18+ years, with a new mBC diagnosis receiving treatment between January 1, 2019, and April 30, 2020 was identified from the Flatiron longitudinal Cancer Database. The database comprises structured electronic health records from >280 cancer clinics and >800 sites of care, representing approximately 2.4 million US patients with cancer who are actively being treated for their disease. First-line treatments were assessed monthly for the study cohort and stratified by new and continuously treated patients in a given month. Types of first-line treatment included CDK4/6 regimen, endocrine monotherapy, chemotherapy, and other treatments (e.g., targeted monotherapy). Demographics, clinical characteristics, and treatment changes were descriptively summarized.
**RESULTS:** 2680 patients with mBC were eligible for the analysis. The median age at metastatic diagnosis was 60 years, 99% were female, and 60% were White. Thirty-four percent had de novo metastatic disease at diagnosis and most received treatment at a community clinic. The most common breast cancer subtype was HR+/HER2- (66%). Between March and April 2020, the number of patients starting first-line therapy decreased 17% (from 121 to 100), whereas the number of continuing patients decreased 2% (from 837 to 817). The proportion of new starts receiving a CDK4/6 regimen averaged 35% between Jan 2019 and March 2020 with a decrease to 29% in April. The proportion of new starts receiving endocrine monotherapy was trending down from 37% in January 2019 to 22% in March 2020 (averaging 27% across this period); in April, the largest month to month change was observed in endocrine monotherapy use when the proportion of new patients increased to 28%. Treatment distributions appeared stable across the study months among continuing patients (Table 1).
**CONCLUSIONS:** In the early stage of the COVID-19 pandemic, a decline in the number of patients initiating first-line treatment was observed as well as a decrease in the proportion of patients receiving CDK4/6i combination treatments and an increase in endocrine monotherapy between March and April 2020. This shift may signal possible diagnosis/treatment initiation delays and prescribing shifts among patients initiating new treatments. Ongoing follow up of these trends through the pandemic is planned to track whether these shifts are sustained and to identify demographic and clinical factors associated with variations in treatment at different stages of COVID-19 epidemic in the US.

Table 1. Percent of Patients Starting or Continuing First-Line Treatment for Metastatic Breast Cancer by Month and Treatment Type, January 1, 2019 through April 30, 2020, United States

| Month and Year | First-Line Treatment (n, %) | | | | | | | | Total (N) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CDK4/6i Regimen | | Endocrine Monotherapy | | Chemotherapy | | Other | | | |
| | Starting | Continuing* | Starting | Continuing* | Starting | Continuing* | Starting | Continuing* | Starting | Continuing* |
| Jan-19 | 27 (35.5) | 0 (0) | 28 (36.8) | 8 (80.0) | 12 (15.7) | 2 (20.0) | 9 (11.8) | 0 (0) | 76 | 10 |
| Feb-19 | 44 (32.5) | 25 (39.0) | 37 (27.4) | 18 (28.1) | 42 (31.1) | 12 (18.7) | 12 (8.8) | 9 (14.0) | 135 | 64 |
| Mar-19 | 57 (35.8) | 61 (38.3) | 43 (27.0) | 41 (25.7) | 45 (28.3) | 42 (26.4) | 14 (8.8) | 15 (9.4) | 159 | 159 |
| Apr-19 | 50 (30.6) | 113 (44.1) | 42 (25.7) | 46 (17.9) | 46 (28.2) | 74 (28.9) | 25 (15.3) | 23 (8.9) | 163 | 256 |
| May-19 | 50 (30.8) | 147 (42.6) | 50 (30.8) | 53 (15.3) | 42 (25.9) | 102 (29.5) | 20 (12.3) | 43 (12.4) | 162 | 345 |
| Jun-19 | 64 (39.5) | 183 (42.5) | 41 (25.3) | 77 (17.9) | 40 (24.6) | 122 (28.3) | 17 (10.4) | 48 (11.1) | 162 | 430 |
| Jul-19 | 63 (35.5) | 223 (47.3) | 49 (27.6) | 86 (18.2) | 40 (22.5) | 109 (23.1) | 25 (14.1) | 53 (11.2) | 177 | 471 |
| Aug-19 | 43 (30.2) | 263 (46.4) | 39 (27.4) | 109 (19.2) | 40 (28.1) | 124 (21.9) | 20 (14.0) | 70 (12.3) | 142 | 566 |
| Sep-19 | 46 (34.0) | 282 (46.8) | 42 (31.1) | 109 (18.1) | 29 (21.4) | 129 (21.4) | 18 (13.3) | 82 (13.6) | 135 | 602 |
| Oct-19 | 59 (37.5) | 306 (47.8) | 47 (29.9) | 116 (18.1) | 28 (17.8) | 131 (20.4) | 23 (14.6) | 87 (13.5) | 157 | 640 |
| Nov-19 | 46 (32.8) | 332 (48.1) | 38 (27.1) | 134 (19.4) | 36 (25.7) | 131 (19.0) | 20 (14.2) | 92 (13.3) | 140 | 689 |
| Dec-19 | 38 (33.6) | 359 (48.5) | 25 (22.1) | 131 (17.7) | 33 (29.2) | 147 (19.8) | 17 (15.0) | 103 (13.9) | 113 | 740 |
| Jan-20 | 62 (37.5) | 372 (51.0) | 42 (25.4) | 119 (16.3) | 26 (15.7) | 143 (19.6) | 35 (21.2) | 95 (13.0) | 165 | 729 |
| Feb-20 | 60 (38.7) | 413 (51.8) | 35 (22.5) | 128 (16.0) | 36 (23.2) | 138 (17.3) | 24 (15.4) | 118 (14.8) | 155 | 797 |
| Mar-20 | 41 (33.8) | 452 (54.0) | 27 (22.3) | 119 (14.2) | 24 (19.8) | 140 (16.7) | 29 (23.9) | 126 (15.0) | 121 | 837 |
| Apr-20 | 29 (29.0) | 444 (54.3) | 28 (28.0) | 110 (13.4) | 17 (17.0) | 128 (15.6) | 26 (26.0) | 135 (16.5) | 100 | 817 |

* Patients continuing prior therapy.

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**Publication Number:** PS12-22

# Maintenance therapy with everolimus plus aromatase inhibitors vs aromatase inhibitors as after first-line chemotherapy in HR+/HER2- metastatic breast cancer: Updated analyses of the phase III randomized MAIN-A trial

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**Background** Despite endocrine therapy is the mainstay of treatment for HR+/HER2- metastatic breast cancer (MBC), patients with high disease burden or those at risk of visceral crisis are still offered first-line chemotherapy (CT). Chemotherapy is generally followed by maintenance hormonal therapy. The MAIN-A study is an investigator-driven, randomized phase III trial designed to compare maintenance everolimus (EVE) combined with aromatase inhibitors (AI) versus AI alone in pts with disease control after first-line CT.**Methods** Postmenopausal pts achieving disease control (stable disease, partial response or complete response) after first-line CT were randomly assigned to EVE 10 mg po daily plus AI or to AI alone. Primary aim was PFS in the ITT. We present here overall survival (OS) results and the impact of tumor characteristics on PFS.**Results** 110 pts were randomized to EVE+AI (n=52) or to AI (n= 58). Primary aim results have been already presented (Guarneri V, ESMO Breast 2019), showing a non-significant prolongation of median PFS in the ITT population for EVE+AI (9.9 mos vs 7.2 mos, HR 0.764, 95% CI 0.501-1.164. Patients with visceral metastases tended to experience shorter PFS as compared with patients with patients with bone/soft tissues metastases (median 11.1 mos vs 6.4 mos, p=0.0746). The levels of estrogen receptor expression (>or< 50%) did not impact PFS, overall and by treatment arm. At the time of this writing, a total of 61 death events have been recorded. No difference in OS was observed between the two arms (median 33.9 mos for EVE+AI vs 33.5 mos for AI, HR 0.97, 95% CI 0.59-1.61).**Conclusions** Maintenance EVE+AI did not significantly impact on the outcome of metastatic breast cancer patients deemed suitable for first line chemotherapy.

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Targeting resistance to current CDK4/6 therapies by RGT-419B, an inhibitor with optimized kinase activity spectrum

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Cyclin-dependent kinases (CDKs) 4/6 inhibitors are a powerful class of therapeutic drugs for the treatment of advanced metastatic breast cancer. However, the currently approved CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib have dose-limiting toxicities that require treatment holidays or reductions to sub-optimal doses, thus limiting full target inhibition. The residual CDK4/6 activity, together with persistent signaling through CDK2/cyclin E are among key resistant mechanisms that can compromise full clinical benefit. RGT-419B is a 3rd generation CDK inhibitor with an optimized kinase activity spectrum that has been discovered employing a **C**omputer **A**ccelerated **R**ational **D**esign technology platform. RGT-419B has potent sub-nM CDK4 activity with desired degrees of selectivity against kinases such as CDK6, CDK9 and GSK3β to enable full target engagement with an improved safety profile. Furthermore, single digit nM CDK2 kinase activity has been incorporated into the design of RGT-419B to combat Cyclin E/CDK2-driven resistance. *In vitro*, RGT-419B showed more robust activity against palbociclib-resistant ER+ breast cancer cells than abemaciclib. In ER+ T47D breast cancer cells with overexpression of Cyclin E1, RGT-419B exhibited better antiproliferation activity than either abemaciclib or palbociclib. RGT-419B also demonstrated more durable *in vivo* tumor growth inhibition when compared with abemaciclib in an ER+ breast cancer xenograft model. The optimized kinase activity spectrum of RGT-419B provides an opportunity to treat ER+ breast cancer patients refractory to the existing CDK4/6 inhibitors, as either a single agent or in combination with other therapies.

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**Publication Number:** PS2-22

# The sensitivity and specificity of routine breast cancer pathology based on breast core biopsies compared with pathology based on surgical resections

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**Background:** Several studies have reported good or reasonable concordance of biomarker panel based on core needle biopsies (CNB) and the pathology based on the surgical specimen (SS). However, as neoadjuvant therapy (NAC) is becoming more common, the result from the preoperative CNB is crucial as it is the only source for the subtyping of the breast tumor. Incorrect results of subtype could result in suboptimal choice of NAC. The aim of this study was to estimate the sensitivity and specificity of biomarkers and surrogate subtypes based on CNB compared with the surgical specimen (SS) in a three-year cohort of primary breast cancer patients diagnosed at Uppsala University Hospital.

**Patients and Methods:** We collected data from all patients diagnosed with breast cancer at the University Hospital Uppsala, between 1$^{st}$ of September 2015 and 31$^{st}$ of August 2018 (n=837). Of these, 319 primary operated tumors were available with full biomarker information on CNB and SS. An additional 71 tumors from patients treated with NAC could be identified (not reported). Histopathological results from CNB and SS (n= 319) were used to divide the tumors in five subtypes; luminal A, luminal B, triple negative (TNBC), HER2-luminal and HER2 non-luminal.

**Results:** The sensitivity/specificity of CNB for the expression of estrogen receptor was 100%/100%, progesterone receptor 96%/77%, HER2 by IHC3+ 77%/99%, Grade 3 49%/89% and high Ki67 72%/78%. The sensitivity and specificity of CNB and SS in subtype TNBC and HER2 non-luminal subtypes was 100%. Out of 37 cases with HER2-luminal subtype, 27 were correctly diagnosed by CNB (sensitivity 73%, specificity 100%). The sensitivity for correct diagnosis of luminal A was 76% with a specificity of 83% and luminal B subtype had a sensitivity of 74% and 99% specificity.

**Conclusions** CNB was very reliable in defining TNBC and HER2 non-luminal subtypes, but less accurate in diagnosing luminal subtypes. There is a clear risk for underdiagnosis of HER2-luminal tumors. These patients might therefore receive suboptimal treatment when treated with NAC.

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**Publication Number:** PS18-22

Association of molecular biomarkers heterogeneity and treatment pattern, disease outcomes in multifocal or multicentric breast cancer patients

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**Background**: To evaluate the rates of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 heterogeneity in multifocal or multicentric breast cancer (MMBC) and its association with treatment pattern and disease outcomes.**Methods**: MMBC patients with ER, PR, HER2, and Ki67 results for each tumor focus were retrospectively analyzed. Patients with concordant ER, PR, HER2, and Ki67 status among all invasive tumor foci were categorized into the Homo group, while the rest were defined as the Hetero group. Chi-square or Fisher test were performed to compare the treatment options between the Hetero and Homo groups. Disease-free survival (DFS) and overall survival (OS) rates were estimated from Kaplan-Meier curves and compared between two groups.**Results**: A total of 330 patients were included. Concordance rates of ER, PR, HER2, Ki67, and molecular subtype were 97.0%, 93.9%, 96.5%, 91.2%, and 88.2%, respectively (all *P* values < 0.001). There were 53 (16.1%) and 287 (83.9%) patients classified into the Hetero and Homo groups. Adjuvant endocrine therapy was more frequently assigned for patients in the Hetero group than in the Homo group (84.9% *vs.* 71.7%, *P* = 0.046). There was no difference in terms of adjuvant anti-HER2 therapy (28.3% *vs.* 19.6%, *P* = 0.196) and chemotherapy (69.9% *vs.* 69.8%, *P* = 0.987) usage between two groups. At a median follow-up of 36 months, DFS rates were 81.2% for the Hetero group and 96.5% for the Homo group (*HR* = 2.81, 95% CI: 1.00-7.88, *P* = 0.041). The estimated 3-year OS rates for these two groups were 95.8% and 99.5%, respectively (*HR* = 4.31, 95% CI: 0.83-22.46, *P* = 0.059).**Conclusion**: Heterogeneity of ER, PR, HER2, or Ki67 was present in 16.1% patients with MMBC. Biomarkers heterogeneity influenced adjuvant endocrine therapy usage and was associated with worse disease outcomes, indicating further clinical evaluation.

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# Pre-pectoral implant-based reconstruction and adjuvant radiation therapy - Surgical outcomes from a multicentre study in United Kingdom

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**Background**Pre-pectoral implant-based reconstruction is the most common form of reconstruction performed in the United Kingdom (UK) after a mastectomy. Implant-based reconstruction is relatively contraindicated in patients known to require adjuvant radiation therapy. There is limited data on surgical outcomes in patients with pre-pectoral implant-based reconstruction who received adjuvant chest wall radiotherapy. We present early post-operative outcomes of in this subset of patients in a large multicentre audit on prepectoral implant based reconstruction.

**Methods**A retrospective multi-centre audit of all post-mastectomy prepectoral breast reconstruction (PBR) using Braxon® acellular dermal matrix was conducted. The demographic details, treatment details, 90-day complication rates and implant loss rates for the entire study period were evaluated. A subset analysis of patients who required adjuvant radiation therapy was performed. Complications were categorized as major and minor based on the Clavien-Dindo classification. All complications grade III or higher were regarded as major complications. Complications reported after 90 days of the reconstruction, were regarded as delayed complications. Implant loss rates were compared to the subset of patients who did not receive adjuvant radiation therapy.

**Results**Eight hundred and twenty two patients underwent 1020 post-mastectomy PBR across 29 centres in the UK from January 2014 to 2019. Of these, 166 (16.28%) reconstructions received adjuvant radiation therapy. Median follow-up period was 18 months for this cohort. Median age was 49 years and the median body mass index was 25 kg/m$^2$. Fifty-six (33.73%) patients had an axillary nodal clearance. Median hospital stay was 1 day. One hundred and twenty eight (77.11%) patients had a single stage reconstruction and 93 (56%) patients received adjuvant chemotherapy. The 90-day major complication rate was 16.26%, readmission rate and return to theatre rate was 14.45% each. Delayed complications were reported in 8.43% patients. The implant loss rate was 7.83% for the entire study period. This was comparable to the implant loss rates in the subset of patients without adjuvant radiation therapy (p = 0.366). Patients with a 2-stage reconstruction had a higher major complication rate (22.71%) as compared to single stage reconstruction (16.40%), which was statistically not significant (p = 0.469).

**Conclusion**Implant-based PBR with acellular dermal matrix has comparable outcomes in patients undergoing adjuvant radiation therapy in terms of early outcomes. Patient reported outcomes need to be evaluated along with incidence of capsular contractures and the possible needs for additional delayed surgical interventions in this group of patients. Larger studies are needed to confirm the findings and the impact of radiotherapy in PBR.

| Characteristic | Number of patients or procedures |
|---|---|
| Total number of procedures | 1020 |
| Procedures with adjuvant radiation therapy | 166 (16.27) |
| Age (years) | 49 |
| BMI (kg/m$^2$) | 25 |
| Management of axilla Axillary nodal clearance | 56 (33.73) |
| Type of reconstruction | |
| One-stage | 128 (77.11) |
| Two-stage | 22 (13.25) |
| Missing | 16 (9.64) |
| Hospital stay (days) | 1 (0-10) |
| Breast specimen weight (grams) | 452 (108-1578) |
| Implant size (cc) | 400 (130-700) |
| Adjuvant chemotherapy | 93 (56.02) |

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**Publication Number:** PS4-22

# Prevalence of HER2-low and HER2-zero subgroups and correlation with response to neoadjuvant chemotherapy (NACT) in patients with HER2-negative breast cancer

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**INTRODUCTION** Current definition of HER2-positive BC follows ASCO/CAP guidelines using immunohistochemistry (IHC) and/or *in situ* hybridization (ISH)-based techniques. However, HER2 expression can be variable in cells that lack ERBB2 amplification. For example, HER2-negative tumors can express some level of HER2 protein by IHC (i.e. 1+ or 2+ and a negative ISH result) and are identified as HER2-low. Others have no expression and are considered HER2-zero. Innovative therapies have shown promising activity in patients in HER2-low BC. The aim of this study is to evaluate the association of HER2-low and HER2-zero status with response to NACT in HER2-negative BC. **METHODS** Retrospective cohort of patients with HER2-negative BC treated with NACT in four institutions in Brazil. Protocols of diagnosis, treatment and follow-up were standardized and based on international guidelines. Tumors with HER2 IHC score 0 were classified as HER2-zero whereas tumors with HER2 score 1+ and those with HER2 score 2+ with FISH-negative were classified as HER2-low. Patients were treated with anthracycline- and taxane- based chemotherapy. The following clinicopathological data were evaluated, when available: age, ER, Ki67, tumor size, lymph node (LN) status and response to NACT according to pCR status and residual cancer burden (RCB) index. Primary objective was to evaluate the prevalences and compare pCR rates among HER2-zero and HER2-low cases. Secondary objectives were to perform the same comparison within the HR-positive (HR+) and HR-negative subgroups. Pearsons chi squared tests were performed and a p value of <0.05 was considered statistically significant. **RESULTS** 331 patients were included in this analysis. 63% were HR+and 37% were TNBC. 50% were HER2-zero and 50% HER-low (36% HER2 IHC 1+ and 14% HER2 IHC 2+/FISH-negative). Median age, initial tumor size, clinical LN status and Ki67 expression were similar among HER2-zero and HER2-low subgroups. In HR+ tumors, 42% (86/207) were HER2-zero and 58% (121/207) were HER2-low. In TNBC, 63% (78/124) were HER2-zero and 37% (46/124) were HER2-low (p<0.001, Pearsons chi squared test). The pCR rate was 26% (85/331) in the entire cohort. As expected, there was a higher rate of pCR in TNBC vs HR+ (50% vs 11%, p<0.001). We found a statistically significant difference in the pCR rates when comparing the HER2-zero versus HER2-low subgroups (31% vs 20%, p=0.03). However, this difference is mostly related to an imbalance between groups (HER2-zero subgroups had a higher proportion of TNBC). Among HR+ tumors, there was no difference in the pCR rates between HER2-zero and HER2-low subgroups (8% vs 13%, p=0.35). In TNBC, we identified an interesting but non-statistically significant difference in pCR in HER2-zero vs. HER2-low tumors (56% vs. 39%, p=0.09). In the TNBC cohort we identified a non-statistically significant difference in RCB 0-I in HER2-zero vs. HER2-low tumors (p=0.06). With a 30 month median follow-up, PFS and OS data are immature. **CONCLUSION** The distribution of HER2-zero and HER2-low cases is different in HR+ and TNBC. HER2-low is more frequent in HR+ and HER2-zero in TNBC. We identified a higher pCR rate in HER2-zero compared to HER2-low tumors, even though this difference is associated with an imbalance between the two groups. Still, we identified a trend to higher pCR rate in HER2-zero compared to HER2-low tumors even within the TNBC subgroup. Identification of HER2-low and HER2-zero tumors may have clinical implications that should be further explored.

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**Publication Number:** PS6-22

# The impact of body mass index (BMI) on presence of ctDNA and survival outcomes after neoadjuvant chemotherapy for triple negative breast cancer: Analysis from BRE12-158

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**Introduction**: Obesity, defined by BMI, is associated with worse overall and disease specific survival in early stage breast cancer. This relationship is clear in hormone receptor positive breast cancer, but is less consistent in triple negative breast cancer (TNBC). Inconsistencies may reflect heterogeneous populations, not accounting for prognostic variables that potentially blunt the effect of obesity in TNBC. There is marked disparity in outcome between those with a pathologic complete response after neoadjuvant therapy, versus residual disease. Furthermore, in those with residual disease, presence of circulating tumor DNA (ctDNA) is a significant predictor of worse DFS and OS. Preclinical evidence supports a role of obesity in mediating TNBC metastases through an inflamed, hypoxic tumor environment; however, no studies have examined the relationship between BMI and ctDNA as a clinical indicator of micrometastatic disease. Here, we investigate this relationship, and the impact of BMI on disease recurrence and survival in the high- risk population of patients with residual TNBC after neoadjuvant chemotherapy. **Methods**: BRE12-158 was a phase II trial of genomically- directed therapy versus physician's choice. Eligible patients had residual TNBC after anthracycline and taxane chemotherapy. Plasma samples were collected following surgery for isolation of ctDNA, categorized as positive or negative. BMI ($kg/m^2$) was measured after surgery and analyzed as both a continuous and categorical variable: normal weight < 25, overweight 25- 30, and obese ≥ 30. Comparison between ctDNA category and BMI was performed using t-test (BMI as continuous) and Fisher's exact test (BMI as categorical). Kaplan-Meier curves and Cox proportional hazards model was used to estimate probability of DFS, distant DFS (DDFS), and OS, and to compare differences by BMI. In multivariate analysis of association between BMI and outcome, covariates included ctDNA positivity, treatment arm, age, race, tumor size at surgery, residual cancer burden classification, histological grade, pathologic stage, and cutoff $p<0.05$ was used to retain a covariate in the regression model. **Results**: Of 177 evaluable patients in BRE12 -158, 172 had BMI available and 140 had ctDNA data. There was no difference in mean BMI between those with ctDNA positivity (29.7, range 18.0-53.1), versus ctDNA negativity (30.5, range 19.9-48.1; $p = 0.48$). There was no relationship between BMI category and presence of ctDNA ($p=0.31$). In multivariate analysis at median follow-up of 17.2 months, continuous BMI was not prognostic of DDFS ($p=0.996$), DFS ($p=0.41$), or OS ($p=0.98$). No association was observed between BMI categories and any survival outcome (p values 0.92, 0.74 and 0.97 for DDFS, DFS and OS, respectively). **Conclusion**: In the disparately high- risk population of TNBC patients with residual disease after neoadjuvant chemotherapy, BMI was not prognostic of DDFS, DFS, or OS. Given that residual pathologic disease and presence of ctDNA are strong prognostic factors in TNBC, lack of accounting for these variables in prior studies may have confounded analyses of the relationship between weight and outcome. Furthermore, analysis in this uniquely chemoresistant population removes questions of the effect of BMI on chemotherapy dosing that have been raised in prior work. We found no signal of a relationship between BMI and presence of ctDNA, contrary to preclinical evidence suggesting obesity facilitates micrometastatic disease in TNBC. These data suggest this is a patient population with inherently aggressive tumor biology, in which host behaviors and phenotype may have less influence. It is hypothesized that impact of weight loss interventions on disease outcome may be blunted by inclusion of populations with high risk disease.

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Shedding light on the dark side of chemo: Post-GWAS functional studies of *rs28714259* in anthracycline-induced cardiotoxicity

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Anthracyclines are commonly used chemotherapies for breast cancer treatment, but can cause dose-related cardiotoxicities and lead to congestive heart failure (CHF) in 2% of patients. Several mechanisms of anthracycline's cardiotoxic effect have been proposed, but the molecular pathogenesis is not fully understood. In addition, there are no clinically available biomarkers to predict cardiotoxicity. Previously we have identified and validated the association of a single nucleotide polymorphism (SNP), *rs28714259* (G/A), with risk of anthracycline-induced CHF through genome-wide association study (GWAS) across three large phase III adjuvant breast cancer trials. *rs28714259* (G/A) locates in a putative glucocorticoid receptor (GR) response element and the risk allele (A) is predicted to disrupt GR binding. The activation of GR signaling pathway by dexamethasone is known to protect cardiomyocytes from doxorubicin-induced apoptosis in rats. To investigate the role of *rs28714259* in CHF post-GWAS, we set out to determine whether *rs28714259* modulates GR signaling pathway through allele-specific GR enhancer activity. We cloned a 1kb DNA sequence on both sides of *rs28714259*, containing either the wildtype (G) or risk allele (A), into a luciferase reporter plasmid. Luciferase assay in iPSC-derived cardiomyocytes (iPSC-CMs) with GR activation by 100nM dexamethasone showed that cardiomyocytes transfected with wildtype construct had 60% increased activity compared to control vector with no enhancer. iPSC-CMs transfected with risk allele constructs did not show increased luciferase activity, suggesting that the A-allele disrupts GR-mediated transcriptional activation. Using electrophoretic mobility shift assay (EMSA) with nuclear extract from iPSC-CMs treated with dexamethasone, we observed a prominent band shift with either G- or A-allele probes. Furthermore, a supershift band was observed with GR antibody, confirming that GR indeed binds to the *rs28714259* region. Notably, the band intensity of risk allele probes decreased by 50% compared to wildtype, suggesting weaker GR binding affinity to risk allele probes, consistent with reduced transcriptional activation. Finally, to identify genes differentially regulated by *rs28714259* with anthracycline exposure, we performed RNA-Seq analysis on iPSC-CMs of each genotype. RNA-Seq data revealed that the top differentially regulated network was the death receptor pathway including: FADD, FAS, and Caspase-8; these effectors are known to induce apoptosis in response to doxorubicin. Moreover, 11 genes in the GR signaling pathway were also differentially regulated by *rs28714259*. Taken together, these findings suggest that the *rs28714259* variant may possess allele-specific GR enhancer activity and differentially regulates genes involved in doxorubicin-induced apoptosis.

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# Breast cancer mortality in women with Her2+ disease treated in a large integrated healthcare system

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**BACKGROUND:** Women with breast cancer are living longer, including those with risk factors such as having HER2+ tumors or diagnosed at later stages, but a dearth of information exists on patients' outcomes beyond clinical trials. Thus, we aimed to describe breast-cancer specific mortality risk for women with HER2+ disease in a large community health plan.
**METHODS:** We assembled a cohort of 3777 adult women (>18 years) with HER2+ breast cancer (AJCC TNM Stages I-IV) from a large California health plan, Kaiser Permanente Southern California, from 2009-2017 and followed them through December 2018. Subjects were identified from the health plan's NCI-SEER affiliated tumor registry. All data elements were captured from the tumor registry and the electronic health records. ER, PR, and HER2 status were assessed by immunohistochemical or FISH techniques. Dates and causes of death were extracted from the inpatient records and state and national death databases. We computed breast cancer-specific mortality rates by exposure to trastuzumab, and by ER, PR, and tumor size. We followed women from the index date up to the date of death or end of study at December 31, 2018, whichever occurred first. Multivariable Cox proportional hazards regression was used to estimated adjusted hazard ratios (HR) and corresponding 95% confidence intervals.
**RESULTS:** Of the 3777 women, the median age at diagnosis was 57 years (range: 22-99 years). The cohort was diverse and included 47% Whites; 12% African American/Blacks; 16% Asian/Pacific Islanders; 24% Hispanics; and 1% of other/mixed backgrounds. Roughly 67% (N=2464) were ER+ and/or PR+. A total of 3170 women (84%) received trastuzumab; N=112 (3%) other chemotherapy only; and N=495 (13%) neither (the majority [85%] had early stage I-II disease). The risk of breast cancer-specific death was 9.3% (351/3777) during a median follow-up of 4.4 years (maximum 10 years).
Breast cancer mortality rate was markedly lower in those with trastuzumab (18.32/1,000 PY) therapy than those who did not receive trastuzumab (27.66/1,000 PY), corresponding to a 44% reduced risk (adj HR=0.56, 95% CI: 0.40-0.76) among those who received trastuzumab. Breast cancer mortality rates were higher in women with greater stage; ER-; PR-; tumors >2 cm and with positive lymph nodes. Compared to women diagnosed at Stage I, those with Stage II-III disease were 2.77 times (adj HR=2.77, 95% CI: 1.87-4.10) more likely to die of breast cancer, and this risk was even higher in those diagnosed at Stage IV (adj HR=11.11, 95% CI: 7.02-17.60), after accounting for trastuzumab use; diagnosis age and year; race/ethnicity; geocoded income; ER and PR status; surgery type; other adjuvant therapy (endocrine, radiation, chemotherapy); lymph node status; histology, BMI, Charlson Comorbidity Index. The adjusted breast cancer mortality risk was 37% greater (adj HR=1.37, 95% CI: 0.99-1.90) in those with ER- disease versus ER+, but the result was of borderline statistical significance. In those with tumors>2cm, breast cancer mortality risk was almost 90% greater (adj HR=0.67, 95% CI: 0.49-0.91) versus those with smaller tumors<2cm.
**CONCLUSION:** This population-based study of patients with HER2+ invasive breast cancer confirms that receiving trastuzumab was significantly associated with a 44% reduced risk of breast-cancer mortality. Further, breast cancer mortality risk was greater in those with higher stages, with large tumors (>2 cm) and positive lymph nodes, even after accounting for trastuzumab use.

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**Publication Number:** PS3-22

# A new computational model for visualization and prediction of breast cancer growth based on reinforcement learning

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**Introduction:** Breast cancer is a complex disease with no simple solution, which is why researchers are tackling it from every angle. A relatively new effort of predictive oncology is to develop a systematic method for predicting the future status of an individual breast tumor given representation of the initial conditions and an appropriate mathematical model. Using a medical imaging-based approach, the goal of this preclinical research project was to obtain high resolution images of the tumor angiogenic network and predict cancer growth using a novel mathematical model that we recently develop.
**Methodology:** In the proposed model, we consider each cell and vessel as an agent and decisions are made based on the state-action-reward-state-action (SARSA) concept, which is an incremental reinforcement learning algorithm. Two types of cells (i.e. cancer and normal) and vessels (i.e. tip and stalk) are used in the environment. This spatial collection of cells and vessels then have six (i.e. apoptosis, hypoxia, necrosis, migration, proliferation and quiescence) and three (i.e. branch, expansion and sprout) allowable actions. The model agent has a high degree of autonomy and performs actions based on the knowledge it receives from the surrounding environment. One of the more important parts of our model is the release and diffusion of select nutrients into the tumor environment, e.g. oxygen, vascular endothelial growth factor (VEGF), etc. Using a breast cancer xenograft mouse model, animals were administrated an intravascular contrast agent (200 microliters, ExiTron Nano 12000, Miltenyi Biotec) and tumors were scanned using an ultrahigh resolution computed tomography (CT) system (OI/CT, MILabs). The tumor microvascular network was segmented and used as an input and initial state of our model that then simulated cancer growth. Subsequent CT scans (on the order of weeks) were performed to validate model accuracy.
**Results:** Initial results demonstrate that the SARSA model can simulate tumor growth. As the concentration of available nutrients around the tumor decreases, normal cells began to decline sharply and were eliminated by selecting the apoptotic phenotype. Cancer cells were more resistant to nutrient deficiencies during simulation. Consequently, these cancer cells proliferated, and tumor volume increased. Our findings also revealed that decreased oxygen availability (i.e. hypoxia) stimulated VEGF production and growth of the microvascular network, which agreed with repeat *in vivo* CT imaging results.
**Conclusion:** A predictive model of breast cancer growth was developed and preliminary preclinical results using *in vivo* medical images of breast cancer-bearing animals highlighted the utility of this new oncological tool.

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# Augmentation of a minimal multidisciplinary tumor board with clinical decision support to triage breast cancer patients in the UK

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**Background**All UK cancer patients undergo required assessments by a full Multidisciplinary Tumor Board (fMTB) at key treatment decision points, placing a resource burden on the healthcare system. Watson for Oncology (WfO) is a decision-support system that presents therapeutic options to cancer-treating clinicians. This study is an initial phase of an evaluation at Guys and St. Thomas' NHS Hospital (GSTT), designed to explore the extent to which WfO can be used by the fMTB to triage less complex patient cases and ultimately reduce workload and time pressures currently experienced by fMTBs. We conducted a concordance study with two minimal MTB teams (mMTB) for Stage I-III breast cancer patients.
**Methods**Breast cancer cases (*N*=63) treated from 2017-2018 at GSTT were evaluated by 2 independent mMTBs, blinded to each other and previous fMTB decisions rendered prior to this study. Each mMTB consisted of a senior medical oncologist and surgeon; GSTT's 12+ member fMTB is comprised of oncologists, surgeons, radiologists, pathologists and others. mMTBs were shown options that were either listed as 'recommended' or 'for consideration' by WfO and given the opportunity to revise prior decisions. The combined 4-person minimal MTB (cmMTB) consisting of both 2-person mMTBs provided a current consensus best-practice plan and systemic therapy recommendations for discordant cases. We evaluated the concordance of WfO's systemic therapeutic recommendations and mMTBs, as well as concordance with the cmMTB. Previous decisions by the fMDTB were also compared to decisions by the cmMTB. Univariate logistic regression explored characteristics predictive of concordance with the cmMTB.
**Results**For treatment plans, WFO's therapeutic options had higher concordance with cmMTB decisions than either mMTB alone (concordance 93.7% vs. 92.1%) or the previous decisions by the fMTB (87.3). For systemic therapy decisions, the WfO-cmMDTB concordance was 70.2%; however, adjusting for non-NICE approved drugs and the common practice of Carboplatin use in the UK, concordance increased to 91.5%. Previous decisions by the fMTB had the lowest concordance with the cmMTB (87.3%). Adjusting for the UK-practice related use of Carboplatin, WfO had slightly higher concordance with cmMTB systemic therapy decisions than either mMTB alone (89.4% and 87.2%). Univariate analysis with this limited sample revealed non-significant trends in association between mMTB's concordance with
WfO and stage of cN at diagnosis, HER2 status, tumor location and grade. For example, mMTBs concordance with WfO tended to improve when tumor grade was high. Non-significant trends were also identified in the association between WfO-treatment concordance and tumor location, where treatment concordance increased with medial tumor location.
**Conclusion**In this small cohort study, a clinical decision-support tool demonstrated better agreement with UK best practice treatment than a 2-person mMTB and may have a role in triaging breast cancer cases in the UK.

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Mutational profile from circulating tumor DNA in triple negative breast cancer: Results from the prospective registry of unresectable locally advanced or metastatic breast cancer GEICAM/2014-03 (RegistEM)

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**Background:** The RegistEM is a non-interventional cohort study enrolling 1,867 patients (pts) (males or females) with advanced breast cancer diagnosed from January 2016 to December 2019, either after recurrence or as first diagnosis, in 38 Spanish sites. Triple negative BC (TNBC) is clinically defined based on lack of expression of both estrogen and progesterone receptors, and HER2 overexpression, and constitutes approximately 16% of BC cases. It is a particularly proliferative and aggressive BC subtype characterized by higher rates of relapse, greater metastatic potential, and shorter overall survival compared with other BC subtypes. Recent studies have shown hormone receptor status can change from the primary (P) to the recurrence tumor (M) in a proportion of cases, inducing a switch to TNBC in the recurrence, while other remains TNBC both in the P and M setting. This feature might impact survival and treatment options. **Methods:** We selected TNBC pts from the RegistEM study with ctDNA plasma samples available from the relapse. TNBC pts were classified into 2 groups according to clinical subtype (CS): 1) CS-converted (CS-C), with a discordant phenotype (TN subtype in M but not in P); and 2) CS-non-converted (CS-NC), with TN phenotype in P and M. To compare the mutation profiles of the 2 groups, next-generation sequencing (NGS) was performed using the AVENIO Expanded ctDNA Analysis Kit (Roche Sequencing Solutions, Inc; 77 genes; SNPs, indels, fusions and CNVs). Genomics alterations at individual level and grouped by pathway were explored for pathogenic and probably pathogenics variants. Genomics findings were correlated with clinicopathological data and outcomes, in terms of progression-free survival (PFS) and response to first line chemotherapy treatment. Kaplan-Meier estimator and Cox regression model were used to analyze PFS, and Fisher's test to analyze contingency tables. Bonferroni correction was used for multiple testing. **Results:** NGS data was available from 32 (17%) TNBC pts; 22 (69%) pts CS-NC and 10 (31%) CS-C. The time from diagnosis to relapse was 29.2 months (m) for CS-NC and 60.2m for CS-C (HR=4.81, 95% confidence interval (CI) (1.59-14.59), p=0.0055; adjusted for confounders: menopausal status, grade, stage). In the metastatic setting, CS-NC had similar PFS than CS-C (8.3m CS-C vs 5.3m CS-NC; HR=1.63, 95% CI (0.71-3.72), p=0.2442). A median of 3 genomic alterations were found, similar in both groups. The most frequent somatic alterations were *TP53* (50%), *MAP2K1* (25%) and *APC* (25%). CS-C were enriched for *MAP2K1* (60% vs. 9% in CS-NC; p=0.0243). No single genomic alteration was associated with outcome. Forty-percent of tumors harbored at least 1 mutation in PI3K-AKT-mTOR pathway (*PIK3CA, PIK3R1, AKT1, AKT2, PTEN* or *MTOR* genes), with similar incidence between CS-NC and CS-C. Pts with an altered PI3K-AKT-mTOR pathway had poor PFS (3.9m mutant vs 6.7m wild-type (WT); HR=3.02, 95% CI (1.4-6.56), p=0.0033) and a trend to worse response (complete or parcial response and stable disease: 23% mutant vs 77% WT, p=0.1581). CS-C tumors presented an altered MAPK-ERK pathway (mutations in *KRAS, NRAS, BRAF, MAP2K1* or *RAF1* genes) more frequently in comparison to CS-NC (60% vs 23%, p=0.0557), with no differences in response or PFS. Finally tumors with a high mutation allele frequency (≥mean) showed poor PFS (HR=3.64, 95% CI (1.52-8.75), p=0.0038). **Conclusion:** Analysis of ctDNA reveals diverse mutational spectrum in metastatic TNBC, suggesting that the presence of *PI3K-AKT-mTOR* pathway alterations associates with worse outcome and poor response to standard therapies. The clinical subtype conversions from luminal primary tumor are enriched in MAPK-ERK pathway alterations.

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# Lipophilic statins for prolonging dormancy and overall survival: A real-world retrospective investigation

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Background: Micrometastases from breast cancer (BC) might undergo quiescence following adjuvant therapies. Oftentimes they reactivate, prompting metastatic relapse and aggressive, uncurable disease. It is necessary to find alternative, safe therapies that could be used as adjuvants for delaying the dormancy process and reduce metastatic breast cancer (MBC) progression. Prior epidemiological studies found prolonged overall survival from chronic statin use. However, the effectiveness of statin use through different stages of progression, including advanced MBC, has not yet been defined. Methods: A real-world, retrospective analysis of 1,016 deceased patients with MBC treated from 1999-2019 at the University of Pittsburgh Medical Center (UPMC). Lipophilic statin (atorvastatin and simvastatin) use and dosing were retrieved from medical records through an IRB-approved R3 request and merged with already available clinical variables. A total of 122 patients were included in the analysis as the statin use group. This included patients who were prescribed statins through the course of their breast cancer. For measuring time to relapse, only patients with statin prescription before being diagnosed with MBC were selected. Log-ranks were used to compute survival. Uni- and multi-variate Cox hazard models were also applied. Statistical analysis was computed using the package *ggpubr* on R v3.6.3.Results: Women who used statins were older at the time of detection of primary (60 vs 52 years of age, respectively) and MBC (66 vs 56 years of age, respectively). An almost 2-fold reduction was found in the onset of liver metastasis as first relapse in the statin group, compared to general population (5.7% vs 10.4%, respectively). Increased overall survival (OS) was found among statin users who had ER (+) ($p<0.05$), and HER2 (-) ($p<0.05$) BC. Statins were associated with an increase in time from diagnosis until relapse, in ER (+) ($p=0.03$) and HER2(-) ($p=0.02$) patients with BC. Patients with ER (-), HER2 (-) MBC also seemed to partially benefit from statin use ($p=0.09$). Multivariate analysis adjusted for age, ER-status, statin use, and adjuvant chemotherapy also predicted increased OS for patients using statins. No differences in survival were seen when measuring time from metastatic diagnosis to death, suggesting that statins may be effective in prolonging dormancy but lack benefit against relapsing MBC.Conclusion: Lipophilic statins may prolong dormancy and overall survival but not slow the progression of relapsing metastatic breast cancer.

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# Multidisciplinary Tumor Board in Breast Cancer: Results from a large international survey involving 71 countries

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**Introduction:** Multidisciplinary tumor boards (MTB) offer patients (pts) access to multidisciplinary care and may lead to more efficient, cost-effective and evidence-based treatments and better outcomes. Data regarding the implementation and functioning of breast cancer (BC) MTB worldwide and according to countries' income are lacking. **Methods:** We developed a survey, which was disseminated to healthcare professionals working in BC through the use of social networks and emails (accessible from 15 May to 3 July 2020). Countries' income classification was defined according to the World Bank Atlas method. **Results:** We obtained 675 responses from 71 countries (40% Western Europe, 14% Eastern Europe, 13% Latin America, 13% Asia, 11% Oceania, 5% North America, 3% Africa; 71% high income, 28% middle income, 1% low income countries). More than half of the respondents were medical oncologists (55%), followed by surgical oncologists (12%), clinical oncologists (11%) and radiation oncologists (7%). Over 60% were between 30-49 years of age and 55% had >10 years of medical practice. MTBs from academic institutions (43%), dedicated cancer centers (30%), public (19%) and private (18%) institutions were reported. Overall, 11% of respondents do not have regular MTBs in their institution, with discrepancies among regions: 34% of respondents from Asia, 18% from Africa, 17% from Eastern Europe, 14% from Latin America, 3% from Western Europe, 2.6% from Oceania and none from North America. This corresponds to 43% of respondents from low income, 22% from middle income and 5.6% from high income countries. Among these, 42% have their patients informally discussed between departments, 23% within a single department and the decision is taken only by the attending physician in 31% of the cases. Eighty-nine percent of respondents (N=602) have regular MTBs, of which 69% are dedicated to BC; 71% discuss all stage I-IV BC cases before any treatment decision, whereas 18% only present new BC cases, before starting any form of treatment and 11% discuss only early BC cases. Above 80% have >4 disciplines represented (18% have 1-3, 44% 4-6, 37% 7-9 and 13% >10). The most represented discipline is medical oncology (98%), followed by surgical oncology (94%), radiation oncology (90%), pathology (87%) and radiology (80%), among others. A nurse is present in 49% of MTB, a psychologist/psychiatrist in 19%, a social worker in 11% and the doctor in charge of the patient in 25%. Pts are not present in 80% of MTB in high income countries, in 44% in middle income and in 29% in low income. Half of respondents reported that it is not mandatory for the treating doctor to implement the decision of the MTB. For 72%, the decision of the MTB is implemented in >75% of the cases, but only 24% have a quality control to check this. When asked about the results of an effective BC MTB, respondents agreed that it resulted in improved clinical decision making (95%), more coordinated patient care (86%), evidence-based treatment decisions (89%), shorter time to tests/treatments (60%) and improved survival (50%). During the COVID19 pandemic, 5% of all MTB were cancelled, 50% switched to virtual meetings, 16% maintained physical MTB with adjustments (social distance/personal protective equipment). Only 7% believe that all MTB will remain virtual, 40% think that MTB will return to their original physical version and 53% that there will be an alternating scheme. **Conclusions:** The vast majority of participants reported having regular MTBs in their institution, with a high rate of uptake of MTB recommendations. Differences in the implementation of MTB according to the countries' level of income can be observed and highlights the need to scale-up MTB coverage around the world, especially in low/middle income countries. The COVID19 pandemic led to a high adoption of virtual MTB, which may have long-term effects.

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Supportive care needs and patient experience of women with metastatic breast cancer in a safety-net system

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**Background:** Metastatic breast cancer (MBC) is an incurable, albeit treatable cancer affecting over 150,000 women in the US. Addressing supportive care needs has become increasingly important as women are living longer with MBC due to advances in treatment. However, most supportive care programs were developed for women with early stage breast cancer. The existing literature also offers limited understanding of the needs of patients receiving care in safety net settings, which are often under-resourced and treat medically underserved populations, who are more likely to be diagnosed with MBC.
**Methods:** This study sought to understand the supportive care needs and experience of MBC patients receiving care in a safety net system. Semi-structured interviews were conducted with 11 patients (average age = 42.8 years, SD = 19.5) who were undergoing treatment for MBC. Questions centered on the diagnosis and treatment experience, patient-provider communication, and perceived barriers to care. Interviews were digitally audio-recorded, transcribed and coded using a Grounded Theory approach. **Results:** Patients noted that a lack of familiarity with medical terminology and insufficient medical knowledge made it difficult for them to evaluate treatment options, make treatment decisions, and communicate their supportive care needs. Half (n=5) did not feel their healthcare concerns were validated when expressed and some even went so far as to exaggerate reports of physical symptom severity in order to receive more timely and attentive care. Patients were dissatisfied with the timeliness of information delivery, scheduling delays, and long wait times. Some also felt that seeing different providers (e.g., residents, fellows) each time they came into the clinic interfered with the doctor-patient bond and continuity of care.
**Conclusion:** This study identified patient, provider, and system-level factors affecting MBC patients' experience of care in a safety-net system. Our findings indicate a strong need for support services including outreach to address health literacy issues, treatment decision making, and symptom management concerns. They also indicate a need for improved disease and treatment information exchange between patients and healthcare providers.

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An open-label, multicenter study evaluating the safety of lasofoxifene in combination with abemaciclib for the treatment of pre and postmenopausal women with locally advanced or metastatic ER+/HER2− breast cancer and have an *ESR1* mutation

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Endocrine therapy is the established treatment for metastatic breast cancer (MBC) in patients that express estrogen receptor (ER) and/or progesterone receptor (PR). Agents targeting the ER pathway such as aromatase inhibitors (AIs) and fulvestrant with or without additional biologic agents are effective, but not curative. Over the last several years, clinical studies have shown that adding a CDK 4/6 inhibitor (CDKi) to endocrine treatment (either AIs or fulvestrant) significantly increases time to progression for MBC patients. Unfortunately, resistance due to a number of causes eventually develops. Secondary mutations in estrogen receptor (*ESR1*), most frequently seen after AI treatment produce constitutive activation of ER and are associated with a worse disease prognosis. Treatment options for MBC patients with an *ESR1* mutation are limited and currently there are no approved therapies. Additionally, limited data exist to justify whether cyclin dependent kinase 4/6 inhibitors (CDK4/6i) should be continued, substituted for another CDK4/6i or discontinued all together. Lasofoxifene is a third generation SERM previously investigated for the treatment of osteoporosis and vulvo-vaginal atrophy (VVA). Clinical data have shown a significant reduction in the incidence of ER+ breast cancer in postmenopausal women with osteoporosis treated with lasofoxifene. These results supported further studies which showed significant *in vitro* and *in vivo* efficacy in pre-clinical breast cancer models. Moreover, a significant benefit was seen in pre-clinical models with lasofoxifene either as monotherapy or in combination with a CDK4/6i over fulvestrant (with or without a CDK4/6i) in breast cancer cells expressing *ESR1* mutations. The multicenter phase 2 (ELAINE 1) study is currently enrolling patients evaluating the activity of lasofoxifene monotherapy compared to fulvestrant. Also, studies have shown that abemaciclib has meaningful clinical activity in patients previously exposed to other CDK4/6i (palbociclib/ribociclib) and chemotherapy. The pre-clinical and clinical study results also provide a strong rationale to pursue a phase 2 clinical trial in BC patients with *ESR1* mutations in combination with a CDK4/6i.The ongoing study (ElAINE 2) is an open-label, multi-center study evaluating the safety of the combination of lasofoxifene and CDK4/6i abemaciclib. Inclusion criteria include pre- and postmenopausal women with ER+ *ESR1*mutation-bearing advanced breast cancer who have progressed on prior hormonal treatment and a CDK4/6i (including abemaciclib); 24 patients with measurable or evaluable disease (i.e. bone only) will be recruited. The primary endpoint will be the safety of the combination. Secondary endpoints will include progression free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), duration of response (DoR) and time to response (TTR), with exploratory serial circulating tumor DNA landscape analysis. The study started in 2Q2020 and will complete recruitment in 1 year. Ten centers in the US will be participating. Recruitment status will be provided at the time of presentation.

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Clinical characteristics, prognostic factors and treatment comes of patients with bone-only metastatic breast cancer

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**Introduction**: Despite efforts in advancing early detection programs, 5-20% of breast cancer patients present with distant metastases at diagnosis. Bone is the most frequent site of breast cancer metastasis, noted in 60-80% of metastatic breast cancer (MBC) patients, and is the first site of metastatic disease in 25-40% of patients. The outcome of patients with bone-only MBC (BOM) is usually better than those with visceral metastasis. However, differences between those who present with De-novo BOM and those who progress to bone-only disease following a diagnosis of early stage breast cancer is not clear. Such differences in clinical course might have an implication on aggressiveness of treatment.The aim of the study is to present the clinical and pathological features along with treatment outcomes of breast cancer patients with BOM in relation to timing and type of bone metastasis. Known prognostics factors that affects treatment outcome will be presented.**Patients and Methods:** Patients with De-novo and those who progressed after an initial diagnosis of early-stage breast cancer with bone-only metastasis diagnosed, treated and followed up at our institution between 2006 and 2018 were included. Data related to characteristic such as, grade, hormonal status, HER-2 status were collected from our electrical medical records, pathology and radiology reports. De-novo BOM was defined as bone metastasis diagnosed at presentation or within the first 4 months of follow up. **Results**: A total of 242 patients fulfilled our inclusion criteria and were included in the analysis. The median age (range) at diagnosis was 52 (27-80) years. Majority of the patients (77.3%) had De-novo BOM and multiple sites of bone involvement was identified in 82.6%. High- grade (G-III), HER2-positive and hormone receptor (HR)-negative disease were identified in 27.2%, 18.2% and 8.7%, respectively. Majority of the patients were treated with endocrine therapy while 31(12.9%) patients received chemotherapy at presentation.With a median follow up of 37.7 months, 185 (76.4%) of patients progressed, the median time to progression was 17.1 months (range 3-280m). The median overall survival (OS) for patients with de novo BOM disease was significantly shorter than those who developed subsequent bone metastasis; 40.8 months (95% CI, 51.1-184.1) compared to 80.9 months (95% CI, 36.4-47.9), $p < 0.001$. Tumor grade, HR status and type of bone lesions (lytic or sclerotic) have significant impact on 5-year OS as detailed in Table-1

| Characteristics | | 5-year Progression-Free Survival | | 5-year Overall Survival | |
|---|---|---|---|---|---|
| | | Percentage | P-value | Percentage | P-value |
| Age (year) | <50 | 22.7 | 0.55 | 44.9 | 0.21 |
| | ≥50 | 22.7 | | 39.2 | |
| Tumor grade | I | 27.3 | 0.005 | 64.9 | 0.01 |
| | II | 23.3 | | 43.6 | |
| | III | 9.6 | | 26.6 | |
| HER2 | Negative | 23.1 | 0.03 | 43.6 | 0.79 |
| | Positive | 15.6 | | 32.9 | |
| Estrogen receptors (ER) | Negative | 16.3 | 0.15 | 13.7 | 0.005 |
| | Positive | 23.1 | | 44.5 | |
| Progesterone receptors (PR) | Negative | 17.7 | 0.09 | 20.6 | 0.004 |
| | Positive | 23.3 | | 45.5 | |
| Number of bone lesions | Multiple | 20.6 | 0.08 | 39.1 | 0.08 |
| | Single | 34.5 | | 54.8 | |
| Type of bone metastasis | Lytic | 28.2 | 0.93 | 46.0 | 0.01 |
| | Sclerotic | 21.5 | | 54.9 | |
| | Mixed | 14.6 | | 43.0 | |
| Time of bone metastasis | De novo | 13.4 | <0.001 | 35.5 | <0.001 |
| | Late | 49.0 | | 60.5 | |

**Conclusions**: Bone-only metastasis breast cancer is distinct clinical entity with a favorable prognosis and a prolonged overall survival. Several risk features for poor OS were identified and might be useful tool to design future clinical trials to trigger upscaling endocrine therapy to include newly introduced resistance modulating agents.

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# Fatty acid synthase enzyme as a mediator of obesity-induced breast cancer

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**INTRODUCTION:** Breast cancer accounts for nearly 40,000 deaths annually with the overall prognosis worsened if the patient is obese. Reprogramming of lipid metabolism in cancer is an established hallmark and contributes to tumorigenesis and drug-resistance. The fatty acid synthase enzyme (FASN) is overexpressed in multiple solid and hematopoietic tumors and its expression is associated with tumor grade as well as resistance to therapy. Targeted therapies against the fatty acid synthase enzyme (FASN) are currently in phase II of clinical trials for the treatment of multiple solid tumors. Previously, our lab has shown enhanced expression of FASN in breast cancer cells exposed to obese sera as well as increased sensitivity to the FASN inhibitor, TVB-3166. The obese phenotype is characterized by increased circulating bioactive growth factors and hormones, such as insulin, estrogen, and insulin-like growth factor 1 (IGF-1), that are ligands for the insulin (IR) and insulin-like growth factor receptor-1 (IGF-1R). Activation of these receptors can lead to downstream signaling through the PI3K-Akt-mTOR pathway that mediates lipogenic gene expression through various transcription factors. Of these transcription factors, sterol regulatory element-binding protein-1 (SREBP-1), drives FASN gene expression and is activated downstream of both Akt and mTORC1. **HYPOTHESIS**: We hypothesize that obesity-induced breast cancer progression is mediated through an SREBP dependent overexpression of FASN. **METHODS:** MCF-7 cells were exposed to obese or non-obese sera and subjected to quantitative RT-PCR for FASN expression. MTT and colony-forming assays using both MCF-7 and T-47D breast cancer cells conditioned in 2% obese and 2% non-obese sera as well as treated with and without a FASN inhibitor (TVB-3166) were utilized to determine cell survival and viability in response to FASN inhibition. FASN expression in obesity-induced breast cancer was investigated by treating MCF-7 cells with either insulin or SREBP processing inhibitor (Betulin) and subjected to chIP-qPCR against anti-SREBP or normal rabbit IgG. **RESULTS:** In response to obese sera exposure, there was a nearly 3-fold increase (p=.010) in FASN expression compared to non -obese control. Obese sera exposure increased sensitivity and decrease cell viability to TVB-3166 treatment compared to non-obese sera. ChIP-qPCR against anti-SREBP showed an increase in FASN expression upon treatment with insulin compared to normal rabbit IgG control. This increase in FASN expression was attenuated upon treatment with the SREBP processing inhibitor, Betulin. **CONCLUSION:** The overexpression of FASN contributes to obesity-induced breast cancer aggression and is regulated by an insulin-SREBP-FASN signaling axis.

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# Intratumoral delivery of tavokinogene telseplasmid (plasmid IL-12) and electroporation induces an immune signature that predicts successful combination in patients

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Interleukin-12 (IL-12) is a pro-inflammatory cytokine involved in the generation of an inflammatory tumor microenvironment and is critical in eliciting a productive anti-tumor immune response. It has been investigated as an anti-cancer therapeutic using various delivery routes, but intratumoral injection of plasmid IL-12 (tavokinogene telseplasmid; TAVO) followed by electroporation is a gene therapy approach that results in more sustained production of IL-12 locally with minimal systemic immune-related toxicity. Here we show that TAVO not only provides protection in the treated triple-negative breast cancer (TNBC) lesion, but also induces a systemic, abscopal effect. Single cell RNAsequencing (scRNAseq) of infiltrating immune cells shows a significant increase in both CD4 and CD8 T cells as well as dendritic cells within the treated lesions, while simultaneously decreasing a granulocytic myeloid derived suppressor population. scRNAseq allows for a detailed look into not only the overall pathway enrichment caused by TAVO treatment, but also the specific receptor-ligand interactions occurring between cell types. A combination of these analyses revealed an enrichment in the IFN-gamma induced PDL1 pathway by TAVO, typified by an increase in the interaction between PDL1 on dendritic cells and PD1 on CD8 T cells. Further, dramatic enrichment of the CXCL9/10/11/CXCR3 axis was observed, consistent with previous studies in melanoma. Analysis of paired TCR alpha and beta chains on T cells additionally demonstrated a dramatic shift in tumor infiltrating T cell (TIL) clonality and frequency. In sum, these preclinical studies identify a signature of increased antigen presentation, T cell infiltration and expansion, and a decrease in the number of granulocytes but also a particular enhancement of the PDL1 immunosuppressive pathway following TAVO treatment. Using this signature, we focus on an in-depth analysis of 2 patients from a single arm, prospective clinical trial of TAVO monotherapy (OMS-I140) in pre-treated advanced TNBC that went on to receive anti-PD-1 as their immediate next therapy with clinical anti-tumor response. Together these data support the combination of TAVO with PD1/PDL1 inhibitors while also identifying other key pathways that may enhance responsiveness in TNBC patients for whom treatment options remain limited.

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Development of a breast cancer organoid resource faithfully representing epithelial heterogeneity and drug response

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Organoid cultures are being explored as intermediate preclinical models in numerous cancer types including colon, liver and brain. Recently it has been demonstrated that organoids can be robustly isolated and cultured from breast cancer subtypes, that they maintain the histological, genomic and transcriptomic signatures of the primary tumor tissue, and that ER expression can be preserved (Sachs et al, 2018). The Institute for Precision Medicine (IPM), a collaboration between UPMC and the University of Pittsburgh initiated a program to develop breast cancer organoids in 2018. The IPM works closely with surgeons to consent patients with primary or metastatic breast cancer for tissue collection, and with an institutional biospecimen core for tissue procurement and deidentification. The IPM receives fresh, deidentified tissue typically within 60 minutes of the patient's operation. Based on the protocol by Sachs et al, to date we have established 49 organoids from a total of 60 tumor samples received from patients undergoing resection of their primary or metastatic breast tumor, resulting in a success rate of 82%. Our current collection includes organoids from 17 treatment-naïve invasive ductal carcinomas, 12 treatment-naïve invasive lobular carcinomas, 10 primary tumors excised after neoadjuvant therapy and 5 from breast cancer metastasized to bone or ovary. Our organoids demonstrate a range of growth morphologies, consistent with those previously described. ER expression can be detected in a subset of our cultures as well as robust response to estradiol as indicated by the induction of GREB1 gene expression. We have further demonstrated that organoids are amenable to transient transfection of siRNA and lentiviral infection of reporter constructs which allows for RFP and luciferase-based detection of cells both *in vitro* and *in vivo* as well as expression of genes of interest. We additionally recognized that some of our organoid cultures can give rise to suspension cultures when maintained in organoid culture medium but without 3D matrix. This observation allows the opportunity for further phenotypic evaluation by increasing the number of assays amenable to these unique patient derived cultures. Single cell RNA sequencing (10X Genomics) of organoid cultures and paired tumor tissue confirms that organoid cultures faithfully maintain the heterogeneity of epithelial subpopulations found in the surgically resected tumors. Further, organoids show greater epithelial diversity and heterogeneity compared to single cell sequencing of breast cancer cell lines. We have further used sequencing data to identify targetable pathways in individual organoid cultures and demonstrate that drug sensitivity can be correlated with gene expression in these models. Collectively, these data indicate that breast cancer organoids represent a valuable model for preclinical breast cancer research.

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Elucidating the role of APC resulting in doxorubicin resistance in breast cancer

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Chemoresistance is a leading cause of breast cancer related deaths. Therefore, understanding the molecularbasis for chemoresistance is essential for novel therapeutic advancement improving patient outcome. TheAdenomatous Polyposis Coli (APC) tumor suppressor is lost in up to 70% of sporadic breast cancer; however,little is known about how APC loss contributes to chemoresistance. Using mammary tumor cells isolated fromthe Apc Min/+ mouse crossed to the Polyoma middle T antigen (PyMT) transgenic model, we werethe first to show that APC loss decreased doxorubicin (DOX) induced apoptosis. Therefore, we investigatedthe mechanisms contributing to DOX resistance with APC loss to identify combination therapy options. DOX, acommonly used chemotherapeutic in breast cancer, inhibits topoisomerase IIa (Topo IIa), causing doublestranded breaks (DSBs), the most lethal form of DNA damage, and APC has been shown to affect Topo IIaactivity. DSB repair is mediated through HRR (homologous recombination repair) or NHEJ (nonhomologousend joining), which are regulated by the repair serine/threonine kinases: ataxia telangiectasia mutated (ATM)or ataxia telangiectasia and Rad3 related (ATR), but only NHEJ activates DNA-dependent protein kinase(DNA-PK). We hypothesized that APC loss prevents DOX-mediated apoptosis through alterations in HRR andNHEJ. To investigate the effect of APC loss on DNA damage repair pathways, we monitored damagerecognition pathways after 24-hour DOX treatment. The MMTV-PyMT;Apc Min/+ cells exhibited decreaseddamage as measured by γH2AX expression and comet assay. We also observed decreased ATMphosphorylation in MMTV-PyMT;Apc Min/+ following DOX treatment compared to control. Decreasedphosphorylation of Chk1 and Chk2 was also observed in DOX-treated MMTV-PyMT;Apc Min/+ cells. Using theATM inhibitor (KU55933) or the DNA-PK inhibitor (NU7441), we observed increased DOX-induced apoptosis inMMTV-PyMT;Apc Min/+ cells. These data suggest enhanced DNA repair in MMTV-PyMT;Apc Min/+ cells and will beconfirmed by measuring repair efficiency via reporter plasmids. In addition, knowing that APC affects activitiesby Topo IIa, we measured the amount of Topo IIa: DNA cleavage complexes following DOX treatment.Taken together, APC loss mediates DOX resistance via increasing DNA repair demonstrating the potential useof combination therapy to overcome chemoresistance.

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# An analysis of the clinical and economic impact of the 21-gene recurrence score (RS) in invasive lobular early-stage breast cancer (ESBC) in Ireland

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**Background:** The use of the 21-gene recurrence score assay (RS) has reduced chemotherapy (CT) administration in patients with hormone receptor (HR)-positive, HER-2 negative, lymph-node negative, early stage breast cancer (ESBC). Invasive lobular carcinoma (ILC) accounts for up to 15% of all breast cancers. This study uses real world data to assess (1) the effect of RS testing on treatment decision making in patients with ILC and (2) the economic benefit of testing in this subgroup.
**Methods:** From October 2011 to February 2019, a retrospective, cross-sectional, observational study was conducted on HR+, HER-2 negative, lymph-node negative, ESBC patients with ILC who had RS testing in Ireland. For the decision impact analysis, a survey of Irish breast medical oncologists presumed that, without RS testing, CT would be recommended to patients with histological grade (G) 2 and 3 tumours and not for G1 tumours. In accordance with TAILOR-x results, patients were classified overall as low risk (RS≤25) and high risk (RS>25) and patients ≤50 years old were low risk (RS 0-15), intermediate risk (RS 16-25), and high risk (RS>25). Data were collected from electronic patient records. Descriptive statistics were used. Cost data were obtained from the National Healthcare Pricing Regulatory Authority. The economic analysis was adjusted for changing treatment and assay costs over the study period.
**Results:** 166 patients with ILC were identified. Mean age was 59 years. Mean tumour size was 2.3cm (range 0.7-5.8). The majority had G2 tumors (n=152, 92%) with a small number of G3 (n=7, 4%) and G1 (n=7,4%). Overall, 153 patients (92.2%) had a low RS (≤25), 12 (7.2%) had high RS (>25), and 1(0.6%) was unknown. All 12 patients with RS>25 had G2 tumours, 6/12 (50%) had tumour size >3cm, 4(33.3%) were PR+ and 8(66.7%) were PR negative. In 29/166 (17.5%) patients, aged ≤50 at diagnosis, RS was ≤15 in 16(55%), 16-20 in 6(21%), 21-25 in 5(17%), >25 in 1(3.5%) and unknown in 1(3.5%). The majority of these patients (27, 93%) had G2 tumours, 1 had G1 and 1 had G3. Post RS testing 124 patients (74.5%) had a change in CT recommendation; all from CT to hormone therapy. In total, only 35 patients (21%) received CT. In this group, RS was 0-15 in 3(9%), RS 16-25 in 19(54%), RS >25 in 12 (34%) and unknown in 1(3%). Eight of 35 patients (23%) were aged ≤50. The most common CT regimen administered was docetaxel plus cyclophosphamide (TC). RS testing achieved a 78% reduction in chemotherapy use. This resulted in savings of €900,000 in treatment costs. With the incorporation of the assay cost, the net savings totalled approximately €400,000.
**Conclusions:** Ireland was the first public health care system to reimburse the 21-gene recurrence score assay in Europe. There is limited evidence demonstrating the benefits of RS in ILC. In our study, the use of the test has resulted in a 78% reduction in chemotherapy use in an Irish ILC patient population and a substantial cost saving (greater than €400,000) to the Irish Healthcare System.

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# Reconsidering the management of palpable DCIS - A single institution audit

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**Background:** Ductal carcinoma in situ (DCIS) identified by screening mammography accounts for 20% of breast cancer diagnoses, and microinvasion (DCIS-M) is found in 5%-10%. There are no defined treatment guidelines for palpable DCIS or DCIS-M. The role of screening mammography is now being questioned across the world and in the developing world with no national screening programs, women with DCIS present with a palpable lump in the breast. We conducted a retrospective audit of women with DCIS treated at our institution to classify palpable DCIS and DCIS-M as distinct clinical stages and emphasize the need for a change in management of 'palpable DCIS'

**Methods:** Annually we register approximately 1700 new cases of early breast cancer of which DCIS and DCIS-M constitutes less than 1%. Between 2005-2016 we registered 784 cases of with DCIS, DCIS-M and early invasive cancer with extensive intraductal component (EIC) at our centre. A retrospective analysis of these cases was performed.

**Results:** Of the 784 patients case records reviewed, 113 (14.4%) had Tis, 87 (11.1% of all early cases and 43.5% of DCIS) had T1mic, the rest had invasive cancer with EIC, of which 46 (5.9%) wereT1a, 28(3.6%) were T1b, 146 (18.6%) were T1c and 364 (46.4%) wereT2. The median age at presentation was 48 years, median clinical tumour size was 3cm; 740 (94.4%) presented with palpable breast lumps.At a median follow up of 86 months , the disease free survival was 95.6% for Tis, 96.6% T1mic, 90.5% T1 and 82.7% T2 (p=0.00). On follow up distant recurrences were noted in 5(4.4%) patients with Tis, 3(3.4%) with T1mic, 21(9.5%) with T1 and 63(17.3%) with T2, (p=0.00). Limited use of adjuvant chemotherapy in Tis and T1mic may have contributed to the high distant recurrences in that group. Also palpable Tis,T1mic and T1a had higher percentage of HR negative compared to those with larger invasive tumours.

**Conclusions:** DCIS presenting in palpable lesions poses a clinical dilemma for the use of adjuvant therapy. In our cohort 43.5% of the palpable DCIS showed evidence of microinvasion with high risk of distant recurrence compared to screen detected DCIS. We thus need to reconsider grossing techniques to accurately identify foci of invasion, redefine DCIS-M based on number and size of foci of invasion and explore the possible role of adjuvant chemotherapy in treating large palpable DCIS.

Results

| | Tis (N%) | T1mic (N%) | T1a (N%) | T1b (N%) | T1c (N%) | T2 (N%) |
|---|---|---|---|---|---|---|
| cT >2 cm | 63 (55.8) | 68 (78.2) | 28 (60.9) | 6 (21.4) | 1 (0.7) | 363 (99.7) |
| Palpable lump | 85 (75.2) | 81 (93.1) | 39 (83) | 28 (100) | 144 (98.6) | 363 (99.7) |
| Nipple discharge | 26 (23) | 6 (6.8) | 7 (14.9) | 0 (0) | 2 (1.3) | 1 (0.3) |
| Hormone receptor positive (HR+ve) | 60 (53.1) | 18 (20.7) | 18 (38.3) | 15 (53.6) | 92 (63) | 218 (60.6) |
| HER2neu +ve | 31 (27.4) | 41 (47.1) | 13 (27.7) | 8 (28.6) | 27 (18.5) | 93 (25) |
| Axilla +ve | 6 (5.3) | 9 (10.3) | 9 (19.1) | 9 (32.1) | 50 (34.2) | 184 (50.7) |

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Evaluation of a beneficial effect of adjuvant chemotherapy in patients with stage I triple-negative breast cancer: A population-based study using the SEER 18 database

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**Background:**Triple-negative breast cancer (TNBC), a subtype of breast cancer, due to the lack of an effective therapy target, the only postoperative approach that seems to work for TNBC is chemotherapy treatment. For TNBC that is less than 1 cm and has no lymph node metastasis, administering chemotherapy is controversial at present. The word "consider" is used in the description of the National Comprehensive Cancer Network (NCCN), and the level of evidence is IIb. The Chinese Society of Clinical Oncology (CSCO) guidelines do not provide a specific recommendation for this group of patients but recommend that all patients with TNBC should receive postoperative chemotherapy. In this study, the SEER database was used to evaluate the benefit of chemotherapy. The results will help confirm whether patients with stage T1aN0M0 and T1bN0M0 TNBC should be administered adjuvant chemotherapy.**Purpose** To evaluate the effect of adjuvant chemotherapy on improving the prognosis of patients with stage I triple-negative breast cancer (TNBC).**Methods** TNBC patients diagnosed in the SEER 18 database from 2010 to 2015 were included. Kaplan-Meier plots and log-rank tests were used to compare the differences in breast cancer-specific survival (BCSS) and overall survival (OS) between subgroups of variables. A Cox proportional hazard model was used to determine the prognostic factors affecting BCSS and OS.**Results** A total of 9,256 patients were enrolled in this study. Among these patients, 380 died from breast cancer, and 703 died from all causes. Patients who received chemotherapy had significantly better BCSS and OS than those who did not receive chemotherapy for stage T1cN0M0 (BCSS, hazard ratio (HR) = 0.68, 95% confidence interval (CI) = 0.51-0.90; OS, HR = 0.54, 95% CI = 0.44-0.67) and stage IB (BCSS, HR = 0.39, 95% CI = 0.16-0.95; OS, HR = 0.41, 95% CI = 0.19-0.87) disease. Patients who received chemotherapy did not have significantly better BCSS or OS than those who did not receive chemotherapy for stage T1aN0M0 or T1bN0M0 disease. The patients who received chemotherapy in the poorly differentiated and undifferentiated groups had better BCSS (HR = 0.68, 95% CI = 0.52-0.88) and OS (HR = 0.54, 95% CI = 0.44-0.66) than the patients who did not receive chemotherapy.**Conclusion** According to current clinical guidelines, patients with stage T1bN0M0 TNBC are probably overtreated. The prognosis of these patients with stage T1aN0M0 or T1bN0M0 disease is good enough that adjuvant chemotherapy cannot improve it further.

TABLE:
The effect of adjuvant chemotherapy on BCSS stratified by the tumor stage

| Stage | Chemotherapy | Cases | Death from breast cancer | log-rank P | Univariate Cox | | Multivariate Cox [a] | |
|---|---|---|---|---|---|---|---|---|
| | | | | | HR (95%CI) | P | HR (95%CI) | P |
| T1aN0M0 | | | | 0.446 | | | | |
| | No | 857 | 12 | | 1.00(reference) | | 1.00(reference) | |
| | Yes | 246 | 5 | | 1.50(0.53-4.25) | 0.449 | 1.17(0.33-4.12) | 0.808 |
| T1bN0M0 | | | | 0.700 | | | | |
| | No | 886 | 28 | | 1.00(reference) | | 1.00(reference) | |
| | Yes | 1341 | 37 | | 0.91(0.56-1.48) | 0.700 | 1.00(0.57-1.74) | 0.999 |
| T1cN0M0 | | | | $2.73\times10^{-5}$ | | | | |
| | No | 1410 | 97 | | 1.00(reference) | | 1.00(reference) | |
| | Yes | 4189 | 171 | | 0.59(0.46-0.76) | $3.41\times10^{-5}$ | 0.68(0.51-0.90) | 0.007 |
| IB | | | | | | | | |
| | No | 49 | 10 | 0.003 | 1.00(reference) | | 1.00(reference) | |
| | Yes | 278 | 20 | | 0.33(0.16-0.71) | 0.005 | 0.39(0.16-0.95) | 0.038 |

[a] Adjusted by age, laterality, grade, total number of malignant tumors per patient and radiotherapy.
Patients who received chemotherapy had significantly better BCSS than those who did not receive chemotherapy for stage T1cN0M0 and stage IB disease. In contrast, no significant associations of chemotherapy with BCSS were observed for stage T1aN0M0 or stage T1bN0M0 disease.

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# Neoadjuvant and adjuvant therapy (NAT/AT) treatment patterns and clinical characteristics in a real-world cohort of US patients with HR+/HER2− early breast cancer (eBC)

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**Background:** Treatment patterns in hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)− eBC continue to evolve. While AT remains the standard of care, NAT has been indicated as a viable approach to downstage higher-stage tumors. As interest in NAT trials increases, detailed data on current treatment patterns may inform future research. The objective of this retrospective observational study was to evaluate patient characteristics and treatment patterns in US patients diagnosed with HR+/HER2− eBC.
**Methods:** This analysis included adults diagnosed with non-metastatic (stage I-III) invasive eBC between January 1, 2011, and March 1, 2019, in the nationwide Flatiron Health electronic health record–derived de-identified database. All patients had HR+/HER2− test results within 90 days of eBC diagnosis and evidence of both primary surgery and systemic treatment in the eBC setting. Patients with records of HER2-targeted treatment were excluded. NAT was defined as systemic treatment before first primary surgery; AT was defined as systemic treatment within 12 months after primary surgery among patients with ≥ 6 months of follow-up after surgery. Pathologic complete response (pCR) was defined as the absence of residual invasive disease in the breast and axillary lymph nodes after NAT and was subsequently confirmed at the time of primary surgery.
**Results:** Among 4739 patients in the study, 341 (7%) received NAT (318/341 received AT following NAT) and 4398 (93%) received AT only. The proportion of patients receiving NAT increased annually from 5% in 2011 to 9% in 2018. Of NAT-treated patients, 7% achieved pCR. Patients who had higher pathology stage, higher tumor grade, younger age and who were Black or Hispanic/Latino had higher proportions of NAT (**Table**). Patients who received NAT were more likely to receive a mastectomy (vs lumpectomy) compared with patients who received AT only. The most common NAT regimens included chemotherapy (54%; primarily anthracycline + cyclophosphamide + taxane [ACT] regimens) or endocrine (ET) monotherapy (36%; primarily aromatase inhibitor [AI]). The most common AT regimens were ET monotherapy (79%; primarily AI or tamoxifen).
**Conclusions:** Although AT remains the standard treatment approach in US clinical practice for HR+/HER2− eBC, interest in NAT has grown in recent years and NAT use has increased. Given the low pCR rates following NAT and since pCR is considered a surrogate marker for survival, further investigation into longer-term clinical benefits of NAT in this population is warranted as NAT may be becoming more common.

Table. Characteristics of patients with HR+/HER2− eBC who received AT or NAT

| | **AT only(first treatment after surgery)N = 4398** | **NAT(first treatment before surgery)N = 341** |
|---|---|---|
| **pCR achieved** | | |
| Yes | NA | 25 (7.3) |
| No | NA | 271 (79) |
| Unknown | NA | 45 (13) |
| **Age at eBC diagnosis** | | |
| Median (IQR), years | 64 (54-72) | 59 (49-68) |
| **Race** | | |
| Non-Hispanic White | 2975 (68) | 208 (61) |
| Non-Hispanic Black | 278 (6.3) | 31 (9.1) |
| Non-Hispanic Asian | 120 (2.7) | 13 (3.8) |
| Non-Hispanic other | 428 (9.7) | 27 (7.9) |
| Hispanic/Latino | 282 (6.4) | 39 (11) |
| Unknown | 315 (7.2) | 23 (6.7) |
| **Year of eBC diagnosis** | | |
| 2011/2012 | 1023 (23) | 53 (16) |
| 2013/2014 | 1136 (26) | 81 (24) |
| 2015/2016 | 1129 (26) | 101 (30) |
| 2017/2018/2019[1] | 1100 (25) | 106 (31) |
| **Pathology group stage** | | |
| I | 2370 (54) | 70 (21) |
| II | 1209 (27) | 86 (25) |
| III | 282 (6.4) | 58 (17) |
| Unknown | 537 (12) | 127 (37) |
| **Tumor grade** | | |
| 1 | 1268 (29) | 41 (12) |
| 2 | 2297 (52) | 186 (55) |
| 3 | 768 (17) | 111 (33) |
| Unknown | 65 (1.5) | 3 (0.9) |
| **Histology** | | |
| IDC | 3486 (79) | 267 (78) |
| ILC | 615 (14) | 51 (15) |
| Other/Unknown | 297 (6.8) | 23 (6.7) |
| **Primary surgery type** | | |
| Lumpectomy | 2911 (66) | 128 (38) |
| Mastectomy | 1487 (34) | 213 (62) |

Data are n (%) unless otherwise specified.AT, adjuvant chemotherapy; eBC, early breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NA, not applicable, NAT, neoadjuvant chemotherapy; pCR, pathologic complete response.* The number of patients diagnosed in 2019 is very low because we only included patients diagnosed through March 2019; thus 2019 is grouped with 2017/18.

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# Experience of contrast-enhanced mammography in patients with breast augmentation surgery

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**Background**: Contrast-enhanced mammography (CEM) is an emerging breast imaging technique utilizing iodinated contrast to highlight areas of neovascularity. The role of CEM in patients with breast implants has not yet been characterized. We report our clinical experience of CEM in patients with breast augmentation surgery to better understand the potential diagnostic utility and limitations of CEM in the setting of breast implants.
**Materials and Methods**: A HIPPA compliant, IRB exempt single-institution review of prospective CEM cases who had “breast implants” in their report between 01/2015 and 03/2020. Medical records were reviewed to supplement database information.
**Results**: Forty-six patients were included with a mean age of 52 years (range 33-72). Clinical indications included: high risk research screen 3 (6%), diagnostic evaluation for abnormal imaging 24 (52%), further evaluation of newly diagnosed breast cancer 12 (26%) or assessment of neoadjuvant treatment response 7 (15%). Thirty patients had malignant lesions. Histology was invasive ductal carcinoma (90%), invasive lobular carcinoma (7%), and ductal carcinoma in situ (3%). CEM identified the index cancer and extent of disease in 28/30 (93%) of malignant cases. In two patients (7%), the malignant lesion was not included in the field-of-view due to its location. One of these lesions was a far medial mass within the breast which was detected by ultrasound alone. The other false negative CEM was a palpable axillary mass negative on both mammogram (MG) and MRI but seen by ultrasound.
Twenty-three (50%) underwent additional breast MRI of which 20 had an already diagnosed cancer. the findings on CEM were concordant with MR imaging for the index lesion in 19/20 (95%) cases (kappa=0.86; $p < 0.001$).
Six additional lesions were found by CEM and confirmed by MRI. Of these lesions, 33% were found to be malignant and changed the surgical procedure. Four were only seen on CEM (no MRI comparison was available) and 75% were found to be malignant. One was only seen on MRI and was benign. One additional lesion was only seen as an asymmetry on MG without CEM or MRI correlate. This was benign on both the biopsy and surgical pathology.
**Conclusions**: CEM appears to be a valuable breast imaging modality for diagnostic evaluations and surgical staging, including patients with breast implants. Due to technical artifacts and positioning limitations for posterior lesions, we recommend performing CEM with implant displaced views. Breast centers that use CEM, should be aware of field of view as a potential limitation when evaluating extent of disease in patients with breast augmentation.

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# Development of H3B-6545, a first-in-class oral selective ER covalent antagonist (SERCA), for the treatment of ERa$^{WT}$ and ERa$^{MUT}$ breast cancer

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Mutations in the ligand-binding domain of estrogen receptor alpha (ERα) are detected in up to 30% of patients (pts) who have relapsed or progressed during endocrine therapy. By favoring the agonistic conformation in ERα, these hotspot mutations promote ligand-independent activation of ERα and confer partial resistance to ER-directed therapies. Of the various hotspot mutations, Y537S is the most constitutively active, promotes the greatest resistance phenotype to current endocrine therapies, and is associated with the worst prognosis relative to other ERα mutations. The fact that current ER-directed therapies have limited activity in the ERα mutant setting emphasizes the critical need to develop the next generation of high affinity ER antagonists that can overcome the aberrant activity of mutant ERα.

H3B-6545 is a first-in-class selective ERα covalent antagonist (SERCA) which inactivates both wild-type and mutant ERα by irreversibly engaging cysteine-530. Biophysical and biochemical analyses confirm the long residence time achieved by covalent binding, and cellular analyses confirm the selectivity and single-digit nanomolar potency of H3B-6545 across a panel of ERα$^{WT}$ and ERα$^{MUT}$ breast cancer cell lines. H3B-6545 as a monotherapy demonstrates superior anti-tumor activity relative to fulvestrant across a set of CDK4/6 inhibitor naïve ERα$^{WT}$ and ERα$^{Y537S}$ cell line-derived xenograft (CDX)/patient-derived xenograft (PDX) models, with regressions being noted in both the ERα$^{WT}$ and ERα$^{MUT}$ settings. Furthermore, H3B-6545 continues to demonstrate single agent activity in CDK4/6 inhibitor-resistant ERα$^{WT}$ and ERα$^{Y537S}$ PDX models, in which fulvestrant fails to demonstrate significant anti-tumor activity. Lastly, improved activity and duration of response are noted when H3B-6545 is combined with several targeted therapies, including CDK4/6 inhibitors palbociclib and abemaciclib across a range of ERα$^{WT}$ and ERα$^{Y537S}$ CDX/PDX models.

The phase I-II trial (NCT03250676) enrolled 130 heavily pretreated pts with ER+, HER2- metastatic breast cancer, including 12 pts harboring high allele frequency clonal *ESR1* Y537S circulating tumor DNA (ctDNA). Median number of prior therapy in the metastatic setting was 3 (range: 1-10). Consistent with the preclinical data, H3B-6545 demonstrated promising clinical activity among these pts with clonal Y537S mutations, with a median progression free survival of 7.3 months and an overall response rate of 25% (3 confirmed partial responses).

In summary, these compelling preclinical data coupled with emerging clinical activity in heavily pretreated poor prognosis pts support further development of H3B-6545 as monotherapy or combination treatment.

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Effect of Wnt5a on drug resistance in estrogen receptor-positive breast cancer

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**Purpose:** We previously showed that Wnt5a-positive breast cancer belongs to a subgroup of estrogen receptor (ER)-positive breast cancers and its prognosis is worse than that of Wnt5a-negative breast cancer. In this study, we aimed to investigate the molecular mechanisms underlying the poor prognosis of patients with Wnt5a-positive breast cancer.**Methods:** A total of 151 patients with ER-positive invasive breast cancer were recruited for this study between January 2011 and February 2014. The association between Wnt5a expression and recurrence rate was examined. To identify the pathways associated with Wnt5a-positive breast cancer, we established a Wnt5a-expressing cell line (MCF-7/Wnt5a cells) and conducted DNA microarray analysis of MCF-7/Wnt5a cells. We also performed pathway analysis associated with Wnt5a expression, and evaluated the effects of Wnt5a *in vitro* using MCF-7/Wnt5a cells.**Results:** Data showed poorer relapse-free survival of patients with Wnt5a-positive breast cancer ($P = 0.047$). The median length of follow-up was 6.08 years (range, 0.027 to 8.47 years) for all patients. According to DNA microarray data, only the cytochrome P450 (CYP) pathway was significantly upregulated and related with Wnt5a ($P = 0.0440$). Moreover, MCF-7/Wnt5a cells were less sensitive to tamoxifen and paclitaxel, which are metabolic substrates of CYP ($P < 0.05$). Although the PI3K-AKT-mTOR signaling pathway is involved in the poor prognosis of ER-positive breast cancer, it was not associated with Wnt5a.**Conclusions:** In ER-positive breast cancer, Wnt5a expression upregulated the CYP metabolic pathway and decreased the sensitivity to tamoxifen and paclitaxel, the standard treatment options for ER-positive breast cancer.

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# Five year median follow-up data from a prospective, randomized, placebo-controlled, single-blinded, multicenter, phase IIb study evaluating the reduction of recurrences using HER2/neu peptide GP2 + GM-CSF vs. GM-CSF alone after adjuvant trastuzumab in HER2 positive women with operable breast cancer

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**Background**: The final analysis of the GP2 prospective, randomized, placebo-controlled, single-blinded, multicenter Phase IIb trial investigating GP2+GM-CSF administered in the adjuvant setting to node-positive and high-risk node-negative breast cancer patients with tumors expressing any degree of HER2 (immuno-histochemistry [IHC] 1-3+) (*NCT00524277*) is now complete with 5 year follow-up. The trial enrolled HLA-A02 patients randomized to receive GP2+GM-CSF versus GM-CSF alone. The trial's primary objective was to determine if treatment with GP2, a HER2-derived peptide, reduces recurrence rates. Three and 4 year interim analyses for this trial and 3 Phase I studies showing GP2 to be safe and immunogenic have been previously reported by Mittendorf et al. **Methods**: Each enrolled and consented GP2-treated patient was scheduled to receive a total of 6 GP2+GM-CSF (500 mcg GP2: 125 mcg GM-CSF) intradermal injections every 3-4 weeks as part of the Primary Immunization Series (PIS) for the first 6 months and 4 GP2+GM-CSF booster intradermal injections every 6 months thereafter. Boosters were introduced during the trial, thus some patients did not receive all 4 boosters. Each enrolled and consented placebo patient was scheduled to receive a total of 6 GM-CSF only intradermal injections every 3-4 weeks for the first 6 months and 4 GM-CSF only booster intradermal injections every 6 months thereafter. **Results:** This 168 patient (ITT: n=180) basket trial across 16 clinical sites explored 96 HER2 3+ patients, who received a standard course of trastuzumab after surgery and subsequently completed the full PIS or placebo, starting the PIS at median 17.1 months after surgery, and 72 HER2 1-2+ patients, who did not receive trastuzumab after surgery and subsequently completed the full PIS or placebo, starting the PIS at median 10.8 months after surgery. Since GP2 is synergistic with trastuzumab, and the HER2 1-2+ patients did not receive trastuzumab, it was prespecified to compare recurrence rates ITT versus per protocol in these 2 distinct, independently reported populations, excluding those patients who did not complete the PIS. GP2 was shown to be well tolerated with no SAEs and elicited a potent immune response measured by local skin tests and immunological assays, which suggest peak immunity is reached at 6 months upon completion of the PIS. After 5 years of follow-up, the Kaplan-Meier estimated 5-year DFS rate in the 46 HER2 3+ patients treated with GP2+GM-CSF, if the patient completed the PIS, was 100% versus 89.4% (95% CI:76.2, 95.5%) in the 50 placebo patients treated with GM-CSF (p = 0.0338). The treated versus placebo HER2 3+ patients were well-matched, where 53% were stage T1, 41% were stages T2-T4, 55% were node positive, 58% were HR positive and received endocrine therapy, 77% received adjuvant radiation, 77% received adjuvant chemotherapy, and 89% received trastuzumab. After 5 years of follow-up, the Kaplan-Meier estimated 5-year DFS rate in the 35 HER2 1-2+ patients treated with GP2+GM-CSF, if the patient completed the PIS, was 77.1% (95% CI:59.5, 87.9%) versus 77.6% (95% CI:60.1, 88.2%) in the 37 placebo patients treated with GM-CSF (p = 0.9142). **Conclusions:** This study demonstrated that completion of the GP2+GM-CSF PIS safely elicited a potent immune response and reduced recurrence rates to 0% in HER2 3+ patients, who received a standard course of trastuzumab after surgery. A pivotal Phase III trial is being initiated to treat HER2 3+ patients in the neoadjuvant setting. GP2 also may be effective when used in parallel to trastuzumab based therapeutics or in combination with trastuzumab based therapeutics in HER2 1-2+ or other HER2 expressing cancers.

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Current landscape in phase 3 trials in breast cancer at major oncology conferences

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**Background:** The oral presentation of studies at conferences may impact treatment practice even before the publication or regulatory approval. Methodological aspects and reporting patterns are evolving, and an assessment of these features may help understand the current landscape and the way forward. **Methods:** We analyzed the characteristics of primary analyses of phase 3 trials from oral sessions presented at ASCO, ESMO and SABCS 2017-19 and the timing of their subsequent publications. We excluded non-inferiority trials and duplicate presentations within the period. **Results:** Of 36 unique trials, 19/10/7 had a first author from Europe/United States/Asia or elsewhere, and 21/15 were in the (neo)adjuvant/palliative settings. All but one trial had 2 arms. The number of patients enrolled ranged from 226 to 4884 (median, 646). All but 2 trials were on systemic therapy, with 16 dedicated exclusively to hormone-receptor+, 8 to HER2+ and 6 to triple-negative disease. According to the authors, 23 (63.9%, 95% CI, 46.2 to 79.2%) trials were positive, and 13 were negative. For only 2 of the negative trials was the conclusion not entirely consistent with results. When sponsor information was available, 18/21 industry vs 4/14 academic trials were positive (P=0.002). Paradoxically, negative trials were larger than positive trials (medians of 2639 and 585 patients; P=0.002), perhaps because all but one of 13 negative trials were in the (neo)adjuvant setting, vs 9/23 among positive trials (P=0.004). The time to publication was significantly shorter for positive than negative trials (medians of 215 vs 785 days; HR=0.32; P=0.013). Of 30 trials with time-to-event endpoints, the ratio between observed:expected HR could be computed for 24: the mean was 0.88 for 15 positive and 1.43 for 9 negative trials (P=0.004; 1.09 overall). **Conclusion:** In recent phase 3 trials in breast cancer, positive trials are more likely than negative trials to be industry-sponsored, to assess the metastatic setting, and to be published earlier. These results also suggest that the treatment effect has been underestimated in positive trials. Research is ongoing to elucidate potential determinants of the latter hypothesis.

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Population pharmacokinetics (Pop PK) of MYL-1401O (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer (mBC)

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**Background:** Mylan trastuzumab (MYL-1401O) is a biosimilar to trastuzumab (Herceptin®). A multicenter, double blind, randomized, phase III study (HERITAGE) compared the efficacy, safety, Pop PK and immunogenicity of MYL-1401O and trastuzumab in patients with HER2-positive mBC. Patients were randomized 1:1 to receive either MYL-1401O or Herceptin®, in combination with taxane Q3W for 24 weeks followed by monotherapy until unacceptable toxicity, disease progression or early discontinuation.**Objectives:** The objectives of the Pop PK analysis were to compare the Pop PK derived AUC, $C_{max}$, clearance, $V_d$, and $T_{1/2}$ profiles of MYL1401O and Herceptin® and to perform an exploratory assessment of the impact of shed extracellular domain (ECD) fragments of the HER2 receptor (HER2/ ECD) on PK parameters.**Methods:** One end of infusion PK sample was collected at Cycle 1 and Cycle 6, and 1 trough sample per cycle from all patients; additional samples were taken in a Pop PK subset (MYL-1401O: 45; Herceptin®: 37) in the first dosing interval and at subsequent times. Pop PK modeling was performed using NONMEM. Individual patient empiric Bayesian parameter estimates were used to estimate PK measures. The impact of HER2/ECD presence on PK levels was evaluated in the primary covariate analysis. **Results:** Two hundred forty-five (245) patients in the PK population received MYL-1401O, while 240 received Herceptin® of which 482 were included in the base model Pop PK analysis. 3170 concentration records with sufficient information were included in the Pop PK analysis. There were no notable demographic differences between the treatment groups. Bayesian parameter based exposure estimates at or near steady-state dosing were comparable between treatments, confirming similar PK (Table 1). Treatment was not a significant covariate of clearance (p=0.177) or volume of the central compartment (p=0.584) using the likelihood ratio Chi-square test.The test-to reference mean ratios of $C_{min}$ for Cycle 1 and Cycle 6 (end of cycle) were 103.11(90% CI = 90.61, 117.33) and 104.16 (90% CI = 94.00, 115.42), respectively.The HER2/ECD concentrations were a significant covariate of trastuzumab clearance.

**Table 1:Bayesian Parameter Based Exposure Estimates at Cycle 6**

| | | **MYL-1401O (N=245)** | **Herceptin®(N=240)** | **Total(N=485)** |
|---|---|---|---|---|
| **Parameter** | n* | 213 | 202 | 415 |
| Dose (mg) | Mean (SD) | 420.70 (90.46) | 421.25 (97.67) | 420.97 (93.92) |
| Clearance (L/day) | | 0.27 (0.10) | 0.28 (0.08) | 0.27 (0.09) |
| Volume of Central Compartment (L) | | 3.16 (0.60) | 3.20 (0.60) | 3.18 (0.60) |
| Volume at Steady State (L) | | 6.36 (1.19) | 6.32 (1.14) | 6.34 (1.16) |
| AUC (ug*day/mL) | | 40501.40 (13037.04) | 38816.90 (11966.26) | 39681.40 (12540.58) |
| Dose-normalized AUC (ug*day/mL/mg) | | 98.50 (30.56) | 94.41 (28.90) | 96.51 (29.80) |
| Cmax,ss (ug/mL) | | 177.00 (37.76) | 171.52 (34.61) | 174.33 (36.32) |
| Dose-normalized Cmax,ss (ug/mL/mg) | | 0.43 (0.10) | 0.42 (0.09) | 0.43 (0.10) |
| Half-life (day) | Median (SD) | 25.12 (7.50) | 24.34 (6.89) | 24.74 (7.21) |

** concentrations below lower limit of quantification and samples before first dose with values >zero were excluded from Pop PK analysis, as were some patients with incomplete information for covariates significant in the final model.***Conclusion:** Pop PK profiles of MYL-1401O vs. Herceptin® were similar in patients with HER2positive mBC. Model-based exposure measures were similar between treatments. HER2/ECD concentrations were a strong determinant of trastuzumab clearance, and clearance was similar between treatments. The observed trough concentrations were similar between treatments at the end of Cycle 1 and at Cycle 6.**Clinical trial identification**: EudraCT Number: 2011-001965-42**Legal entity responsible for the study**: Mylan GmbH**Funding:** Mylan GmbH

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Impact of genetic cancer risk assessment on males with breast cancer predisposing mutations

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**Background:** The implementation of genetic cancer risk assessment (GCRA) has resulted in an increased identification of adult males with breast cancer (BC) predisposing mutations. However, its effect on adherence to cancer prevention strategies and the psychological impact of receiving a positive genetic test result have not been sufficiently explored in men. The aim of this study is to determine the impact of GCRA on men with BC predisposing mutations.
**Methods:** Men aged ≥18 years that underwent genetic testing between 2017 and 2019 in a center located in Monterrey, Mexico were invited to answer a telephone survey in which clinical information was collected. In addition, a section with an adapted Multidimensional Impact of Cancer Risk Assessment (MICRA) was incorporated. Total MICRA score was determined as the mean of items 1-21. Furthermore, seven sections were analyzed separately: distress (items 1-4 and 7-8), uncertainty (items 9-12, 14-17 and 20), positive experiences (items 5-6 and 18-19), understanding choices (item 13), testing regret (item 21), worry about children (items 22-23) and worry about cancer (items 24-25). Differences between categorical variables were explored using Mann Whitney U tests.
**Results:** A total of 31 patients were eligible for this study, of which 29 consented to participate. Of these, 15 were mutation carriers (8 BRCA1, 3 BRCA2, 2 ATM, 1 CHEK2 and 1 PALB2) with a median age of 45 years (range 20-71). Only one of the carriers surveyed had a personal history of BC. The median time elapsed from disclosure of positive carrier status to survey application was 13 months. Remarkably, 3/15 ignored their test result despite previous GCRA, and only 4/15 were able to identify the specific mutated gene. Most had disclosed their mutation status to close relatives (67%). Regarding psychological impact, 2/15 thought that their genetic test result had a significant impact in their life and 1/15 claimed that undergoing genetic testing generated feelings of anxiety or depression. In addition, two out of three childless carriers reported that their mutation status made them seriously doubt whether to have biological children. Notably, only 47% were aware about the mode of transmission of their mutation. Concerning medical support, 87% felt that the support offered by the medical team was sufficient, but only 60% considered that they had enough information about the implications of their carrier status. With respect to prevention strategies, 67% claimed to be unaware about the general recommendations according to their mutational status and age. Furthermore, 87% did not use sunscreen, 80% had never visited a dermatologist, 73% could not correctly identify suspicious signs for skin cancer, 8/11 (72%) of eligible patients did not perform routine breast self-exams, and 10/11 (91%) had not visited a physician for a clinical breast exam. In addition, 0/6 (0%) of the eligible patients had had a colonoscopy and 5/6 (83%) eligible patients had not undergone screening for prostate cancer. Concerning the MICRA score, patients with BC predisposing mutations had a higher total mean score than non-carriers (21.7 vs. 14.3; $p$=0.01), particularly due to the positive experiences subscale (11.5 vs. 5.4; $p$=0.01).
**Conclusion:** Low awareness and poor adherence to recommended prevention strategies were found in male mutation carriers despite a high impact of GCRA in this group. Hence, efforts to elucidate the specific barriers that limit adherence to these strategies in men are warranted.

MICRA scores. Results are shown as mean (standard deviation).

| | **Mutation carriers (*n*=15)** | **Non-carriers (*n*=14)** | ***p* value** |
|---|---|---|---|
| **Total score** | 21.7 (8.5) | 14.3 (7.8) | 0.008 |
| **Distress subscale** | 2.1 (4.0) | 1.1 (1.9) | 0.617 |
| **Uncertainty subscale** | 6.0 (6.3) | 5.6 (7.1) | 0.603 |
| **Positive experiences subscale** | 11.5 (5.2) | 5.4 (7.2) | 0.013 |
| **Understanding choices item** | 2.0 (2.2) | 2.1 (2.1) | 0.841 |
| **Testing regret item** | 0.1 (0.3) | 0.0 (0.0) | 0.779 |
| **Worry about children section** | 2.5 (3.1) | 3.7 (3.3) | 0.569 |
| **Worry about cancer section** | 5.0 (0.0) | 5.0 (0.0) | >0.99 |

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# A randomized, open-label, parallel-group, multicenter phase 2 study comparing the efficacy and safety of oral AZD9833 versus fulvestrant in women with advanced ER-positive HER2-negative breast cancer (SERENA-2)

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**Background** AZD9833 is a next-generation oral selective estrogen receptor (ER) antagonist and degrader (SERD) that has shown anti-tumor efficacy in a range of pre-clinical xenograft models of breast cancer. The first-in-human study, assessing AZD9833 as a monotherapy and in combination with palbociclib (SERENA-1; NCT03616587), established a dose-dependent safety profile with clinical benefit and target engagement in pre- and post-menopausal women at all dose levels. Here, we describe the design of SERENA-2, a Phase 2 randomized, open-label trial of three different doses of AZD9833 versus fulvestrant. **Methods** SERENA-2 is a global comparative study of three different doses of AZD9833 versus fulvestrant in post-menopausal women with advanced ER+, HER2- breast cancer with disease recurrence or progression after ≥1 endocrine therapy. The study will evaluate the efficacy and safety of AZD9833 monotherapy once daily at three dose levels, versus fulvestrant monotherapy administered according to its label. Eligible patients will have received no prior fulvestrant or other oral SERD, and no more than one endocrine therapy and one chemotherapy in the advanced setting. Prior treatment with CDK4/6 inhibitors is permitted. Patients will be randomized 1:1:1:1 to one of four treatment groups: AZD9833 75 mg, 150 mg, 300 mg, or fulvestrant. The primary objective of the study is to determine the clinical efficacy of AZD9833 as assessed by progression-free survival, compared with fulvestrant. Secondary objectives include objective response rate, duration of response, percentage change in tumor size at 16 weeks, clinical benefit rate at 24 weeks, and overall survival. Pharmacokinetics, pharmacodynamic biomarker changes from baseline, and effects of AZD9833 and fulvestrant on patients' health-related quality of life will also be assessed. Exploratory endpoints include predictive markers of response and/or acquired resistance to AZD9833 and fulvestrant, including circulating tumor DNA mutation profiling and dynamics, circulating tumor cell enumeration, and analysis of tumor samples. Patient enrollment commenced in Q2 2020, with a target enrollment of 288 patients across approximately 100 sites in up to 17 countries. Efficacy analyses will compare each dose of AZD9833 with fulvestrant. Sample size was calculated to provide 80% power for the primary endpoint. The primary analysis will use a Cox proportional hazards model stratified by prior use of CDK4/6 inhibitors and presence of lung and/or liver metastases to compare progression-free survival in each dose of AZD9833 versus fulvestrant. Another randomized, open-label, parallel-group, pre-surgical study investigating the biological effects of AZD9833 in ER+, HER2- primary breast cancer (SERENA-3) is also ongoing. For more information please contact Dr Mafalda Oliveira at: moliveira@vhio.net.

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# Prospective study of circulating cancer-associated macrophage-like cells (CAMLs) in obese patients with advanced breast cancer

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**Background**
Cancer-associated macrophage-like cells (CAMLs) are rare circulating gigantic atypical cells exclusively found in the peripheral blood of patients with solid cancers. CAMLs potentially originate from tumor-associated macrophages in the tumor microenvironment and may have a prognostic role in breast cancer. Obesity-induced local hypoxia attracts macrophages to the tumor microenvironment and activates macrophages to induce chronic inflammation, which can lead to breast cancer progression. However, little is known about the relationship between CAMLs, obesity, and body fat distribution. Also, the role of the CAMLs on breast cancer development needs to be investigated. We hypothesized that the number and size of CAMLs are correlated with body mass index (BMI), and we investigated the relationship between CAMLs and body composition.
**Materials and methods**
We prospectively collected 10 ml of peripheral blood from 30 patients initially diagnosed with advanced breast cancer who underwent computed tomography. Blood samples were drawn in CellSave tubes to preserve peripheral blood mononuclear cells. We used the CellSieve microfiltering system to isolate and identify CAMLs. After enumerating cells, we analyzed immunofluorescent staining for DAPI, CD14, CD45, CXCR4, and cytokeratin. CAMLs were identified by cell surface markers (CD14+, CD45+, and cytokeratin+) and morphology (multinuclear and giant cells >30 µm). BMI was measured at the time of diagnosis. The in-house 3D imaging analysis software Medical Executable for the Efficient and Robust Quantification of Adipose Tissue was used to calculate the total amount of abdominal visceral fat tissue (VAT) and subcutaneous fat tissue (SAT) between the upper diaphragm and pelvic end using multi-detector computed tomography data. The VAT:SAT ratio was also calculated. We quantified the expression of C-X-C chemokine receptor type 4 (CXCR4) in CAMLs to investigate the metastatic potential of the cells. Finally, we determined the relationship between the characteristics of CAMLs and BMI, body composition parameters, and CXCR4 using the Pearson correlation test.
**Results**
Of 30 collected samples, two had an inadequate amount of blood for evaluation. Among the remaining 28, we detected CAMLs in 24. The median BMI was 30.4 kg/m$^2$, and half of the patients were categorized as obese by the World Health Organization BMI classification. BMI was correlated with the number (r=0.39, p=0.043), average size (r=0.42, p=0.039), and maximum size (r=0.50, p=0.013) of CAMLs. In body composition analysis, the maximum size of CAMLs was correlated with the total amount of VAT (r=0.51, p=0.012) and SAT (r=0.44, p=0.037) but not the VAT:SAT ratio. The number of CAMLs was correlated with maximum CXCR4 expression in CAMLs (r=0.58, p=0.004). CAMLs size and CXCR4 expression were inversely correlated.
**Conclusion**
The number and size of CAMLs are correlated with BMI, but CAMLs characteristics are not related to body composition. The number of CAMLs was associated with CXCR4, which indicated its metastatic potential. Further studies are needed to elucidate the biological role of CAMLs, especially whether the increased number and size of CAMLs in obesity reflect the tumor microenvironment.

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Second-generation HR-pQCT analysis of bone mineral density and microstructure in women with breast cancer who underwent adjuvant endocrine therapy

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**Background:** Adjuvant endocrine therapy for 5-10 years reduces breast cancer (BC) mortality in women with hormone receptor-positive BC. However, aromatase inhibitors (AIs) decrease bone mineral density (BMD), and increase fractures, joint stiffness, and joint pain. Although dual energy X-ray absorptiometry (DXA) is widely used to assess BMD, it is a two-dimensional method and thus cannot analyze trabecular and cortical bone microstructure. High-resolution peripheral quantitative computed tomography (HR-pQCT) allows in vivo analysis of peripheral bone microarchitecture with high spatial resolution and low radiation exposure. We used HR-pQCT to evaluate changes in volumetric bone density and microstructure consisting of trabecular and cortical bone associated with AI treatment in patients with early BC. **Methods:** This was a prospective single-center observational study of nonosteoporotic, postmenopausal women with hormone receptor-positive BC, whose baseline DXA lumber spine and femoral neck T-scores were > −2.5. All patients were scheduled to receive DXA and HR-pQCT at baseline and at 6 and 12 months after starting AI therapy. The primary endpoint was to examine changes in total volumetric BMD (Tt. vBMD), trabecular volumetric BMD (Tb. vBMD), cortical volumetric BMD (Ct. vBMD) change at the distal radius and the distal radius between baseline and 6 and 12 months after starting endocrine therapy. **Results:** Of the 20 women in the study (median age: 57.5 years; range: 55-72 years), 8 had undergone chemotherapy before registration. Their mean change in Tt. vBMD between baseline and 1 year were distal radius: −5.7% (SD: 2.5%, $P<0.01$); distal tibia: −3.8% (SD: 1.8%, $P<0.01$), Tb. vBMD distal radius: −4.0% (SD: 3.9%, $P<0.01$); distal tibia: −0.9% (SD: 2.4%, $P<0.05$), Ct. vBMD distal radius: −3.1% (SD: 1.6%, $P<0.01$); distal tibia: −2.9% (SD: 1.7%, $P<0.01$). Furthermore, at 1 year in trabecular bone, mean trabecular bone volume fraction ($p<0.01$), trabecular thickness ($p<0.05$), and trabecular number ($p<0.01$) were significantly decreased, and trabecular separation ($p<0.01$) increased, in both the distal radius and tibia. At 1 year in cortical bone, mean changes in cortical thickness ($p<0.01$) and cortical bone area ($p<0.01$) were significantly decreased in both the distal radius and tibia; however, the endocortical perimeter of cortical bone did not significantly change and cortical porosity ($p<0.05$) was significantly greater than that at baseline. At 1 year, DXA decreased at the total hip (−4.4%, $P<0.01$) and femoral neck (−0.6%, $P=0.03$) compared with baseline. However, no significant difference was seen in median values for lumbar spine BMD at 1 year, or for tartrate-resistant acid phosphatase-5b (TRACP-5b) or procollagen type-I N-terminal propeptide (PINP). **Conclusion:** Postmenopausal women who took AIs for early BC experience volumetric bone density decline and both trabecular and cortical bone deterioration. A decade of AI treatment is a standard treatment for early BC; however, healthcare professionals should monitor bone health during and after these treatments.

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# Comparison between the American joint committee on cancer (AJCC) anatomic and prognostic stages for breast cancer

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**Introduction**: The knowledge regarding the tumor biology of breast cancer has grown substantially and resulted in the identification of different breast cancer subtypes based on their molecular profile, which led to an important change in treatment, it went from standardized therapy for personalized therapy. A panel of experts and representatives from AJCC were responsible for preparing the newest Cancer Staging Manual. The panel recognized the clinical usefulness of biological factors such as histological grade, expression of hormone receptors - HR (estrogen and progesterone) and overexpression and / or amplification of the human epidermal growth factor 2 (HER2) receptor in predicting patient survival and incorporated data regarding these biomarkers in the new staging system. In addition, for eligible cases, the 'Recurrence score' was also incorporated, a score generated by the analysis of OncotypeDx (genomic test). The new manual, therefore, started to use 3 stays. Anatomical staging - based on the classic TNM; the clinical prognostic staging and pathological prognosis staging - TNM association with the prognostic biomarkers (using clinical data in the first and data after surgical treatment in the second). **Objective**: To verify the concordance between anatomical staging from the 7th edition of the AJCC manual and the prognosis from its 8th edition in a cohort of patients with breast cancer at the Hospital do Servidor Público Estadual de São Paulo. **Methodology**: Observational and cross-sectional study, which evaluated patients undergoing surgical treatment at Hospital do Servidor Público Estadual from March 2014 to March 2019. Information was collected regarding age, menopausal status, tumor characteristics, anatomical and clinical staging, neoadjuvant chemotherapy, adjuvant chemotherapy and radiotherapy and type of surgery performed. The patients were staged using the digital platform "TNM8 Breast Cancer Calculator". **Results**: 805 patients were included in the analysis. All patients were female, aged between 29 and 97 years, mostly in the post-menopausal period (78.88%). 74.04% of the cases were positive for ER, 66.21% positive PR and 88.07% HER2 negative. Prognostic staging downgraded a total of 285 out of 805 patients (35.4%). Almost all of the cases that decreased in staging were ER and / or PR + (283 of 285). Most of those who went up were Triple Negatives (100 out of 111). **Conclusion**: Prognostic Staging changes staging in almost half of the cases and there was a greater number of staging decreases in total and an association of increased staging with tumors considered to have a worse prognosis, which is in agreement with several studies already carried out since the launch of the new manual.

| Table 1. Changes in the staging groups. Anatomical Staging vs. Prognostic Staging | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Anatomical Staging (%) | | | | | | | | | | |
| | Stage | IA | IB | IIA | IIB | IIIA | IIIB | IIIC | IV | |
| Prognostic Staging (%) | IA | 248 | 6 | 97 | 2 | | | | | Total that decreased staging285 (35,4%) |
| | IB | 21 | | 47 | 26 | 19 | | | | |
| | IIA | | | 60 | 27 | 27 | | | | |
| | IIB | | | 22 | 29 | 4 | | | | |
| | IIIA | | | | 3 | 42 | 9 | 7 | | |
| | IIIB | | | | 17 | 12 | 20 | 14 | | |
| | IIIC | | | | | 14 | 22 | 6 | | |
| | IV | | | | | | | | 4 | |
| | Total staging that increased 111(13,8%) | | | | | | | | | Total unchanged 409 (50,8%) |

| Table 2. Relationship of the immunohistochemical profile and change of staging | | | |
|---|---|---|---|
| Biomarkers | **Total (%)** | **Difference** | **Total** |
| HR + / HER2 - | 575 (71,42%) | | |
| | | -1 | 96 (16,70%) |
| | | -2 | 140 (24,34%) |
| | | -3 | 21 (3,65%) |
| | | 0 | 308 (53,57%) |
| | | +1 | 10 (1,74%) |
| HR + / HER2 + | 49 (6,09%) | | |
| | | -1 | 9 (18,37%) |
| | | -2 | 17 (34,69%) |
| | | 0 | 22 (44,90%) |
| | | +1 | 1 (2,04%) |
| HR - / HER2 + | 47 (5,84%) | | |
| | | -1 | 2 (4,3%) |
| | | 0 | 45 (95,7%) |
| HR - / HER2 - | 134 (16,65%) | | |
| | | 0 | 34 (25,4%) |
| | | +1 | 69 (51,5%) |
| | | +2 | 31 (23,1%) |
| | 805 (100%) | | |

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# Symmetry of breasts following reconstructive surgery

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## INTRODUCTION

Breast reconstruction surgery is an integral part of breast cancer treatment that aims to restore breast appearance after mastectomy. We assessed breast symmetry following breast reconstruction using measures of distance and volume.

## MATERIAL AND METHODS

Patients undergoing breast reconstruction surgery were enrolled in an IRB approved study from 2011 to 2014 at The University of Texas MD Anderson Cancer Center. We utilized pre- and post-operative 3D surface images (3dMDtorso, 3dMD LLC, Atlanta, GA) from 53 women who had completed the breast reconstruction process (83% at 18 months (M), 9.4% at 12M and 7.6% at 9M). Patients provided approved consent. Thirty-six women had bilateral and 17 had unilateral surgery. Eleven patients in the unilateral group had symmetry surgery on the contralateral breast (5 had mastopexy, 4 had reduction, 1 had augmentation, and 1 had augmentation and mastopexy). Within the bilateral group, 9 patients underwent autologous reconstruction, 21 received implants, and 6 had mixed (autologous and implant) procedures. Within the unilateral group, there were 10 implant and 7 autologous reconstructions. We measured the sternal notch (SN) to lowest visible point (LVP) distance and volume for each breast. Breast symmetry was assessed using 1) Difference between the left and right breasts for the SN-LVP distance and volume measures, 2) SN-LVP distance ratio and volume ratio computed using values for the left and right breast. The smaller value was divided by the larger, so that a ratio of 1.0 indicated perfect symmetry [1]. Differences < 5 mm for SN-LVP distance and < 50 cc for breast volume were used as indicators of symmetry [1].

## RESULTS

Overall, pre-operatively 50.9% patients showed a SN-LVP difference < 5 mm compared to 35.9% post-operatively, whereas 43.4% showed a breast volume difference < 50 cc pre-operatively compared to 62.3% post-operatively.

Mean pre- and post-operative SN-LVP distance ratios were found to be 0.97 ± 0.03 and 0.96 ± 0.03, respectively, whereas the breast volume ratios were 0.91 ± 0.06 and 0.92 ± 0.08, respectively. Shapiro-Wilk tests showed non-normal distribution for both ratios; thus, non-parametric analysis was performed using Mann-Whitney U-test and, for matched pairs, the Wilcoxon Matched Pairs Sign-Ranked test. For both distance and volume ratios, we failed to reject the null hypothesis that the median of the paired differences between the pre- and post-operative values was zero. Also, no significant differences were found for both ratios when comparing autologous and implant-based surgeries. Bilateral reconstructions were compared to unilateral procedures that included a contralateral symmetry procedure. Significantly higher distance ratios (0.97 ± 0.03, median of 0.98, $p = 0.005$) were found for bilateral reconstructions compared to unilateral (0.94 ± 0.04, median of 0.94), but no differences in volume ratios were noted. Significant differences were noted for both distance ($p = 0.033$) and volume ($p = 0.009$) ratios when comparing bilateral (distance: 0.96 ± 0.02, median of 0.97 and volume: 0.96 ± 0.03, median of 0.97) to unilateral implant-based reconstructions (distance: 0.93 ± 0.04, median of 0.94 and volume: 0.91 ± 0.05, median of 0.90), but no difference in symmetry was found between unilateral and bilateral autologous reconstructions.

## CONCLUSION

Distance symmetry was noted in a higher percentage of the pre-operative population compared to post-operative, whereas a larger proportion of the post-operative patients showed volume symmetry compared to the pre-operative group. Implant-based bilateral procedures showed improved symmetry compared to the unilateral procedures.

## REFERENCES

1.Cheong AL, Liu J, Reece GP, Nicklaus KM, Bordes MC, Hanson SE, Markey MK, Merchant, FA “Natural Breast Symmetry in Preoperative Breast Cancer Patients”, Plastic and Reconstructive Surgery - Global Open: 2019;7(7):e2297.

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Mechanisms underlying obesity-induced enrichment of stem-like breast cancer cells

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**Background:** Breast cancer represents the most common nonskin malignancy in women worldwide, and most deaths result from metastatic dissemination of the disease. At the same time, studies indicate that obesity induces a stem cell-like phenotype, required for tumor metastases and associated with cancer progression and mortality. Although the precise mechanism behind this reprogramming event remains to be elucidated, preliminary data from our lab demonstrate that the epithelial-mesenchymal transition (EMT) associated with obese conditions is linked to IL-6 mechanistically. Because IL-6 cannot be targeted clinically, it will be of the utmost importance to identify downstream effectors of this IL-6-mediated response. This said, we hypothesize that increased levels of IL-6 in obese conditions are at least partially responsible for inducing a stem cell-like phenotype in breast cancer cells through activation of the Akt-mTOR pathway.**Methods:** MCF-7 and T47D breast cancer cells will be exposed to sera pooled from normoweight (BMI<25 kg/m$^2$) or obese (BMI≥30 kg/m$^2$) women as an *in vitro* model of the systemic inflammation present in obesity. The cells will then be assessed for changes in expression of genes and proteins involved in induction of EMT using qPCR and western immunoblotting, respectively. Finally, flow cytometry will be used to confirm establishment of an EMT phenotype with measurement of the stem cell markers CD24 and CD44.**Results:** Our gene expression analyses confirm that obese conditions increase expression of EMT-related genes, including those encoding the transcription factors Snail and Twist. Our flow cytometric analyses also indicate an increase in the stem cell population following a 10-day IL-6 exposure. Additionally, supplementation of IL-6 to non-obese sera increased expression of Twist and Snail in breast cancer cells, while inhibition of IL-6 in obese sera reduced expression of these transcription factors. Finally, western blot analyses demonstrate mechanistic involvement of the Akt-mTOR pathway.**Conclusions:** These data contribute to our understanding of the means by which obesity induces a stem-like phenotype in breast cancer cells and will ultimately bring light to a therapeutic target that can be used to modulate IL-6-induced activation of the Akt-mTOR signaling pathway leading to an EMT phenotype in obese conditions.

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# Are we missing something? Increased recurrence rates in patients with an oncotype DX score < 26 and a modified magee score > 18: A multi-institutional study

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**INTRODUCTION:** Oncotype DX® (ODX) is a multigene assay estimating risk of distant recurrence and chemotherapy benefit in estrogen receptor (ER) positive breast cancer patients. Cost ($4,620.00) impedes its adoption in poorer countries, and the cost is unnecessary in certain patients. TAILORx results suggest that adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-positive, HER2-negative, node-negative invasive breast carcinomas with an ODX recurrence score < 26. Bhargava et al. and Turner et al. have suggested that a Magee score™ or a modified Magee score, respectively, of < 18 will identify patients who are highly likely to have an ODX recurrence score of < 26, and we previously presented data at SABCS 2019 (Abstract P3-07-06) that there is no significant difference in recurrence rate between patients with a modified Magee score of ≤ 18 and patients with an ODX recurrence score < 26 (in preparation for publication). We now present additional recurrence data on patients with a modified Magee score of > 18. **METHODS:** A total of 301 consecutive patients with ER+ invasive breast cancer from the University of Rochester and the University of Louisville were included in this study, with a mean of 6.6 years of follow-up. All patients had at least 5 years of follow-up (range 5-11 years) except for seven patients , who had a breast cancer recurrence prior to five years. Information on ER, PR, HER-2, Ki-67, Nottingham score , and tumor size were extracted from the pathology report in order to calculate the modified Magee score. Information, on hormone therapy, chemotherapy, radiation therapy, recurrence status, and mortality were extracted from the medical record. For all results, a p-value of < 0.05 was considered significant. **RESULTS:** 117/301 (39%) patients had a modified Magee score of > 18. The recuurence rate for patients with a modified Magee score > 18 was 11.1%. There was no significant difference in recurrence rate between patients with *both a modified Magee score > 18 and ODX recurrence score < 26* compared to patients with *both a modified Magee score >18 and ODX recurrence score ≥ 26* (p = 0.547, Table 1). **CONCLUSIONS:** Patients with a modified Magee score > 18 may be at increased risk for breast cancer recurrence, *even if the ODX recurrence score is < 26*. Additional studies are necessary to further evaluate these findings.

**Table 1: Modified Magee score > 18, Oncotype DX recurrence score (ODXRS), and outcome**

| | Recurrence | No recurrence |
|---|---|---|
| **Modified Magee score > 18 and ODXRS < 26** | **8** | **70** |
| **Modified Magee score > 18 and ODXRS ≥ 26** | **6** | **33** |

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# Dynamics of a multi-parametric liquid biopsy, including CTCs, EVs, and cfDNA, during therapy in metastatic breast cancer patients provide useful insights for therapy management

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**Background:** Extensive knowledge about the molecular complexity could benefit therapy management in metastatic breast cancer (MBC). Consequently, we isolated and analyzed mRNA from circulating tumor cells (CTCs), mRNA from extracellular vesicles (EVs), and cell-free DNA (cfDNA) from a minimized blood volume and aimed to assess the dynamics of these analytes to elucidate the relevance of multi-parametric liquid biopsies for therapy monitoring and therapeutic decision-making by studying them at various points in time during the course of the therapy. **Methods:** 2x 9 ml of EDTA blood was drawn from 35 MBC patients with hormone receptor-positive and HER2 negative primary tumors at the time of disease progression and at two consecutive staging time points. CTCs and their mRNA were isolated using the AdnaTest EMT2/StemCell Select/Detect. Plasma from CTC-depleted blood was used for cfDNA isolation, while mRNA from EVs was isolated using exoRNeasy and the remaining blood. mRNA purified from CTCs and EVs was analyzed by a multimarker qPCR panel targeting 17 transcripts. cfDNA was analyzed with a customized QIAseq Targeted DNA Panel (targeting 17 genes) for Illumina with unique molecular indices. Consumables: QIAGEN, Germany. **Results:** Data from 35 patients at three time points (105 samples) and 51 parameters [results of 17 genes in three analytes (CTCs, EVs, and cfDNA)] were correlated with therapy outcomes defined by visual staging to examine their value for monitoring. Among the top 15 parameters with the best sensitivity and specificity - regardless of whether or not sensitivity and specificity were jointly examined - most parameters originated from the analysis of CTCs. Among these parameters, a two-tailed Fisher's exact test revealed *ERBB3* CTC signals (96% spec; 22% sens; p=0.022) or a combination of *ERBB3* CTC signals or *ERBB2* CTC signals (87% spec; 37% sens; p=0.008) to be highly correlated with the time of disease progression. Interestingly, an evaluation of the development of signals during the therapy resulted in EV parameters having the best sensitivity and specificity. The appearance of signals associated with resistance (*ERCC1)* in EVs was significantly correlated with worse therapy outcomes reaching a specificity of 98% (24% sens; p=0.007). A visualization of all results from seven index patients demonstrated the diversity within CTC signals and the dynamics of EV signals during treatment. Some of the CTC signals and their matched EVs (e.g. *BRCA1* signals) showed opposed behavior during the treatment for a given patient. *PIK3CA* and *ESR1* variants, known to be associated with resistance, were frequently found in those index patients receiving anti-hormonal treatment. Allele frequencies of *PIK3CA* variants in cfDNA and *PIK3CA* CTC signals showed a similar reduction after successful chemotherapy. In contrast, a switch to chemotherapy induced *ERCC1* CTC signals in two cases. In three other cases, *ERCC1* CTC signals persisted despite the patients having successfully responded to the chemotherapy administered. In individual patients, only signals from a single analyte were particularly prominent at all time points. **Conclusion:** Among the parameters tested for the purposes of monitoring, most of the top 15 originated from the analysis of CTCs and therefore, underscore their salience in the field of liquid biopsy. Additionally, the dynamic development of overexpression signals in EVs during the course of therapy proved to be an important indicator of disease progression and might therefore also be useful for therapy monitoring. Combination of these results with the analysis of cfDNA variants over time, as done with our index patients, underlines the usefulness of this multimodal liquid biopsy approach for therapeutic decision-making in the future.

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# Using big data to gauge effectiveness of breast cancer awareness month

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Introduction: Breast Cancer Awareness Month (BCAM) has been used for decades to increase awareness and screening for breast cancer but it's reach and effectiveness is difficult to judge. Using Internet Search Interest (ISI) could allow better evaluation of BCAM effects.Methods: Using Google Trends, we evaluated the ISI of a given term(s) as compared to that cancer's awareness month. The ISI represents population level Google internet searches relative to the highest number of searches for the United States from 2004-2019 with a max number of 100. The ISI for breast cancer and mammogram in October, which is BCAM, was compared against all other months during this period. Results: The BCAM of October was associated with statistically significant more ISI for breast cancer 77.0 vs. 34.6 (95% CI 69.5-84.5, CI 32.9-35.3, $p < 0.0005$) as compared to the rest of the year. ISI for mammogram was similar (41.6 vs. 60.2, 95% CI 39.4-43.7, 48.5-71.9, $p = 0.007$). There was significant differences between the top half of states with Mississippi (100), Delaware (97) and West Virginia (95) having the highest ISI while Nevada (60), Oregon (60) and Utah (57) the lowest (87.6 vs 71.8, 95% CI, 85.5-89.7, 69.0-74.6, $p < 0.0005$). There was significant differences between the top half of 208 United States metro areas with Rochester MN (100), Greenwood MS (85) and Jackson MS (80) having the highest ISI while Salt Lake City UT (43), Idaho Falls UT (41) and Roanoke VA (40) the lowest (67.5 vs 54.4, 95% CI, 66.4-68.6, 53.4-55.4, $p < 0.0005$). Conclusion: ISI suggests that BCAM is effective at increasing breast cancer awareness with significant heterogeneity across states and metro areas. This publicly available free tool can be used to assess penetrance of awareness campaigns in a time sensitive manor for future targeting of populations with low breast cancer awareness. Future research is needed to correlate outcomes and ISI.

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Inhibition of short-form ron eliminates breast cancer metastases through an immune-mediated mechanism

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Metastatic breast cancer is the overwhelming cause of breast cancer mortality and is still incurable. The rapid development of immunotherapy is an exciting new area of research in metastatic breast cancer. However, the extreme immunosuppressive tumor environment poses a major challenge. A better understanding of how the immune system can be harnessed against metastatic cancer is required to improve patient outcomes. We previously showed that expression of the receptor tyrosine kinase Ron in the host, rather than Ron's tumor expression, contributed to tumor-associated immunosuppression and duo inhibition of Ron and CTLA-4 significantly reduced metastatic outgrowth. However, the actual mechanism remains unclear.

The present study provides evidence that the N-terminal truncated isoform, short-form Ron (SF-Ron), is the major contributor in suppressing the anti-tumor immune responses and promoting metastatic outgrowth. Genetic deletion of host SF-Ron nearly eliminated breast cancer metastasis in mice, lead to systemic immune-activation, increased recruitment of lymphocytes to the site of metastasis, and augmented tumor-specific T-cell responses. Lack of SF-Ron also leads to the accumulation of CD4+ T-cells in the metastatic lungs and endowed with anti-tumor potential. Importantly, mice treated with small molecule Ron kinase inhibitor that targets both Ron and SF-Ron, produced significantly higher, active, tumor-specific CD8+ T-cells. Our study indicates that blocking Ron, especially the SF-Ron, remodels the metastatic lung microenvironment to enhance anti-tumor immunity. This study sheds light on the potential non-redundant roles of full-length and SF-Ron isoforms in mediating breast cancer metastasis and anti-tumor immune responses; and highlights the relevance of combining Ron inhibitors with immunotherapeutic agents to potentially improve treatment efficacy for metastatic breast cancer patients.

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# Clinical and pathologic characteristics of Turkish breast cancer (BC) patients screened with BRCA1, BRCA2 or 26 - gene inherited cancer panel testing: Single institution experience

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Background: BRCA1 and BRCA2 mutations are responsible for two thirds of hereditary BC. Germline genetic testing for BC susceptibility has evolved from a single-gene analysis to a multigene panel testing. Identification of a pathogenic mutation in BRCA and other panel represent a therapeutic opportunity today. Methods: We aimed to investigate clinical and pathologic characteristics of BC patients who were referred to our center between 2011-2019 and underwent BRCA1, BRCA2 or 26-gene inherited cancer panel testing based on NCCN criteria for hereditary breast/ovarian cancer testing. We analyzed the frequency of pathogenic mutations and its relationship with clinical and pathologic factors. Results: A total of 576 patients were identified. Among them 356 (63%) had their test in our university, 218 (38%) patients had their test at other centers. Sixty-six % (n:376) of patients had panel testing, 34% had only BRCA 1-2 mutation test. Median age was 42(22-87) and 5 patients were male. Ten % of patients had metastatic disease, 70% had early BC and 20% had locally advanced stage at the time of referral. The indication for genetic testing was family history in 169 (29%) patients, triple negative (TN) subtype in 100 (17%) patients and age <45 years in 260 (45%) patients. Seventy-nine % of patients were premenopausal. A total of 114 (19%) patients had pathogenic mutations. The most commonly mutated genes were BRCA1 (n:38, 6%), BRCA2 (n:35, 6%), ATM (n:6), p53 (n:5), PALB2 (n:5), CHEK2 (n:5). Six patients had more than one pathogenic mutation. Among patients with pathogenic mutations 58% had ER positive, 27% had TN and 15 % had Her-2 positive disease. Thirty-four % of patients with TN tumors have pathogenic mutations, 23% of patients with TN tumors had BRCA mutations. TP53, PALB2 and CHEK2 mutations were more frequent in HR positive disease. Age <35 (p:0.002), triple negative subtype (p: 0.005) and menopausal status (p:0.001) were significantly associated with having pathogenic mutations in multivariate analysis. Conclusion: Two thirds of BC patients <35 years-old and one third of patients with TN tumors have pathogenic germline mutations in BC predisposing genes when they were screened in line with NCCN criteria.

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# Incident comorbidities in a diverse cohort of women treated for early-stage, hormone receptor-positive breast cancer

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**Background**: The prognosis of early-stage, hormone receptor-positive breast cancer is excellent with 5-year overall survival rates greater than 90%. In the context of excellent survival, it is important to quantify the long-term comorbidities associated with endocrine therapy.
**Methods**: Eligible patients were women diagnosed with stages 1-3, hormone receptor-positive and Her2-negative breast cancer from January 1999 to December 2016 and treated at one or more of two healthcare systems in the San Francisco Bay Area (Stanford University or the community-based Palo Alto Medical Foundation, N=3,044). Duration of therapy with aromatase inhibitors and/or tamoxifen was ascertained. Long-term comorbidities analyzed were congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cerebrovascular accidents (CVA), dementia, depression/anxiety, diabetes mellitus (DM), peptic ulcer disease (PUD), hyperlipidemia (HLD), myocardial infarction (MI), non-alcoholic steatohepatitis (NASH), osteonecrosis of the jaw, osteoporosis, peripheral vascular disease (PVD), and venous thrombotic events (VTE). Pre-existing comorbidities were defined as those diagnosed any time up to 1 year after breast cancer diagnosis. Incident comorbidities that developed on or after endocrine therapy were defined as those diagnosed any time after 1 year following breast cancer diagnosis.
**Results**: The median patient age was 58.1 years. Patients were 67.8% non-Hispanic white, 22.1% Asian, 7.6% Hispanic, 1.7% non-Hispanic Black, and 0.8% other. Most (69.6%) had private insurance. For endocrine therapy, almost half (48.3%) used aromatase inhibitors only (median duration 35.1 months), 20.6% used tamoxifen only (median duration 29.4 months), and the remainder used both aromatase inhibitors (AI) and tamoxifen (median duration of any endocrine therapy: 47.8 months). Comorbidity results are in the Table.
**Table**. Comorbidities relative to timing of breast cancer diagnosis

| **Comorbidity** | **Prevalence before cancer diagnosis** | **Incidence after cancer diagnosis** |
|---|---|---|
| Congestive heart failure | 65 (2.1) | 70 (2.3) |
| Chronic obstructive pulmonary disease | 348 (11.4) | 127 (4.2) |
| Cerebrovascular accident | 83 (2.7) | 77 (2.5) |
| Dementia | 15 (0.5) | 25 (0.8) |
| Depression/Anxiety | 599 (19.7) | 245 (8) |
| Diabetes | 239 (7.9) | 101 (3.3) |
| Peptic ulcer disease | 36 (1.2) | 19 (0.6) |
| Hyperlipidemia | 870 (28.6) | 363 (11.9) |
| Myocardial infarction | 12 (0.4) | 18 (0.6) |
| Non-alcoholic steatohepatitis | 40 (1.3) | 62 (2) |
| Osteonecrosis of jaw | NA (NA) | 2 (0.1) |
| Osteoporosis/Fracture | 791 (26) | 608 (20) |
| Peripheral vascular disease | 22 (0.7) | 31 (1) |
| Venous thrombotic event | 65 (2.1) | 74 (2.4) |

Notable unadjusted hazard ratios for the association of incident comorbidities with tamoxifen (versus AI) use include: HLD 0.45 [95% confidence interval, CI 0.25-0.8]; MI 0.66 [CI 0.04-9.88]; CHF 1.23 [CI 0.29-5.1]; CVA 0.46 [CI 0.14-1.54]; depression/anxiety 0.89 [CI 0.45-1.76]; osteoporosis 0.37 [CI 0.23-0.59]; and DM 1.34 [CI
0.44-4.07]. Results of multivariable analysis will be presented, adjusting for comorbidities present before cancer diagnosis, age, race and insurance status.
**Conclusions**: In a diverse, real-world cohort of breast cancer patients treated in two healthcare systems, incident HLD and osteoporosis were significantly less common with tamoxifen versus AI use, while other comorbidities did not vary with type of endocrine therapy. These results may inform clinical decision-making about endocrine therapy for early-stage, hormone receptor-positive breast cancer.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS11-24

# Neoadjuvant pyrotinib plus trastuzumab and chemotherapy for stage I-III HER2-positive breast cancer: Results of a single-arm pilot clinical trial

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**Aim:** Pyrotinib is an irreversible tyrosine kinase inhibitor (TKI) of human epidermal growth factor receptor 1 (HER1), HER2, and HER4, which exhibits well-tolerated antitumor activity in patients with HER2-postive metastatic breast cancer; however, its performance in neoadjuvant therapy remains uncertain. Thus, the efficacy and safety of neoadjuvant therapy of pyrotinib plus trastuzumab was estimated in patients with HER2-positive breast cancer in this pilot study.
**Methods:** Chinese female patients with stage I-III HER2-positive breast cancer were assigned to receive eight cycles of neoadjuvant pyrotinib (P) (400 mg) orally daily in combination with four cycles of epirubicin (E) (100 mg/m$^2$), cyclophosphamide (C) (600 mg/m$^2$) intravenously followed by four cycles of docetaxel (T) (100 mg/m$^2$), trastuzumab (H) (8 mg/kg in the first load followed by 6 mg/kg) intravenously, once every three weeks, referred to as P + EC-TH, before definitive surgery. The primary endpoint was the proportion of patients who achieved a total pathological complete response (tpCR) in the breast and axilla (ypT0/is ypN0) in the intention-to-treat population. Safety was analyzed in patients who received at least one neoadjuvant treatment cycle according to the actual treatment received. This trial is registered with the Chinese Clinical Trial Registry (number: ChiCTR1900022293), and the follow up randomized, controlled phase III trial is ongoing.
**Results:** Between February 19, 2019, and May 25, 2019, 19 eligible patients were administrated pyrotinib neoadjuvant therapy with epirubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab. A total of 18 patients completed the therapy and final surgery. The tpCR rate was 72.2% (95% CI: 46.5 - 90.3), and no recurrence or metastasis occurred during the short-term follow-up period. The objective response rate (ORR) was 100% (95% CI: 81.5 - 100) at the end of eighth cycle. The most common adverse events (AEs) were diarrhea and leukopenia in 17 of 19 patients (89.5 %). The most severe AEs were grade 4 leukopenia and neutropenia; however, no grade 5 AEs were reported.
**Conclusions:** This pilot study initially reported that neoadjuvant therapy of P + EC-TH improved the tpCR rate in HER2-positive operable or locally advanced breast cancer by approximately one time higher than EC-TH neoadjuvant therapy reported in other trials, with tolerable side effects. A subsequent randomized phase III clinical trial is warranted.

| | P + EC-TH (n=18) | | |
|---|---|---|---|
| Characteristic | No. | tpCR (No.) | pCR rate (%) |
| Patients | 18 | 13 | 72.2 |
| Lymph-nodes status | | | |
| Positive | 11 | 8 | 72.7 |
| Negative | 7 | 5 | 71.4 |
| Tumor size | | | |
| 1 | 3 | 2 | 66.7 |
| 2 | 15 | 11 | 73.3 |
| 3 | 0 | | |
| cTNM | | | |
| I | 3 | 2 | 66.7 |
| II | 14 | 10 | 71.4 |
| III | 1 | 1 | 100.0 |
| HR status | | | |
| Positive | 11 | 7 | 61.1 |
| Negative | 7 | 6 | 85.7 |
| Ki-67 | | | |
| <20% | 5 | 2 | 40.0 |
| ≥20% | 13 | 11 | 84.6 |
| Pre-TILs | | | |
| Low | 5 | 2 | 40.0 |
| Intermediate | 10 | 8 | 80.0 |
| High | 3 | 3 | 100.0 |

Abbreviations: tpCR, total pathological complete response; cTNM, clinical TNM stage; HR, hormone receptor; Pre-TILs, previous treatment tumor infiltrating lymphocytes.

**Table 1.** Differences in the tpCR rates in the subgroups

| | All Grades | Grade 1 | Grade 2 | Grade 3 | Grades 4 |
|---|---|---|---|---|---|
| AE | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| Diarrhea | 17(89.5%) | 10(52.6%) | 14(73.7%) | 9(47.4%) | 0 |
| Leukopenia | 17(89.5%) | 10(52.6%) | 10(52.6%) | 6(31.6%) | 2(10.5%) |
| Decreased hemoglobin | 16(84.2%) | 16(84.2%) | 6(31.6%) | 0 | 0 |
| Alopecia | 13(68.4%) | 6(31.6%) | 7(36.8%) | 0 | 0 |
| Vomiting | 12(63.2%) | 10(52.6%) | 2(10.5%) | 0 | 0 |
| Decreased appetite | 12(63.2%) | 12(63.2%) | 0 | 0 | 0 |
| Oral ulceration | 11(57.9%) | 11(57.9%) | 0 | 0 | 0 |
| Nausea | 10(52.6%) | 8(42.1%) | 2(10.5%) | 0 | 0 |
| Skin pigmentation | 10(52.6%) | 10(52.6%) | 0 | 0 | 0 |
| Neutropenia | 10(52.6%) | 3(15.8%) | 4(21.1%) | 3(15.8%) | 1(5.3%) |
| Headache | 8(42.1%) | 8(42.1%) | 1(5.3%) | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| Increased ALT | 7(36.8%) | 5(26.3%) | 1(5.3%) | 3(15.8%) | 0 |
| Fatigue | 7(36.8%) | 7(36.8%) | 1(5.3%) | 0 | 0 |
| Weight loss | 6(31.6%) | 6(31.6%) | 0 | 0 | 0 |
| Increased AST | 5(26.3%) | 4(21.1%) | 1(5.3%) | 1(5.3%) | 0 |
| Muscle spasms | 5(26.3%) | 5(26.3%) | 0 | 0 | 0 |
| Thrombocytopenia | 5(26.3%) | 5(26.3%) | 0 | 0 | 0 |
| Rash | 3(15.8%) | 3(15.8%) | 0 | 0 | 0 |
| Dizziness | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Cough | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Hypokalemia | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Upper respiratory tract infection | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Increased total bilirubin | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Stomachache | 2(10.5%) | 1(5.3%) | 1(5.3%) | 0 | 0 |
| Palpitation | 2(10.5%) | 2(10.5%) | 0 | 0 | 0 |
| Abbreviation: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase. | | | | | |
| **Table 2**. P + EC-TH related AEs of all grades that occurred in all patients (n = 19) | | | | | |

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# Infusion related reactions in the phase 3 SOPHIA trial of margetuximab + chemotherapy vs trastuzumab + chemotherapy in patients with pretreated HER2+ metastatic breast cancer

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**Background:** Margetuximab (M) is an investigational Fc-engineered, anti-HER2 monoclonal antibody with the same epitope specificity as trastuzumab (T). Relative to T, Fc engineering of M increases binding affinity for the activating Fc receptor (FcR) CD16A and decreases affinity for the inhibitory FcR CD32B. The SOPHIA trial (NCT02492711) randomized pretreated HER2+ MBC patients to either M or T, each with chemotherapy (C). M+C improved progression-free survival (PFS) benefit over T+C. Infusion related reactions (IRR) have been observed after infusion of therapeutic proteins, typically during the first infusion, with a first-dose incidence of up to 40% for T (Herceptin Prescribing Information®). A retrospective analysis of 197 patients showed 16% IRRs on T, mostly after the first infusion; this rate was lower with (10%) compared to without (19%) premedication (Thompson, 2014). Here, we report IRR safety and tolerability data in the SOPHIA trial patients following HER2-targeted antibody therapy. **Methods:** The open-label Phase 3 SOPHIA trial enrolled patients with HER2+ MBC after at least 2 prior anti-HER2 therapies, including pertuzumab; 91% in both groups also received ado-trastuzumab emtansine. Randomization of 536 patients was 1:1 to M (15 mg/kg IV q3w) or T (6 [8 loading dose] mg/kg IV q3w), each with Investigator selected C (standard dose capecitabine, eribulin, gemcitabine, or vinorelbine). M was given as 120-minute infusions. T was given as a 90-minute infusion in Cycle 1, then a 30-minute infusion from Cycle 2 onward. Recommended elective premedication included acetaminophen, ibuprofen, diphenhydramine, ranitidine, dexamethasone, or equivalents. IRR safety analyses were conducted on 530 patients (264 M+C and 266 T+C) that received any study therapy. **Results:** A higher proportion of patients experienced IRRs on the M arm (35 [13.3%]) than on the T arm (9 [3.4%])**.** Most IRRs in both groups were severity Grade 1 or 2, occurred on Cycle 1 Day 1, and resolved within 24 hours. In patients receiving M, Grade 3 IRR occurred in 4 patients (1.5%), including 3 after vinorelbine and 1 after eribulin. Adverse events associated with Grade 3 IRRs included chills, fever, nausea, diarrhea, dyspnea, and/or hypertension. Two patients receiving M (0.8%) discontinued due to IRR, versus none on T. Of patients with IRRs, the most common symptoms in both treatment groups were chills (M: 17 [48.6%]; T: 5 [55.6%]) and fever (M: 13 [37.1%]; T: 2 [22.2%]). There was no observed hypotension in either group. In both groups, more than half of IRR events were addressed by dose interruption only. All IRRs all were medically manageable. IRR rates were higher in patients without premedication for both groups. Of 264 subjects receiving M, 218 (82.6%) received premedication and 46 (17.4%) did not; IRRs were observed in 28 (12.8%) of those receiving premedication and 7 (15.2%) of those not premedicated. All 4 patients on M with Grade 3 IRRs received premedication, 3 with steroids. Of 266 subjects receiving T, 173 (65%) received premedication and 93 (35%) did not; IRRs were observed in 5 (2.9%) of those receiving premedication and 4 (4.3%) of those not premedicated. IRR risk was unaffected by chemotherapy subgroup or CD16A genotype. **Conclusions:** In the SOPHIA trial, IRR events occurred in a greater proportion of patients on M than on T. Most were mild to moderate in severity, limited to Cycle 1, and resolved on the same day. Symptom patterns were similar between groups, and premedication did not eliminate the hazard of IRRs in either group. Severe IRRs and discontinuations due to IRRs were rare. IRRs on first infusion of M appear to resemble those observed following first infusion of T.

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Impact of protein corona formation on Fn14-targeted DART nanoparticle selectivity, uptake, and cytotoxicity on TNBC cells

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Despite dramatic improvements in the treatment of primary breast cancers, there currently are no effective targeted therapeutics for women diagnosed with metastatic triple negative breast cancer (mTNBC), resulting in an overall survival of just ~13 months in these patients. Drug-loaded nanoparticles (NPs) offer the potential to improve the therapeutic efficacy and pharmacokinetic profile of drugs through use of passive and active targeting to metastatic tumors. However, effective and active targeting of nanodrug formulations to tumor cells is complicated by the adsorption of proteins to NP surfaces upon exposure to the systemic circulation. Termed ‘protein coronas’, this protein coat can drastically reduce the blood circulation time and targeting capability of NPs *in vivo*. We have developed paclitaxel (PTX)-loaded NPs that are engineered for decreased non-specific adhesivity and receptor-targeting (‘DART’) characteristics, which balance minimal recognition by circulating immune cells and low non-specific binding to tumor extracellular matrix proteins with maximal targeting to tumor tissues. These DARTs selectively bind the fibroblast growth factor-inducible 14 (Fn14) cell surface receptor, which is overexpressed in over a dozen solid cancers and their metastases, including mTNBC tumors. We recently demonstrated the enhanced therapeutic efficacy of Fn14-targeted DARTs in comparison to a non-targeted nanoformulation and Abraxane, an FDA-approved nanoformulation for mTNBC, in xenograft models of primary and intracranial TNBC. In addition, we found that these DARTs retain targeting capability and traffic to Fn14+ tumors in the presence of an endogenous protein corona *in vitro* and *in vivo*. This encouraged further investigation into the specific mechanisms of DART NP uptake in tumor cells in both the presence and absence of protein coronas using surface plasmon resonance, flow cytometry, total internal reflection fluorescence and confocal microscopy, and cytotoxicity assays. Understanding the role of protein coronas on this drug delivery platform is crucial for its clinical development and these results provide valuable new information pertaining to the optimization of NP surface properties for minimizing the impact of protein coronas and improving mTNBC tumor targeting *in vivo*.

**Publication Number:** OT-09-03

EMBER: A phase 1a/b trial of LY3484356, a novel, oral selective estrogen-receptor degrader (SERD), in advanced ER+ breast cancer and endometroid endometrial cancer

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**Background**: Estrogen receptor (ER) is the key therapeutic target for the most common breast cancer (BC) subtype affecting patients worldwide. Novel degraders and antagonists of ER are under evaluation, to overcome both ER mediated resistance and the bioavailability and dosing limitations of fulvestrant (fulv), the only approved SERD. ER is also overexpressed in approximately 80% of endometroid endometrial cancers and endocrine therapy (ET) is a standard of care (SOC) option for this disease, though no ER-directed therapies are specifically approved in this setting. LY3484356 is a novel, orally bioavailable SERD with pure antagonistic properties which results in sustained inhibition of ER-dependent gene transcription and -cell growth. Preclinically, LY3484356 monotherapy shows favorable efficacy and pharmacokinetic (PK) properties, including antitumor activity in ESR1 mutants, along with enhanced antitumor efficacy when combined with abemaciclib, everolimus, or alpelisib. This trial investigates LY3484356 alone and in combination with other SOC anticancer therapies, in women with ER+ advanced BC and ER+ endometroid endometrial cancer. **Trial Design**: This global first-in-human phase 1a/b, study of LY3484356, includes dose escalation of LY3484356 monotherapy (n=100), followed by dose expansion (n=360) at the recommended phase 2 dose (RP2D) of LY3484356 alone and in combination with other anticancer therapies (**Table**). Monotherapy dose escalation will be evaluated using an interval 3+3 design. In dose expansion (Parts A-D), each combination cohort will include a safety lead-in of 3-6 patients. Premenopausal women must receive concomitant treatment with a GnRH agonist. **Eligibility criteria:** Eligible patients must have pre- or post-menopausal ER+, HER2- or HER2+, advanced BC or ER+ endometroid endometrial cancer. ER+, HER2- BC patients must have either untreated de novo disease or prior ET sensitivity. In dose escalation, BC patients may have received up to 3 prior therapies for metastatic disease. In dose expansion, prior therapy requirements are outlined in the **Table** below. ER+ endometroid endometrial cancer patients must have progressed on platinum-based therapy. **Key Study endpoints**: Recommended phase 2 dose determination; safety and tolerability assessment, PK evaluation, objective response rate and clinical benefit rate assessment per RECIST v1.1. Recruitment for the EMBER study is ongoing (NCT04188548).

Table. Dose Expansion (Phase 1b)

| **Patient Subgroup** | **Key Eligibility** | **Study Drugs** |
|---|---|---|
| ER+, HER2- BC *Randomized* (Part A) | -≤1 prior metastatic therapy<br>-No prior CDK4 & 6 inhibitor | -LY3484356 + Abemaciclib<br>-LY3484356 + Abemaciclib + Physician's Choice AI* |
| ER+, HER2- BC (Part B) | -≤2 prior metastatic therapies (≤1 prior ET)<br>-Prior CDK4 & 6 inhibitor required<br>-No prior Everolimus/Alpelisib<br>-PIK3CA mutation required for Alpelisib | -LY3484356 monotherapy<br>-LY3484356 + Everolimus<br>-LY3484356 + Alpelisib |
| ER+, HER2+ BC *Randomized* (Part C) | -≥2 prior HER2 therapies<br>-No prior fulv or CDK4 & 6 inhibitor | -LY3484356 + Trastuzumab<br>-LY3484356 + Trastuzumab + Abemaciclib |
| ER+ endometroid endometrial cancer *Randomized* (Part D) | -Progressed on platinum-based therapy<br>-No prior AI or fulv | -LY3484356 monotherapy<br>-LY3484356 + Abemaciclib |

*- anastrozole, letrozole, or exemestane

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS12-24

From clinical trials to clinical practice: Real-life outcome data of everolimus and exemestane in the treatment of patients with metastatic breast cancer

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**Background**: Endocrine therapy is commonly utilized in metastatic breast cancer (mBC) especially so among those with limited visceral metastasis. However, resistance to endocrine therapy is commonly encountered. The addition of the mTOR inhibitor everolimus to exemestane, an aromatase inhibitor (AI), can modulate this resistance. This combination was evaluated in phase-III clinical trials and showed significant improvement in progression-free survival (PFS). However, its occasional serious adverse events, especially pneumonitis, had limited its wider adoption and utilization in clinical practice. In this study, we evaluate the efficacy and the prevalence of serious adverse events encountered in real-life practice outside the stringent setup of clinical trials. **Methods**: Patients with mBC treated with everolimus plus exemestane and followed at our institution were retrospectively reviewed. Diagnosis of interstitial pneumonitis was based on clinical findings and confirmed by imaging studies. **Results**: Between January 2017 and October 2019, a total of 91 patients fulfilled the inclusion criteria. Patients' median age (range) was 45 (23-71) years. All were pathologically confirmed hormone receptor positive (HR+) and Human Epidermal Growth Receptor-2 (HER2) negative. The difference between patients enrolled in this study and the randomized Phase-3 BOLERO-2 trial are details in attached Table.

| **Clinical Characteristics** | **Our Cohort (%)** | **Bolero (%)** | **p-value** |
|---|---|---|---|
| **Median age** | 46 | 62 | - |
| **Visceral Disease** | 67 | 56 | 0.052 |
| **Metastatic Sites** | | | |
| **Lung** | 21 | 29 | 0.118 |
| **Liver** | 30 | 33 | 0.534 |
| **Bone** | 75 | 76 | 0.781 |
| **≥ 3 Sites** | 35 | 36 | 0.974 |
| **Prior treatment with Letrozole/Anastrozole** | 93 | 100 | <0.001 |
| **Prior treatment with Tamoxifen** | 66 | 47 | <0.001 |
| **Prior treatment with Fulvestrant** | 59 | 17 | <0.001 |
| **Prior treatment with chemotherapy for metastatic disease** | 84 | 26 | <0.001 |

The majority, 85 (93.4%) had invasive ductal carcinoma (IDC), and 4 (4.4%) had invasive lobular carcinoma. Almost two thirds (n=61, 67.0%) had visceral metastasis involving the liver (n=27, 29.7%) and lung (n=19, 20.9%) with 32 (35.2%) had ≥ 3 metastatic sites. Prior to the designated treatment, patients were subjected to several lines of therapy. Prior treatment with aromatase inhibitors, letrozole or anastrozole, was given to 85 (93.4%) patients while 60 (66.0%) have been treated with tamoxifen. Fulvestrant was given as a third line endocrine therapy in 54 (59.3%) patients. In total, 64 (70.3%) patients had three lines of hormonal therapy prior to everolimus and exemestane. After a median (range) follow up of 13 (1-31) months, 26 (28.6%) had partial response and 32 (35.2%) had stable disease. The median time to disease progression (PFS) was 7.8 months. Seventeen (18.7%) of the patients stopped the treatment due to adverse events mostly due to G3-4 interstitial pneumonitis (n=6, 6.6%), stomatitis (n=6, 6.6%) and one case of membranous nephropathy with nephrotic syndrome. Twenty-eight patients (30.8%) required dose reduction due to elevated liver enzymes (n=12, 13.2%), and stomatitis (n=5, 5.5%). **Conclusions**: Despite enrolling sicker and heavier-pretreated patients, our real-life outcome data for both efficacy and safety of exemestane and everolimus matches those reported in major clinical trials. Such results should assure clinicians and should lead to wider utilization of this oral, chemotherapy-sparing regimen.

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# Role of combined, easily accessible immune blood parameter signatures as predictive biomarkers of chemotherapy response in early breast cancers

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**Introduction:** Neoadjuvant chemotherapy (NAC) is increasingly given preoperatively to shrink breast tumours prior to surgery. The role of an inflammatory response within the local tumour microenvironment in inducing a pathological complete response (pCR) NAC is now well recognised. Recently, easily accessible inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as predictive factors of response to NAC. However, the clinical significance of the combination of these markers is unclear. The objective of this research is to assess the clinical utility of a new blood score combining baseline and/or on treatment values of blood parameters (lymphocytes, neutrophils, monocytes, lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), NLR and PLR as a predictors of response to NAC and prognosis in early breast cancers. **Methods:** This retrospective research has been conducted on a total of 260 breast cancer patients treated with NAC between 2006 and 2019. Patients were categorized into responders (pCR and residual cancer burden (RCB) 1) and non-responder (RCB 2 and 3) groups according to pathological response at the time of surgery. The correlations between baseline and post-cycle one NLR/PLR/LMR and clinico-pathological features, prognosis, and pathological complete response (pCR) rate of NAC were evaluated retrospectively. Univariate and multivariate COX regression analyses were used to investigate the association between blood inflammatory markers and response to treatment. **Results:** Median follow up was 3.7 years (range 1.9-5.8) and the mean age was 47 years (range 40-55). With regard to tumour response, 41.2% (n=107) and 48.5% (n=126) patients had pCR/RCB1 and RCB2/3, respectively. Median NLR at baseline and following one cycle of NAC was 1.9 (range: 1.5-2.7) and 1.7 (range 1.1-2.3) respectively. Median PLR at baseline and following one cycle of NAC was 126 (range: 91.8-169.8) and 206.8 (range:139.9-285.3). Data analysis for LMR are currently premature. Based on the receiver operating characteristic (ROC) curve analyses, values for NLR were set as 1.9 at baseline and 1.7 post cycle 1 of NAC. The values for PLR were set as 126 at baseline and 206 following cycle 1 NAC. Using these cut-offs we did not observe any significant correlations with NLR/PLR as predictive biomarkers for NAC response. However, we observed significantly higher values in NLR and PLR values in the non-responders compared to responders (p= 0.0085 for NLR and p=0.029 for PLR for bloods taken following cycle 1 NAC). In house advanced statistical modelling, with multivariate longitudinal extensions of COX-type regression analyses with exponentially decaying temporal impact functions on the instantaneous hazard rate will be used to investigate the association between longitudinal blood inflammatory markers and response to treatment. **Conclusion:** Low-cost stratification according to the peripheral blood parameters (such as lymphocytes, neutrophils, monocytes, LMR, NLR, NMR, NLR and PLR score) might be a promising approach for predicting early response to NAC for early breast cancers.

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Multi-center trial in the treatment of ductal carcinoma in situ of breast using intra-operative electronic brachytherapy technique, results

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**Purpose:** To report on the technique of intra-operative electronic brachytherapy, local control, side effects and complications after a single fraction of 2000 cGy at the time of partial mastectomy.
**Material & Methods:** 1200 patients with early stage invasive ductal carcinoma and carcinoma in situ were enrolled in the Multi-Center Trial. 246 (20.5%) patients among these 1200 patients had carcinoma in situ and were treated by a single fraction of 2000 cGy dose by intra-operative irradiation to the lumpectomy cavity using Xoft system of electronic brachytherapy at the time of partial mastectomy. 80% of the patients were Caucasian, 7% African American, 7% Hispanic and 6% others. Estrogen receptor was positive in 211 patients, negative in 28 patients and unknown/not assessed in 7 patients. Progesterone receptor was positive in 190 patients, negative in 45 patients and unknown/not assessed in 11 patients. All patients were BRCA negative. 34 (14%) patients had low grade tumors, 109 (44%) intermediate grade tumors, and 103 (42%) high grade tumors. Seroma occurred in 9.8%, induration in 7.6%, and significant fibrosis in 3.5% of the patients. 2/246 (1%) developed ipsilateral recurrence and one patient developed a gastrointestinal cancer. 118 (48%) patients had characteristics of ASTRO criteria being suitable, 108 (44%) cautionary and 20 (8%) unsuitable.
**Conclusion:** The relatively early 2.3 year results of a single fraction of 2000 cGy by IORT to the lumpectomy cavity at the time of partial mastectomy using Xoft Axxent electronic brachytherapy in the treatment of carcinoma in situ of the breast is safe and associated with low morbidity and local recurrence with good to excellent cosmesis in 80% of the patients.

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**Publication Number:** PS1-25

Axillary management after neoadjuvant chemotherapy in initially node positive early breast cancer

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Response to neoadjuvant treatment could modify axillary management of those with node involvement at diagnosis. We investigated whether histological response correlates with node response and could avoid axillary dissection. A series of 339 patients with node positive early breast cancer who received neoadjuvant chemotherapy was analysed. We reported the axillary conversion (ypN0) rate and its association between clinical/pathological parameters. Median age was of 52 (24-89), median tumor size of 38mm; 120 (35%) patients were HER2 positive, 132 (39%) were luminal, and 87 (26%) were triple negative breast cancer. 113 (33%) patients obtained breast pathological complete response (breastpCR): 53/120 (44%) in HER2 positive, 21/132 (16%) in luminal and 39/87 (45%) in triple negative breast cancer. Axillary conversion to ypN0 rate was of 157/339 (46%): 71/120 (59%) in HER2 positive, 40/132 (30%) in luminal and 46/87 (53%) in triple negative breast cancer. It was found a 105/339 (31%) of relapse, and mean survival was of 147 months (CI 95% 134-159). Of 113 patients with breastpCR, 94 achieved axillary ypN0 (83%) (OD=12.8, p=0.000): 45/53 of breastpCR in HER2 positive (85%) (OD=8.8; p=0.069); 16/21 of breastpCR in luminal (76%) (OD=11.6; p=0.000); 33/39 (85%) of breastpCR in triple negative breast cancer (OD=14.8; p=0.002). Residual axillary involvement in breastpCR is reported in the table.Conclusion: Global axillary conversion in patients with breastpCR was of 83%; being HER2 and triple negative those with major association. BreastpCR could predict axillary conversion in triple negative breast cancer (OD=14.8; p=0.002) and the residual node involvement never was more than 3 positive nodes. These patients could avoid axillary dissection if an adequate sentinel node biopsy is performed.

Axillary conversion in breastpCR

| | Global (113) | HER2 (53) | Luminal (21) | TN (39) |
|---|---|---|---|---|
| ypN0 | 94 (83%) | 45 (85%) | 16 (76%) | 33 (85%) |
| 1 node | 8 (7%) | 3 (5%) | 1 (5%) | 4 (10%) |
| 2 nodes | 1 (0.8%) | 0 | 0 | 1 (2.5%) |
| 3 nodes | 1 (0.8%) | 0 | 0 | 1 (2.5%) |
| >3nodes | 9 (7.9%) | 5 (10%) | 4 (19%) | 0 |

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# CDK 4/6 inhibitors are associated with a high incidence of thrombotic events in real world practice

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**Background:** Cyclin dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy are an integral therapy for advanced hormone receptor positive breast cancer. Rates of venous thromboembolic events (VTE) were between 1-5% in clinical trials leading to CDK 4/6 inhibitor approval. Abemaciclib currently carries an FDA warning for VTE risk. However, rates of thrombosis in real world practice remain poorly described. We aim to better define the thrombotic risk associated with CDK 4/6 inhibitors, expanding to evaluate venous and arterial events. Additionally, factors that predispose to thrombosis while on CDK 4/6 inhibitors are unclear. We hypothesize the Khorana thrombosis risk score may predict which patients will experience thrombosis on CDK 4/6 therapy.
**Methods:** We conducted a retrospective analysis of breast cancer patients aged □18 years who were prescribed a CDK 4/6 inhibitor (palbociclib, ribociclib, abemiciclib) at the Knight Cancer Institute and affiliated clinics between February 2015 and March 2020. Venous and arterial thrombosis occurring during treatment or within 30 days of discontinuation were included. We collected data including pre-treatment lab values, age, BMI, prior thrombosis, and smoking status and calculated a Khorana risk score for each patient. Utilizing univariate and multivariate logistic regression we compared these variables in patients who developed thrombosis and those who did not. We calculated overall survival of the two groups. **Results:** There were 270 patients included in the analysis and 29 patients (10.7%) developed a thrombotic event. Of these, 66% were venous, 28% were arterial, and 10% experienced >1 clot. Ribociclib had the highest incidence of thrombosis; 17%, followed by palbociclib; 9% and abemaciclib; 5% (Table 1). Multivariate analysis evaluating risk factors for thrombosis did not find any statistically significant predictors of thrombosis (Table 2). Khorana scores did not predict which patients experienced thrombosis. Median overall survival did not significantly differ between those who developed thrombosis and those who did not (23 months vs 17.5 months respectively, p value = 0.37).
**Discussion:** Incidence of thrombosis in our institutional analysis is higher than reported in clinical trials. Interestingly, we found arterial thrombosis comprised over one-third of events. Patients on ribociclib experienced the highest incidence of thrombosis, suggesting the FDA thrombosis warning may need to be expanded to the drug class. Khorna scores were not predictive of thrombosis risk in our population, however only 1% of study patients had a high risk score over 2. Larger, real world studies are needed to define the risk of thrombosis with CDK 4/6 inhibitors. The role of prophylactic anticoagulation is yet to be defined in this patient population.

| TABLE 1: Incidence of thrombosis | |
|---|---|
| Cumulative Incidence: | |
| Total CDK 4/6 inhibitor population | n = 270 |
| Number of thrombotic events | 29 (11%) |
| Total arterial | 8 (28%) |
| Total venous | 19 (66%) |
| Total arterial + venous | 2 (6.9%) |
| Incidence by CDK4/6 inhibitor | |
| Abemaciclib (n = 20) | 1 (5%) |
| Palbociclib (n = 233) | 22 (9.4%) |
| Ribociclib (n = 17) | 3 (17.6%) |
| Site of event | |
| *First thrombotic event* | n = 26 |
| CVA | 2 (6.9%) |
| CVA + DVT | 1 (3.5%) |
| CVA + MI | 1 (3.5%) |
| DVT | 10 (34.5%) |
| MI | 1 (3.5%) |
| PE | 4 (13.8%) |
| PE + DVT | 2 (7%) |
| Line associated DVT | 1 (3.5%) |
| Retinal vein thrombosis | 1 (3.5%) |
| TIA | 3 (10.3%) |
| *Second thrombotic event* | n = 3 |
| DVT | 1 (3.5%) |
| PE + MI | 1 (3.5%) |
| TIA | 1 (3.5%) |

| **TABLE 2 Predictors of thrombosis** | | | |
|---|---|---|---|
| **Characteristic** | **OR** | **95% CI** | ***P*-Value** |
| Age | 1.02 | 0.98 - 1.06 | 0.28 |
| BMI | 1.04 | 0.98 - 1.1 | 0.24 |
| Hemoglobin | 0.83 | 0.69 - 1.00 | 0.06 |
| History of thrombosis | 1.91 | 0.72 - 5.09 | 0.20 |
| Platelet | 1.0 | 0.99 - 1.01 | 0.86 |
| Smoking | 2.61 | 0.75 - 9.11 | 0.13 |
| WBC | 0.97 | 0.84 - 1.11 | 0.64 |

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# Low expression MicroRNA-195 enriched the cell cycle and cell proliferation gene sets and is associated with advanced grades and worse overall survival of ER positive breast cancer patients

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**Background:** MicroRNA-195 (miR-195) exerts the tumor suppressive functions in various cancers, including breast cancer, by targeting and inhibiting the expressions of the cell cycle and cell proliferation associated genes. In this study, we hypothesized that miR-195 low expressing tumors associate with high proliferative characteristics and poor survival. **Material and Methods:** We obtained the clinicopathological data and survival information of breast cancer patients from two large publicly available databases; The Cancer Genome Atlas (TCGA) and The Molecular Taxonomy of Breast Cancer International Consortium (METARBRIC). Total of 755 and 1287 patients' data were obtained from TCGA and METABRIC respectively. Survival analysis, Overall survival (OS) and Disease-free survival (DFS) was performed by comparing the high and low expression groups. CYT score, xCell, and other immunological factors were used to evaluate intratumoral immune cell composition. Also, gene set enrichment analysis (GSEA) was performed between miR-195 high and low expression groups. **Results:** The patients were divided into miR-195 high and low groups by utilizing median cutoff. Advanced grades were significantly associated with lower expression of miR-195 in ER positive/HER2 negative (ER+/HER2) subtype with both TCGA and METABRIC cohorts ($p<0.001$ and $p<0.001$, respectively). On the contrary this was not consistent with other subtypes, HER2+ and triple negative (TN). Also, Low miR-195 expressing tumors demonstrated higher MKI67 expressions in ER+/HER2- subtype with TCGA ($p<0.001$). This was validated with METABRIC cohort ($p<0.001$). Furthermore, GSEA demonstrated that low miR-195 expressing tumors enriched the gene sets related with cell cycle or cell proliferation, such as MYC signaling, mTOR signaling, E2F signaling, G2M Checkpoint signaling and PI3K_Akt_mTOR signaling, compared with high miR-195 expressing tumors in ER+/HER2-. **Conclusion:** Low expression of miR-195 was associated with improved OS in ER positive breast cancer patients. Also, low miR-195 expressing tumors were found to associate with advanced grades as well as enriching the genes relating to cell proliferation and cell cycle, which may explain the poor survival of low miR-195 expressing patients in ER positive breast cancer.

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# Novel genomic variants and pathways associated with baseline serum thymidine kinase 1 levels in HR-positive HER2-negative MBC patients commencing palbociclib and letrozole

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**Background:** Cyclin dependent 4/6 kinase inhibitors (CDK4/6i) and endocrine therapy (ET) have improved progression-free survival (PFS) and overall survival in hormone-receptor (HR)-positive metastatic breast cancer (MBC), but progression of disease is inevitable. Serum thymidine kinase-1 (TK1) is a secreted marker of proliferation that is prognostic in patients (pts) with HR-positive, HER2-negative MBC and may be predictive of ET and CDK 4/6i response. PROMISE (NCT0281902) is a prospective study enrolling women with HR-positive MBC starting palbociclib (Pb) + letrozole (L) (1$^{st}$ line) or Pb + fulvestrant (2$^{nd}$ line). We undertook a comprehensive “omic” assessment of blood, tumor, urine and the fecal microbiome in order to identify novel genomic variants and pathways associated with an early decline in TK1 (measured after 2 months) and PFS. Additionally, patient derived xenografts/organoids were generated at baseline and progression to test new therapeutic approaches to overcome resistance to CDK4/6i and ET. We report the initial association between the baseline genomic landscape and baseline TK1 levels. **Methods:** FFPE tumor biopsies were obtained for DNA/RNA sequencing (Tempus™) and blood samples for TK1 (Divitum® assay, Biovica) were collected pretreatment (pre-Pb) and after 2 cycles of Pb + ET (post-Pb2). Both whole-exome (exome capture) sequencing (WES) and RNA-Seq used the Integrated DNA Technologies xGen Exome Research Panel v1.0 capture kit. TK1+ disease was defined as > 200 Du/L and TK1- disease as below limit of detection up to 200 Du/L. We tested the association between genomic and transcriptomic characteristics with baseline TK1 data in pretreatment samples where both WES and RNA-seq and TK1 was available. The data were analyzed using bioinformatics pipelines for somatic and germline mutations and copy number alterations. The current analysis focuses on baseline 1$^{st}$-line pre-Pb omics data in conjunction with baseline TK1 levels. The database was locked for analysis on 5/29/2020. **Results:** Thirty-three pts (median age: 59 yrs.) were evaluable, with paired samples for TK1 in 32. Six pts had TK1+ disease pre-Pb and post-Pb2. Twenty-two pts had TK1- disease pre-Pb and post-Pb2. Four pts had a decrease in TK1 after 2 cycles of treatment that altered the classification from TK1+ to TK1-. Both baseline RNA seq and serum TK1 (n=16) were available for 4 TK1+ and 12 TK1- pts. In this group, 476 genes were differentially regulated (398 upregulated; 78 downregulated). Pathway analysis demonstrated enrichment in complement and coagulation cascade pathway, PPAR signaling pathway, and metabolism-related pathways related to up-regulation of CYP and UGT gene families. Further testing for the association of WES data with baseline TK1+ (n=8) and TK1- (n=16) disease demonstrated somatic copy number variations on chromosomes 6, 11, 12 and 15. *CDK4* copy number gains were observed in 3/8 TK1+ pts and 0/16 TK1- pts. We also observed that somatic mutations (LOH, copy number and/or SNV/INDELs) were more prevalent in the TK1+ compared to the TK1- pre-Pb group in several cancer-associated genes (*FAS [p=0.06] PTEN*, *PIK3CB, NAB2, SOX9 and FAT1 [p=0.08], TP53*, and *MAP2K4* [*p=0.22]*). Conversely, we also noted that 6/7 pts with *GATA3* mutations had TK1- disease (*p=0.23*). **Conclusions:** Using a comprehensive “omics” approach, our data suggest that a secreted biomarker of proliferation (TK1) obtained prior to initiating CDK4/6i and ET for the first line treatment of HR+ MBC is associated with established and novel genes and pathways associated with prognosis of pts receiving ET and CDK 4/6i. Analysis of on-treatment (after 2 cycles) tumor RNA seq and its association with change in TK1 as well as data from the 2$^{nd}$-line cohort will be presented at the meeting.

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Characteristics of HR+/HER2- patients with recurrent disease by HER2 expression from a prospective registry of unresectable locally advanced or metastatic breast cancer: GEICAM/2014-03 (RegistEM)

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**Background:** The RegistEM study is a non-interventional cohort study that will provide prospective data from >1,800 advanced breast cancer (ABC) patients (pts), either after recurrence or as first diagnosis in 38 Spanish sites. Primary objective is the distribution of BC subtypes. A new nomenclature has been proposed for those cases with immunohistochemistry (IHC) 1+ or 2+ and negative in situ hybridization (ISH), HER2-low BC. In clinical practice these tumors are reported as HER2 negative. This subpopulation has been identified as an interesting group from a clinical perspective. **Methods:** In this analysis (cut-off date 01/April/2020; database is ongoing) we describe the characteristics of 229 pts with hormone receptor (HR)+/HER2-low BC documented in a metastatic lesion after early disease recurrence and who received adjuvant endocrine therapy (ET). Three subgroups of pts have been considered for this analysis based on HER2 results: HER2 IHC 0, HER2-low, and HER2 ISH- (without IHC). Biological samples collection is part of study procedures. **Results:** The distribution of HER2 IHC 0, HER2-low, and HER2 ISH- subgroups was 52.4%, 42.8% and 4.8%, respectively. The median time to advance disease was 98.6, 88.8 and 106.9 mo in each group. Almost all pts were female and Caucasian (99%), and at ABC diagnosis, 75.5% were postmenopausal. Median age was 59 years (range 33-88). Fourteen (6.1%) pts had HER2+ (IHC 3+ or ISH amplified) BC subtype during their disease. Family history of BC and/or ovarian cancer was reported in 31.4% pts, an hereditary-risk genetic test was performed in 11.4% (n=26) pts in total and BRCA2 gene mutation (n=6) was the only one reported. The most frequent metastases are included in Table 1. Visceral disease was present in 63.3% pts and 76% pts had ≤2 locations. The most frequent 1$^{st}$-line therapies were ET/biological therapy (BT) (46.7%) and ET (28.8%), and were equal distributed in the 3 subgroups. The most common ET/BT regimens were aromatase inhibitor (AI)/cyclin-dependent kinase 4/6 inhibitor (CDKi) (49.1%/48.9%/42.9% in each subgroup) and fulvestrant (FUL)/CDKi (35.8%/27.7%/28.6%); AIs (50%/64%/66.7%) and FUL (31.6%/20%/0%) were also the most common drugs for monotherapy ET. A 2$^{nd}$-line therapy was reported in ~53% pts in HER2 IHC 0 and HER2-low, and in 36% pts in HER2 ISH-. The median time to progression (TTP) to 1$^{st}$-line therapy was 11.4 mo (1.2-37.0), being similar in pts with HER2 IHC 0 and HER2-low (~11 mo), and higher in pts with HER2 ISH- (16 mo). The most frequent 2$^{nd}$-line therapies were ET/BT (~34% in HER2 IHC 0 and HER2-low, and 25% in HER2 ISH-) [FUL/CDKi (36.4%/47.1%/100%), AI/CDKi (36.4%/23.5%/0%)], chemotherapy as monotherapy (17 pts out of 63 in HER2 IHC 0, 17 pts out of 53 in HER2-low and 1 pt (capecitabine) out of 4 in HER2 FISH-) (capecitabine 29.4%/52.9% in HER2 IHC 0 and HER2-low). Median duration of 2$^{nd}$-line therapy was ~5 mo in HER2 IHC 0 and ~8 mo in HER2-low and HER2 ISH-; disease progression was reported in 52.4%/62.3%/50% pts, respectively. **Conclusions:** In this population of HR+ tumors, the proportion of HER2 IHC 0 and HER2-low groups was similar. Time to advance relapse and the distribution of distant metastases were similar among the groups. The most common first- and second-line therapy was the ET/BT combination, with AI/CDKi and FUL/CDKi, respectively.

**Table 1**

| Location of metastatic lesions | IHC 0 N=120 N (%) | HER2-low N=98 N (%) | ISH- non IHC N=11 N (%) |
|---|---|---|---|
| **Bone** | 74 (61.7) | 55 (56.1) | 6 (54.5) |
| **Liver** | 36 (30.0) | 37 (37.8) | 3 (27.3) |
| **Lung** | 27 (22.5) | 21 (21.4) | 5 (45.5) |
| **Lymph Node** | 27 (22.5) | 21 (21.4) | 2 (18.2) |
| **Soft Tissue** | 6 (5.0) | 11 (11.2) | 0 |
| **CNS** | 3 (2.5) | 4 (4.1) | 0 |
| **Other** | 43 (35.8) | 31 (31.6) | 5 (45.5) |

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Quantitation of serum thioredoxin 1 could mitigate difficulty to detect breast cancer from dense breasts by mammography

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**Background:** Even though almost half of women have dense breasts (DB), the density of breasts has been an obstacle to detect breast cancer (BC) correctly by the gold standard of screening, mammography. It is strongly recommended to take consideration of breast density in analyzing mammogram. We have reported the possibility of serum level of thioredoxin 1 (Trx1) as a novel means to assess the risk of BC regardless of various conditions of breasts. In present study, we have evaluated how serum level of Trx1 can mitigate the difficulty to detect BC from dense breast by mammography. **Methods:** We have generated monoclonal antibodies against Trx1 and developed an ELISA kit that quantitates Trx1 in serum. The level of Trx1 was determined in each serum from BC patients (n=106) who had been confirmed as BC by various examinations including mammography as well as surgery. Each Trx1 level was analyzed with corresponding patient's mammography results such as patterns, asymmetry, shapes, margin, and density. The analyzed results were compared with those from other biomarker tests including CA15-5 and CEA to evaluate the clinical validity of Trx1 in this study. Each test was duplicated two times, and test results were analyzed by ROC analysis, one-way ANOVA tests, and unpaired t-tests.**Results:** Most of BC patients (82.6%, n=86) was classified as mammography pattern 3 and 4, and BI-RADS score higher than 4 (74.0%, n=77). More than half of patients' breast density was in high density group (54.8%, n=57), whereas 5.8% of iso density (n=6) and 39.4% of not determined (n=41). The blood Trx1 levels of patients were higher than the cut-off value of 14 U/ml indicating BC regardless of characteristics of breasts. Although other breast cancer biomarker tests such as CA15-3 and CEA could not identify BC, Trx1 level could correctly detect BC even in the cases that mammography could not show the mass clearly. The sensitivity/specificity of mammography and Trx1 test were 75.2%/74.0% and 96.2%/99.0%, respectively. When mammography and Trx1 test were combined, the whole sensitivity/specificity was 99.3%/100.0%. **Conclusion**: Even though it is obvious that larger size of further study necessary, the serum Trx1 level showed that it could identify BC in dense breasts easily. These results indicated that serum Trx1 level could efficiently mitigate the difficulty to detect BC from dense breasts by mammography. **Keywords:** Thioredoxin 1, Breast cancer, Dense breast, Diagnostics, Sensitivity, Specificity, Blood

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# Receipt of preventive care and health promotion in a cohort of early stage breast cancer survivors

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Introduction: Prior studies have demonstrated that breast cancer survivors are less likely to receive primary care preventive services than non-cancer patients. However, even recent studies have largely assessed survivors diagnosed over a decade ago. Further, studies have not considered patient receipt of health promotion guidance, critical to maintaining a healthy lifestyle. We examined the receipt of preventive care and health promotion in a modern cohort of early stage breast cancer survivors seen within our breast program. Methods: A cross-sectional cohort of women with a history of stage I/II, hormone receptor +, HER2neu- breast cancer within 5 years from diagnosis who did not receive chemotherapy were consented (n=101). Survivors completed a survey evaluating aspects of survivorship, including provider discussions regarding health promotion. Electronic medical record (EMR) abstraction captured receipt of preventive care (see Table). We excluded survivors with a primary care provider outside our health care system to ensure complete capture of screening (n=36). Results: Our final cohort (n=62) was a median 2 years from diagnosis (range 0.5-5 years) and a median age of 61 years (range 30-84). Most were stage I (73%) and white (95%). The majority of survivors received preventive care (Table). Survivors were less likely to report health promotion guidance from their provider, including: discussing “things you could do to improve your health” (66%), getting “help you wanted to make changes in your habits” (52%), discussing “how much or what kinds of food you eat” (24%), and “how much or what kind of exercise” (42%). Conclusion: In a modern cohort of early stage breast cancer survivors from a single breast center homed within our health care system, documented receipt of preventive care was high (≥75%). These high rates may reflect the implementation of EMRs (which could facilitate care coordination and provide best practice alerts), participation of our health system in state-wide quality improvement programs, and/or heightened awareness of the importance of preventive care by oncology providers. However, survivors perceive limited discussions surrounding health promotion, presenting an opportunity to improve survivorship care.

Table. Summary of Receipt of Preventive Care for Early Stage Breast Cancer Survivors

| **Recommended Preventive Care Services** | **Definition of Receipt** | **Proportion of Eligible Patients** |
|---|---|---|
| Influenza vaccine | Any since diagnosis* | 76% (44/58) |
| Pneumococcal vaccine | If >65 yo, any since diagnosis* | 93% (38/41) |
| Lipid screening | Any within 5 years | 84% (52/62) |
| Colorectal cancer screening | If >50 yo, colonoscopy within 10 years, cologuard within 5 years, fecal occult test within 1 year | 77% (37/48) |
| Cervical cancer screening | If cervix present and <65 yo, within 5 years | 79% (27/34) |
| Mammogram screening | If breast tissue present, annual | 100% (56/56) |
| *if <1 year from diagnosis, ineligible for this metric | | |

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Association of OPG rs2073618 and aromatase inhibitor induced musculoskeletal symptoms

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Background: Adjuvant aromatase inhibitors (AI) reduce recurrence and mortality after early stage hormone receptor-positive (HR+) breast cancer (BC). Treatment-related toxicities, including AI-induced musculoskeletal symptoms (AIMSS), are common during adjuvant AI therapy. Prior work suggests the risk of AIMSS is associated with inherited germline genetic polymorphisms in several genes, such as *TCL1A, CYP19A1, OPG*, and *VDR*. These pharmacogenetic associations require replication in independent cohorts prior to clinical translation to identify patients at risk for AIMSS. The objective of this retrospective pharmacogenetic analysis was to replicate previously reported associations for candidate germline genetic polymorphisms with AIMSS. Methods: Women with stage 0-III HR+ BC initiating adjuvant endocrine therapy (ET) with tamoxifen or an AI were enrolled in a prospective clinic-based observational cohort. The type of ET was selected by the provider. A baseline (BL) blood sample was collected for isolation of germline DNA for pharmacogenetic analysis. AIMSS were assessed by patient-reported outcomes (PRO). Participants completed PROMIS pain interference (PI), PROMIS physical function (PF) and Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES) measures at BL and after 3, 6, 9, 12, 24, 48 and 60 months (mo). The FACT-ES includes one question about joint pain, rated on a 5-point scale ("not at all" to "very much"). This secondary retrospective pharmacogenetic analysis was conducted in participants receiving AI therapy for whom blood samples and PRO scores at BL and 3 and/or 6 mo were available. For the primary analysis, we defined AIMSS as a ≥4 point increase in PI T score from BL to 3 and/or 6 mo. For secondary analyses, we evaluated alternate definitions of AIMSS including a ≥4 point decrease in PF T score and a ≥1 category increase on the FACT-ES joint pain question from BL to 3 and/or 6 mo. The primary hypothesis was that *TCL1A* rs11849538 is associated with AIMSS. Twelve other germline variants in *CYP19A1*, *VDR*, *PIRC66*, *OPG*, *ESR1*, *CYP27B1*, *CYP17A1*, and *RANKL* previously reported to be associated with AIMSS were also analyzed. We assumed a dominant genetic effect and pre-specified the direction of effect on AIMSS for each variant. We conducted univariate logistic regression to evaluate associations between each definition of AIMSS and candidate polymorphism using an unadjusted α=0.05. Significant univariate associations in the expected direction were adjusted for age, race, body mass index (BMI), prior taxane and type of AI using multivariable logistic regression. Results: Of 182 participants on AI, 143 with PRO and genetic data available were included in this analysis. Median age was 67, 85% were white, median BMI was 27.8 and 27% had prior taxane. 78% received anastrozole, 20% letrozole and 2% exemestane. On primary analysis, participants carrying *TCL1A* rs11849538 were not more likely to develop AIMSS as defined by increase in PI T score by ≥4 (OR=1.29, 95% CI: 0.55-3.07, p=0.56). None of the other polymorphisms was associated with increase in PI T score by ≥4. On secondary analysis, *OPG* rs2073618 was associated with AIMSS, as defined by an increase on the FACT-ES joint pain question ≥1 (OR=3.33, 95% CI: 1.48-7.49, p=0.004) and this association maintained significance after covariate adjustment (OR=3.98, 95% CI: 1.61-9.84, p=0.003). Age, race, BMI, prior taxane and type of AI were not associated with AIMSS on multivariate analysis. No other polymorphisms were associated with AIMSS on secondary analyses.
Conclusions: Carriers of *OPG* rs2073618 may be at increased risk of AIMSS. If confirmed in other cohorts, OPG genotyping may be able to identify individuals with HR+ early BC at increased risk for AIMSS during AI therapy. Alternate ET or interventions to reduce musculoskeletal symptoms may be needed for this population.

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Concordance of immunohistochemical assays between peri-operative and post-operative breast tumor specimens: A prospective observational study of 18 cases

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**Background and Rationale:** Biomarker evaluation on breast tumor tissue is an important component of clinical research. There is a concern that tissues collected at different times (pre- vs intra-op) and with different techniques (core biopsy vs. surgical excision) produce different results that may confound comparisons of patient samples. Our objective is to address the difference between tumor tissue from the same patient collected pre- vs intra-op and by core biopsy (Core Bx) vs surgical excision, with an emphasis on ER/PgR/HER2/Ki-67 and biomarkers related to insulin metabolism.
**Design:** Following a protocol approved by the IRB, patients with Core Bx proven invasive breast cancer (BC) >1.5 cm in size by imaging underwent a peri-operative Core Bx followed by surgical excision. No neoadjuvant therapy was administered. Formalin-fixed paraffin-embedded tumor sections of the diagnostic and peri-operative Core Bx and surgical excision were immunohistochemically (IHC) stained for ER, PgR, HER2, Ki-67, insulin receptor (IR), phospho-AKT (pAKT), and phospho-AMPK (pAMPK) using standardized protocols on the same platforms. A pathologist (MCC) scored all sections in blinded order to yield H-Scores (which combine percentage of stain-positive cells and staining intensity). The level of agreement for each assay between specimens was assessed by using pairwise models based on normal theory.
**Results:** 18 women (mean age = 66.8 years, 16/18 postmenopausal) provided all specimens. Mean (± SD) invasive tumor size was 2.7 (± 1.2) cm. 1 BC was Nottingham Grade 1 (6%), 9 Grade 2 (50%), and 8 Grade 3 (44%). An in situ component was present in 4/18 (22%) cases (all non-extensive). Lymphovascular invasion was present in 6/18 (33%) cases. 10/18 were node-negative (N0, 56%), 2/18 had isolated tumor cells (pN0[i+], 22%), 5/18 had 1 to 3 nodes (pN1, 28%), 1/18 had >9 nodes involved (pN3, 6%).There was high concordance between diagnostic Core Bx, peri-op Core Bx, and excisions for the standard prognostic markers ER, PgR, and HER2. ER was concordant in all samples including 16/18 (89%) ER-positive and 2/19 (11%) ER-negative BCs. PgR was concordant in 16/18 (89%) of cases. In the 2 discordant cases, PgR was negative in 2 of 3 tissue samples with low expression in the 3rd sample (1 diagnostic Core Bx and 1 excision). HER2 was concordant in all samples in 16/18 (89%) HER2-negative cases and in 2/18 (11%) HER2-positive cases including 1/18 cases (6%) positive by IHC, and 1/18 cases (6%) positive by ISH.
Table 1 summarizes the agreement between samples for Ki-67, IR, pAKT, and pAMPK. Ki-67 scores were statistically similar between diagnostic and peri-op Core Bx and excision samples. The IR, pAKT, and pAMPK H-Scores were statistically similar between diagnostic and peri-op Core Bx, but significantly different between Core Bxs versus excisional specimens. There was a systematic tendency towards lower IHC H-Scores in the excisional specimen for IR, pAKT, and pAMPK.
**Conclusion:** Tissue from surgical excisions are susceptible to reduced IHC staining for metabolic markers such as IR, and phosphorylated kinases, when compared to core biopsies. When evaluating non-standard biomarkers for research, core biopsies should be used when possible.
**Funding:** This study was funded by the Hold'Em For Life Charity and the Breast Cancer Research Foundation

Table 1: Concordance Between IHC Scores for Ki-67, Insulin Receptor, pAKT, and pAMPK

| | Score: Mean ? Standard Deviation | | | Peri-Operative Core Bx versus Diagnostic Core Bx | | Excision versus Diagnostic Core Bx | |
|---|---|---|---|---|---|---|---|
| | Diagnostic Core Bx | Peri-Operative Core Bx | Excision | Difference | P-value | Difference | P-value |
| Ki-67 (% Positive) | 33.5 ? 28.2 | 35.9 ? 31.0 | 34.2 ? 29.1 | Mean ? SD: 2.4 ? 5.6<br>Range: -7.7 to 12.3 | 0.09 | Mean ? SD: 0.6 ? 6.3<br>Range: -11.5 to 12.2 | 0.68 |
| Insulin Receptor (H-Score**) | 136 ? 102 | 124 ? 99 | 86 ? 78 | Mean ? SD: -13 ? 53<br>Range: -215 to 40 | 0.32 | Mean ? SD: -51 ? 54<br>Range: -150 to 5 | 0.001* |
| Phospho-AKT (H-Score**) | 102 ? 70 | 100 ? 86 | 41 ? 41 | Mean ? SD: -1 ? 75<br>Range: -170 to 170 | 0.95 | Mean ? SD: -61 ? 52<br>Range: -144 to 0 | 0.0001* |
| Phospho-AMPK (H-Score**) | 201 ? 79 | 185 ? 78 | 157 ? 86 | Mean ? SD: -15 ? 76<br>Range: -225 to 120 | 0.41 | Mean ? SD: -44 ? 69<br>Range: -215 to 70 | 0.016* |

* Statistically significant difference in pairwise values based on t-test
** H-Score is the percentage of stain-positive cells multiplied by the average intensity score (0 = absent, 1 = faint, 2 = moderate, 3 = strong)

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Cell-free DNA based detection of mono-allelic versus bi-allelic loss of function for essential genes in breast cancer

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**Background**: Breast cancer is the top cancer in women, accounting for over 30% of new cancer cases in women worldwide. Breast cancer is a highly heterogenous disease. Treatment of breast cancer is a very active area in cancer research with significant progresses in recent years. Despite of recent progress in liquid biopsy molecular profiling, blood-based detection of mono-allelic versus bi-allelic loss of function for essential genes such as BRCA, PTEN etc. remains an unmet clinical need for targeted therapy in breast cancer.
**Methods:** We tested over 1000 plasma samples of breast cancer patients using PredicneCARE, a proprietary cell-free DNA (cfDNA) assay, which covered the DNA Damage Repair (DDR) genes in addition to most genes under research in cancer pathways. This blood-based cfDNA assay has a well-tuned capability to reliably detect copy number gain and loss, discriminating bi-allelic versus mono-allelic gene deletions. The assay also has an HRD (Homologous Recombination Deficiency) add-on for the generation of HRD score.
**Results:** PredicineCARE was used to test over 1000 breast cancer patients. The most frequently mutated genes include *TP53*(59.7%), *PIK3CA*(47.6%), *BRCA2*(16.1%), *ATM*(12.9%), *ESR1*(12.1%), and *ARID1A*(10.1%), with cancer variant detection capability down to 0.1% for hotspots; for copy number gain at ≥2.23 and for copy number loss at ≤1.75; and for rearrangements at 0.375%. Interestingly, cfDNA-based gene amplifications were founded in *ERBB2*, *PIK3CA*, *FGFR1*, *MYC*, etc. and gene deletions were found in important genes such as PTEN, RB, BRCA1/2 etc. Interestingly, we observed significant difference in mutations of key driver genes such as *PIK3CA* in Chinese versus Caucasian mBC cohorts.
**Conclusion:** The PredicineCARE assay detects blood-based cancer alterations including copy number loss, fusion detection and somatic status evaluation, providing a non-invasive approach to profile important targets including *HER2*, *EGFR*, *VEGFR*, *DNA* damage repair (*BRCA1/2*), cell cycle and growth regulations (*CDK4/6-RB* and *PTEN/PI3K/AKT/mTOR*), and *TRK/ROS1/RET* fusions for the treatment of breast cancer.

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# Pilot trial of priming with oral TAK-228 and TAK-117 (PIKTOR) to increase DNA damage repair deficiency (DDRD) followed by cisplatin (cis) and nab paclitaxel (nab pac) in chemotherapy-pretreated metastatic triple negative breast cancer (metTNBC) pts

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BACKGROUND: A subset of TNBCs have homologous recombination deficiency with upregulation of compensatory DNA repair pathways. The combination of TAK-228 and TAK-117 (PIKTOR), investigational oral TORC1/2 and PI3Kα selective inhibitors, respectively, is hypothesized to increase genomic instability (GI) and to increase DDRD, leading to increased sensitivity to DNA damaging chemotherapy and to checkpoint inhibitors in metTNBC pts. METHODS: 10 metTNBC pts received 4 mg PO TAK-228 and 200 mg PO TAK-117 QDx3d QW until disease progression (PD), followed by cis 75 mg/m$^2$ plus nab pac 220 mg/m$^2$ for up to 6 cycles. Primary endpoints were objective response rate with cis/nab pac and safety. Blood samples and biopsies of metastatic lesions were collected prior to and at PD on PIKTOR. Blood CTC analyses included enumeration, cell morphology, phenotypic heterogeneity, and predicted genomic instability (pGI) derived from cell phenotypes. RESULTS: 10 pts received PIKTOR followed by cis/nab pac. Median age: 51 yrs; median number of prior chemotherapy regimens was 3 (range, 1-5); 7 pts had prior carboplatin; sites of metastases: lymph nodes (n=8); lung (n=6); chest wall (n=1); bone (n=1); brain (n=1). Median time on PIKTOR was 8 wks (range, 3-14). With cis/nab pac, 1 pt had PR, 2 had SD > 6 mos, 1 had SD and 6 had PD. 2 SD pts (sites LNs and bone) and 1 PD pt (sites LNs), all carboplatin-pretreated, whose pre-PIKTOR BCs were PDL1-negative (2 pts) or unknown (1 pt) have durable SD on pembrolizumab post-cis/nab pac for 1+ yrs. PIKTOR related AEs ≥30% included: fatigue (90%); nausea (80%); diarrhea (60%); vomiting (40%); stomatitis (40%); hyperglycemia (30%); rash (30%); cough (30%); chest pain (30%). Incidence and grade of cis/nab pac-related AEs were not greater than expected with this regimen. At PD on PIKTOR, higher CTC burden and pGI+ CTCs were observed in a subset of pts suggesting that some CTCs may have developed greater GI with PIKTOR treatment. Next generation sequencing (NGS) and reverse phase protein array (RPPA) analyses of biomarkers of DNA repair pathways pre-and post-PIKTOR tissues are underway and will be presented at the meeting. CONCLUSIONS: Priming pts' metTNBC with PIKTOR did not lead to durable responses with cis/nab pac in most pts in this pretreated population. However, 3/10 pts who had carboplatin-pretreated disease in LNs +/- bone, have highly durable SD on pembrolizumab following PIKTOR therapy.

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Comprehensive genomic analysis reveals molecular correlates of response to immune checkpoint inhibitors (ICI) in metastatic triple-negative breast cancer (mTNBC)

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Background: Genomic mechanisms associated with response to ICI in mTNBC are largely unknown. The aim of this work is to assess the genomic and immune profiles of mTNBC samples collected from patients (pts) treated with ICI. Methods: We identified 31 women with mTNBC treated with ICI (pembrolizumab, n=6, NCT02447003; atezolizumab, n=4, NCT01375842; nivolumab + cabozantinib, n = 6, NCT03316586; pembrolizumab + eribulin, n=8, NCT02513472; atezolizumab + nab-paclitaxel, n=7, NCT01633970) who had tumor tissue or blood available for sequencing obtained before and after ICI. Clinical benefit (CB), here defined as any objective response or stable disease (SD) for ≥ 24 weeks, was observed in 20 pts (65%). An extraordinary responder was defined as having CB ≥ 2 yrs; 5 pts were considered extraordinary responders (range 26-60months). Whole exome sequencing (WES) was done on each tumor and on germline DNA from blood (23 pts had successful WES performed on samples collected before ICI; 5 of these had WES on samples taken after disease progression). RNA sequencing (RNAseq) was successfully performed in 18 of the tumors with WES performed on samples before ICI; and 3 of these had RNAseq on samples taken after disease progression. 18 pts had tumors assessed by multiplex immunofluorescence (mIF) panels encompassing CD4, CD8, PD-1, PD-L1, and cytokeratin on samples collected before ICI. WES, deep targeted panel and low coverage whole genome sequencing were performed on serially collected plasma samples from 22 pts to evaluate tumor fraction and specific mutations. The association between biomarkers and clinical benefit to ICI was assessed. Results: 21 of 31 pts (67%) had received □1 prior lines of systemic therapy in the metastatic setting before starting ICI. Among the most frequently mutated genes at baseline are: TP53 (57%); PIK3CA (18%); DNAH5, MYH8 (both 13%); KMT2C, AKT1, LAMA2 (all 9%). Pts with CB had a higher tumor mutational burden (TMB) than pts with no CB (p=0.018). Differential expression analysis of RNAseq data revealed an upregulation of several immune-related genes in pts with CB, indicating increased immune infiltration in that group. Gene set enrichment analysis of this expression data using hallmark and canonical pathway gene sets from MSigDB (nominal p-val < 0.05) showed that, compared to samples from pts without CB, extraordinary responders had elevated transcriptional signatures of several cancer-related pathways associated with cell survival, proliferation and metabolism, as well as genes associated with increased immune infiltration and upregulation of inflammatory response programs. The mIF showed that the tumor microenvironment (TME) of pts with CB were enriched in Cytokeratin-negative/PD-L1-positive cells compared to those without CB (p=0.014). Expression of CD4, CD8 and PD-1 was not significantly different between pts with and without CB. Genomic analysis of circulating tumor DNA, and tumor evolutionary analysis for pts with both pre- and post-ICI samples (acquired resistance) will be presented. Conclusions: Clinical benefit to ICI in mTNBC was associated with upregulation of immune-related pathways, enrichment of non-tumoral PD-L1-positive cells in TME, and high TMB.

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# Genetic cancer risk assessment and its impact on the uptake of cancer risk reduction strategies: The experience of a Mexican center

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Background: The implementation of genetic cancer risk assessment (GCRA) in resource-constrained settings is limited due to multiple factors, including insufficient access to preventive strategies. In our center, GCRA was formally established in 2014, and access to genetic testing is provided to underserved patients through a research collaboration with City of Hope's CCGCRN. The aim of this study is to determine the proportion of patients with germline mutations that underwent risk-reducing surgeries (RRS) and followed recommended breast cancer (BC) screening strategies.
Methods: Patients that received GCRA in a center located in Monterrey, Mexico who met NCCN criteria for testing for BC predisposition genes were eligible. Information on mutation status, performance of RRS and BC screening strategies was prospectively collected. The patients were grouped by type of healthcare (i.e. private vs public), with differences explored using Fisher's exact or Mann Whitney U tests, as appropriate.
Results: Between 2014 and 2019, a total of 437 probands and 139 of their relatives underwent GCRA. Of these, 23% and 37% were identified as mutation carriers, respectively: BRCA1/2 (72.5%), PALB2 (6.4%), CHEK2 (6.4%) and others (14.7%). The median time elapsed from disclosure of genetic test results to collection of data was 16 months. The median age was 41 years, with no statistical difference according to type of healthcare. Based on NCCN guidelines, 151 RRS were recommended according to mutational status and age, of which 52 (34%) were performed: 28 risk-reducing mastectomies (RRM) and 24 risk-reducing salpingo-oophorectomies (RRSO). A substantial proportion of these were funded by non-governmental organizations, while the rest were covered by public health insurance (as adjuvant treatment), private health insurance or the patient herself. Regarding BC screening, after excluding 78 patients because of active BC treatment, bilateral mastectomy or male sex, 92% of eligible patients followed NCCN recommendations. No differences in the performance of RRS or BC screening strategies were found according to type of healthcare delivery.
Conclusion: In this cohort, an adequate adherence to recommended screening strategies was observed but only one-third of recommended RRS were performed. Notably, type of healthcare was not a determining factor for the adherence to NCCN's recommended prevention strategies, suggesting that economical barriers might not be the main limiting factor. Efforts to elucidate if sociocultural barriers limit adherence to RRS are being conducted in order to enhance standard of care at Mexican centers with GCRA programs.

Characteristics according to healthcare coverage.

| | **Private insurance** | **Public insurance** | ***p* value** |
|---|---|---|---|
| **Mutational status**<br>**- Probands: carriers/tested**<br>**- Relatives: carriers/tested** | 32/117 (27%)<br>10/42 (24%) | 67/320 (21%)<br>42/97 (43%) | NS<br>0.036 |
| **RRS**<br>**- RRM performed/recommended**<br>**- RRSO performed/recommended**<br>**- RRS covered by NGOs** | 9/24 (38%)<br>6/18 (33%)<br>0 (0%) | 19/65 (29%)<br>18/44 (41%)<br>11/37 (30%) | NS<br>NS<br>0.022 |
| **Current BC screening modality**<br>**- Mammogram (MMG) ? US**<br>**- MRI ? MMG ? US**<br>**- None**<br>**- Unknown** | 9 (41%)<br>9 (41%)<br>3 (14%)<br>1 (5%) | 33 (65%)<br>6 (12%)<br>1 (2%)<br>11 (22%) | 0.033 |
| **Follow BC screening recommendations**<br>**- Yes**<br>**- No** | 19 (90%)<br>2 (10%) | 37 (93%)<br>3 (8%) | NS |

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# Management of abemaciclib associated diarrhea in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: Analysis of the MONARCH plus study

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Background:
In the phase III MONARCH plus study (NCT02763566) the cyclin-dependent kinase (CDK) 4&6 inhibitor abemaciclib in combination with non-steroidal aromatase inhibitors (NSAI) or with fulvestrant compared with placebo demonstrated its efficacy and acceptable safety profile at interim analysis in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) locoregionally recurrent or metastatic breast cancer. One of the most common treatment-emergent adverse event (TEAE) was diarrhea, typically low grade and of early onset. We will further characterize abemaciclib-associated diarrhea and describe its management in MONARCH plus trial.
Methods:
MONARCH plus study included two cohorts of patients. Cohort A enrolled patients with initial treatment of endocrine therapy, received abemaciclib or placebo plus NSAI (anastrozole or letrozole); Cohort B enrolled patients who progressed on prior endocrine therapy, receiving abemaciclib or placebo plus fulvestrant. The relative dose intensity was defined as the percentage of actual dose received relative to the planned dose. The severity of diarrhea was reported by investigators and graded according to Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0). Further analysis on diarrhea included time to onset, duration, supportive medication and dose modifications. Progression-free survival (PFS) was defined as time from randomization to death or progression (RECIST v1.1), and a stratified Cox proportional hazard model was used to estimate the hazard ratio (HR) between study intervention arm and placebo arm.
Results:
The median relative dose intensity of abemaciclib in abemaciclib plus NSAI arm and abemaciclib plus fulvestrant arm were 96.77% and 96.30% respectively. In abemaciclib plus NSAI arm and abemaciclib plus fulvestrant arm, the median time to onset of first reported diarrhea was 7 and 6 days and majority of diarrhea events occurred early (66.3% and 71.2% of patients reported diarrhea in Cycle 1 respectively). Diarrhea was typically of low grade (3.9% and 1.9% of patients reported Grade 3 in abemaciclib plus NSAI arm and abemaciclib plus fulvestrant arm, no Grade 4 diarrhea was reported in either arm). Median duration of grade ≥ 3 diarrhea was 2.5 and 3.5 days. Diarrhea was managed by dose adjustments and/or supportive medication (Table 1). Dose reductions were present in 2.0% and 2.9% of patients, and anti-diarrhea therapy was received in 30.2% and 32.7% of patients with abemaciclib plus NSAI and abemaciclib plus fulvestrant arm, respectively. As data cutoff, most diarrhea events were reported as resolved, and the incidence dropped below 10% (Grade 2) and 1% (Grade 3) by Cycle 2 in both arms and kept low incidence over time. Compared to the placebo arm, patients treated with abemaciclib combination who reported diarrhea within the first 7 days (abemaciclib + NSAI, HR [95% CI]: 0.289 [0.166, 0.502]; abemaciclib + fulvestrant, HR [95% CI]: 0.371 [0.213, 0.647]) had significant improvement in PFS.
Conclusion:
Majority of diarrhea events were of low grade in severity and well managed by anti-diarrheal medications, dose omissions or/and dose reductions in MONARCH plus patients.

**Table 1. Summary of dose adjustments and supportive medications in patients experiencing diarrhea**

| | **Cohort A Abemaciclib + NSAI N = 205** | **Cohort B Abemaciclib + Fulvestrant N = 104** |
|---|---|---|
| **Diarrhea (any grade), n (%)** | 164 (80.0) | 82 (78.8) |
| 1 | 105 (51.2) | 52 (50.0) |
| 2 | 51 (24.9) | 28 (26.9) |
| 3 | 8 (3.9) | 2 (1.9) |
| **Outcome, number of events, n** | 796 | 333 |
| Recovered/resolved, n (%) | 757 (95.1) | 318 (95.5) |
| Not recovered/resolved, n (%) | 17 (2.1) | 7 (2.1) |
| **Treatment change, n (%)** | | |
| Dose reduction | 4 (2.0) | 3 (2.9) |
| Dose omission | 3 (1.5) | 3 (2.9) |

| | | |
|---|---|---|
| Treatment discontinuation | 0 | 0 |
| **Anti-diarrhea therapies, n (%)** | 62 (30.2) | 34 (32.7) |
| loperamide | 48 (23.4) | 21 (20.2) |
| berberine | 6 (2.9) | 6 (5.8) |

**Publication Number:** OT-09-04

Analysis of genomic alterations in cell free DNA and gut bacterial diversity in metastatic breast cancer (MBC) patients on endocrine therapy: A pilot study

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***Background***: Endocrine therapies have been associated with an overall survival benefit in MBC. However, a majority of patients eventually develop endocrine resistance and the factors associated with short versus long term response to endocrine therapies have not been well defined. These factors include key genomic alterations as well as alterations in steroid metabolism pathways. Gut bacteria play an important role in estrogen metabolism and may thus impact response to endocrine-based therapies. Our study aims to investigate both genomic and gut bacterial profiles in patients treated with endocrine therapies in MBC to further elucidate potential mechanisms of acquired endocrine resistance. ***Specific Aims***: (1) To examine mutational profiles in cell free DNA of ER+/HER2- MBC patients treated with Aromatase Inhibitors (AI) + CDK 4/6 inhibitors to identify common oncogenic alterations associated clinical outcomes. (2) To identify gut bacterial profiles predictive of short versus long term response to endocrine therapy with AI + CDK 4/6 inhibitors. (3) To identify dietary factors associated with clinical outcomes on AI + CDK 4/6 inhibitor treatment. ***Patients and Methods***: This is a prospective pilot study with the aim of collecting blood and fecal samples for biomarker analysis. Patients with advanced ER+/HER2- breast cancer initiating on standard of care first line palliative systemic therapy with an AI in combination with a CDK 4/6 inhibitor will be screened for eligibility. Patients with relapse on prior endocrine therapy or within 6 months of discontinuation of prior adjuvant endocrine therapy as well as patients with a history of inflammatory bowel disease, chronic diarrhea, malabsorption syndromes and prior bowel resection will be excluded. Taxonomic composition of fecal samples will be assessed by 16S rRNA gene microbiota sequencing. A subset of samples will undergo shotgun metagenomic sequencing. Targeted qPCR will be used to quantitate total bacterial density (by 16S rRNA gene qPCR), as well as genus/ species identified from published studies. Molecular alterations in cell free DNA extracted from peripheral blood samples will be analyzed using the Oncomine (ThermoFisher) Breast cfDNA assay. Droplet digital PCR assays will be designed to investigate common hotspot mutations in additional genes of interest. Dietary information will be assessed through standardized food frequency questionnaire administered at the start of treatment. Study outcomes will be mainly exploratory and hypothesis-generating. The sample size of 20 patients was determined in order to formulate an acceptable confidence interval (>95%) and to account for drop-outs and patients with insufficient number or quality of samples. The primary outcome is to compare genomic and gut bacterial profiles in patients with short (<6 months) versus long (≥24 months) time-to-treatment failure (TTF), defined as the time from first treatment on study until the date of treatment discontinuation for whatever reason (including toxicity). Secondary outcomes include overall survival, toxicity and frequency of genomic and bacterial alterations. ***Expected Results and Conclusions***: We have enrolled two patients after an accrual period of 4 months. Detailed analysis of the genomic profiles in cell free DNA and gut bacterial diversity will provide a comprehensive portrait of the molecular and gut bacterial profiles associated with short versus long term responders to endocrine therapy and might shed light on new therapeutic targets.

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**Publication Number:** PS17-25

# Repurposing anti-depressant imipramine for treating breast cancers

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About 1 in 8 women will develop invasive breast cancer during their life time and more than 41,000 women die every year in the United States alone. Most of these deaths are attributed to relapse, distant metastasis and therapy resistance. For example, despite initial response to therapy, a significant proportion of $ER^+$ BCs become therapy resistant and progress to incurable metastases. Similarly, TNBCs, which is highly aggressive and are more likely to occur in Hispanic and black women, have higher propensity to relapse and contribute to disproportionate number of deaths. Unfortunately, the patients who do survive, have reduced quality of life due to the chemotherapy-associated toxicity. One mechanism that helps BCs to survive and become therapy-resistant is their unique ability to keep repairing their DNA. The aim of this study was to identify and test whether any FDA-approved non-cancer drug/s can block DNA repair ability and consequently growth of BC cells. Treatment of BC cells with a set of FDA approved drugs showed that antidepressants imipramine can inhibit the BC cell growth. Imipramine treatment significantly reduced the short and long-term viability of TNBC and ER+ breast cancer cells. Further, imipramine treatment inhibited the migration and invasion of breast cancer cells. Systemic delivery of imipramine suppressed the breast cancer cells growth in orthotopic mouse xenograft model. Our results revealed that imipramine treatment induced G1/S cell cycle arrest and apoptosis in breast cancer cells. Importantly, imipramine blocked the DNA repair capacity of BC cells by inhibiting the expression of DNA repair proteins including FOXM1 and RAAD51. Notably, imipramine treatment improved the efficacy of the PARP inhibitor “olapraib” in TNBC and sensitized the tamoxifen response in tamoxifen resistant ER+ breast cancer cells. Our results suggest that imipramine can be used as a single or therapeutic adjuvant for treating therapy sensitive and therapy resistant breast cancers. Based on these results, we are currently conducting a clinical trial to test the therapeutic efficacy of imipramine for treating breast cancer patients (https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCI-2017 01937&r=1).

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**Publication Number:** PS6-25

Cts5 tested in a Brazilian population: A tool that can predict global survival in early breast cancer ER+/HER2-, as well as the response to extended endocrine therapy

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**Background:** Breast cancer (BC) accounts for 30% of female cancer, is the most commonly diagnosed cancer worldwide and the second most common cause of cancer-related deaths among females. The majority (79%) of breast cancers express the estrogen receptor (ER+) and 91% of them are diagnosed at an early stage. But it is also known that late recurrence (5 years or more after diagnosis) represents about 50% of all recurrences of ER+ BC. Identify those patients who are at greatest risk for late recurrence and develop strategies to prevent it has emerged as a major unmet need in ER+ BC. In an attempt to reduce late recurrences, several studies have recently proposed that endocrine therapy (ET) prolonged beyond five years would achieve this goal. Conversely, extended ET increases the rates of side-effects, compared to conventional ET. Therefore, selecting patients who would really benefit from extended ET is crucial, as this would spare low-risk patients from potentially greater side effects and impacts in quality of life, restricting the treatment only for those who really could take advantage of this approach. That is why, currently, the subject late recurrence is being studied so much. CTS 5 (Clinical Treatment Score after 5 years) is a simple clinical-pathological tool developed to estimate the residual risk of distant recurrence after 5 years of ET.
**Objective:** To assess the prognostic and predictive impact of CTS5 in overall survival (OS) of ER+BC patients treated with conventional or extended ET in a Brazilian Cancer Center.
**Study design and statistical analysis**: A retrospective cohort study was conducted, selecting, through administrative databases of AC Camargo Cancer Center, 1085 ER+ BC patients with at least 5 years of adjuvant ET. Patients who missed follow-up before completing ET were excluded, but we kept those who presented any event related to illness or treatment. Statistical analysis includes a Kaplan-Meier analysis and the Log Rank test. Prognostic factors were assessed using univariate and multivariate Cox analysis.
**Results:** The demographic and clinical characteristics of patients are described in table 1. In this cohort, continuous CTS5 was a significant predictor for OS (HR = 4,49 [3.12-6.46], p<0.001). In addition, in the high CTS5 group a significant benefit was observed with prolongation of adjuvant ET beyond 5 years (HR = 4,91 [3.41-7.06], p<0.001), not observed for low and intermediate risks.
**Conclusion:** In this cohort, composed of real-life Brazilian women with ER+/ HER2- BC, irrespective of menopausal status, CTS5 proved to be an excellent predictor of OS. In addition, it was shown to be a predictor of response to extended ET. CTS5 score can identify a group of high-risk patients who benefits from extended ET.
We consider that it would be of great value to expand the study population and follow-up, especially to analyze whether this tool also has a predictive value in contraindicating extended ET in low- risk and intermediate-risk patients.

Table 1. Demographic and Clinical Characteristics

| Characteristic | No. (%) |
|---|---|
| **Age, years**<br>Median<br>IQR<br>< 50 years<br>>50 years | 53<br>26-91<br>446 (41.1)<br>639 (58.9) |
| **Tumor size, mm**<br>≤ 10<br>10-20<br>20-50<br>>50 | 285 (24.1)<br>458 (38.7)<br>378 (31.9)<br>60 (5.1) |
| **Grade**<br>Well<br>Intermediate<br>Poor | 142 (11,9)<br>385 (32,5)<br>654 (55,2) |
| **Nodal status (No. of positive nodes)**<br>0<br>1 -3<br>≥ 4 | 756 (64.0)<br>305 (25.8)<br>120 (10.2) |
| **Chemotherapy**<br>Adjuvant<br>Neoadjuvant | 592 (50.1)<br>118 (10.0) |
| **Endocrine Terapy**<br>ET 5 years<br>ET extendend<br>ET for less than 5 years. | 1060 (89,7)<br>100 (8.4)<br>21 (1,8) |
| **CTS5**<br>Low<br>Intermediate<br>High | 587 (49.6)<br>344 (29.1)<br>250 (21.1) |
| **Recurrence**<br>Distant<br>Local | 147 (12,4)<br>39 (3,3) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS7-25

Geicam/2014-03 (RegisTEM): A prospective registry of unresectable locally advanced or metastatic breast cancer: Characteristics of a subset of patients with triple negative subtype

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**Background:** There is limited prospective data for advanced breast cancer (ABC) patients (pts), both unresectable locally (ULABC) or metastatic (MBC) treated as per clinical practice. RegistEM study will provide epidemiological, pathological and clinical data, including treatments for different disease settings. Understanding the real distribution of BC subtypes is the primary objective. This is a non-interventional cohort study that will enroll around 1,867 pts (males or females) with ABC diagnosed from January 2016 to December 2019, either after recurrence or as first diagnosis, in 38 Spanish sites. Triple negative (TN) subtype histologically confirmed in the primary tumor (PT) and/or in a metastatic tumor lesion (M1) and recurrent disease from early stage, has been identified as an interesting group from a clinical perspective for detailed analysis. **Methods**: In this analysis, we describe the characteristics of 131 pts with TN subtype by local evaluation at any disease stage [in PT only (PT group), in M1 only (M1 group) and in both PT and M1 (group PT/M1)] until progressive disease (PD) at first-line and data of therapeutic options at second-line. **Results:** Distribution of 131 pts within the groups; PT, M1 and PT/M1, was 45.8%, 27.5% and 26.7%, respectively. To date, 32.1% pts have shown a change of subtype along their BC evolution, >50% of those changes was between TN and Luminal B HER2-. Median time from early BC (EBC) diagnosis until recurrent disease in terms of MBC or ULABC was 33.4 months (mo) (PT and PT/M1-26.0 mo; M1-60.2 mo), with the majority of pts recurring >12 mo (91.6%). Median age at diagnosis of ABC was 58 years (range 31-84), most pts were Caucasian (96.9%), female (99.2%) and postmenopausal (65.6%). Family history of BC and/or ovarian cancer was reported in 41.2% pts, a hereditary-risk genetic test was performed in 21.4% pts (8 pts with BRCA1/2 mutation). Lung (40.5%), lymph nodes (35.9%), bone (35.9%) and liver (20.6%) were the most frequent metastatic locations; central nervous system metastases were developed by 12.2% pts. The rate of visceral involment (60-70% pts) was similar among the 3 subgroups. The most frequent first-line therapies were chemotherapy (CT) (51.1%) and CT/biological therapy (BT) (32.8%). Most pts (68.7%) received CT in monotherapy (capecitabine 50%, taxanes 26.1%). Bevacizumab was the most frequent BT within the CT/BT combination (76.7%). Median duration of first line therapy was 4 mo (range 0.2-20.0). Progression to the first-line CT +/- bevacizumab was reported in 51.1% pts with a median time to progression (TTP) of 4.7 mo (range 0.8-19.0) in the whole group, being similar in pts with TN in and PT and PT/M1 (4.4 mo), and higher in pts with TN in M1 (7.1 mo), no statistically significant difference (*p=0.38*). A second-line therapy was reported in 57.3% pts and the most frequent therapies were CT (78.7%) (eribulin 33.9%, capecitabine 22.0%, platinum-based 22.0%) and CT/BT (12.0%) (CT-containing bevacizumab 77.8%). Median duration of second-line therapy was 3 mo (range 0.03-15.8) and PD has been reported in 80.0% pts. Third-line therapy was reported in 35.9% pts of this subset. **Conclusion:** In this subset of pts with TN ABC due to recurrent disease, lung, lymph nodes and bone are the most frequent metastatic locations. The main first- and second-line therapies were CT in monotherapy. Progression to the first-line conventional therapy (CT +/- bevacizumab) was reported in 51.1% pts with a median TTP of 4.7 mo (range 0.8-19.0) in the whole group, being similar in pts with TN in PT and PT/M1 (4.4 mo), and higher in pts with TN in M1 (7.1 mo), no statistically significant difference. 36% of the initial subset of pts reported to be treated in the third-line setting. Pts with TN only in M1 seem to have a longer time to progression from EBC.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS19-25

# Metastatic TNBC is highly associated with a fused mitochondrial morphology and a glycolytic and lipogenic metabolism programmation

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**Background:** Triple negative breast cancer (TNBC) is characterized by heterogeneous metastatic and metabolic properties, which difficult the diagnosis and development of specific treatment. Therefore, the understanding of the mitochondria´s role in the different grades of TNBC could be relevant for the design of novel specific TNBC treatments. This research aimed to explore the mitochondria morphology and gene expression of proteins related to oxidative and non-oxidative metabolism in metastatic and non-metastatic TNBC cell lines. **Methods**: We performed a gene expression analysis of mitochondrial biogenesis, EMT and principal metabolism-related genes (Integrated DNA Technologies, CA, USA) in three breast cancer cell lines HCC-1395, MDA-MB-231 and MCF-12A. After the gene expression qPCR data mining, in sílico analisis were performed using confocal microscopy (Leica Microsystems,WZL, DE) in the cell lines where mitochondrial distribution, morphology, function and ROS production were measured. **Results:** The metastatic TNBC-cell line showed a preference for fatty acid biosynthesis and glycolytic metabolism since overexpression of genes related to both pathways was observed. These metabolism features were accompanied by a fused mitochondrial morphology and lower mitochondrial activity since was observed less mitochondrial density accompanied by the downregulated expression of biogenesis-related genes such as PGC1α. In contrast, the non-metastatic TNBC-cell line presented a hyperfragmented mitochondria, a stress associated mitochondrial morphology accompanied by upregulated expression of mitochondrial biogenesis-related genes, both characteristics related to the higher ROS production observed in this cell line. **Conclusions:** Metastatic TNBC was characterized by a mitochondrial function and morphology similar to control ranges with a metabolic gene program directed to glycolysis and FA usage. While mitochondria of the non-metastatic TNBC cell line was characterized by a higher density and potential, related to an increase of mitochondrial biogenesis, which in turn was associated with higher levels of ROS and with the consequence of a hyperfragmented mitochondrial morphology. These characteristics can provide a better understanding of the metastasis observed in TNBC and contribute to the development of a specific and personalized TNBC therapy. **Key words:** Triple Negative Breast Cancer, Mitochondria, Cell-metabolism.

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**Publication Number:** PS16-25

# Comparison of the genetic mutations in sporadic and BRCA1 carrier breast cancer through targeted next generation sequencing

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**Introduction**Women who carry a germline mutation in BRCA1 (breast cancer type 1 susceptibility protein) have an increased risk of developing breast cancer in their lifetimes. Carriers tend to develop breast cancer at a younger age and their tumors are generally aggressive. Although BRCA1 breast cancers have been researched, many questions remain. The purpose of this study was to analyze the mutational landscape of tumors from BRCA1 carriers and compare them to tumors of sporadic breast cancer. **Methods**Pathology reports were reviewed to identify cases of breast cancer (BC) and the ER/PR/HER2 status was noted as well as the Ki67 proliferation index and patient age. Next generation sequencing (NGS) was performed on 72 BC tumors; 26 from BRCA1 carriers and 46 sporadic BC tumors. Two targeted panels were used for sequencing, the Oncomine Comprehensive Assay by Thermo Fisher Scientific on an Ion Torrent S5 XL sequencer and the AmpliSeq for Illumina Cancer HotSpot Panel. Mutations in a total of 44 cancer associated genes common to both panels were analyzed including TP53, RB1, PTEN, NRAS, ERBB2, PIK3CA, and BRAF. Missense and nonsense single nucleotide variants with a variant allele frequency >3% and coverage >150 reads were considered as well as insertions/deletions. Pathogenicity was determined using ClinVar and Varsome. Mutations were classified as benign, likely benign, variants of uncertain significance, likely pathogenic, and pathogenic.**Results**Pathogenic/likely pathogenic variants were identified in 15 genes. TP53 was the most commonly mutated gene with pathogenic/likely pathogenic variants in 13 (50%) BRCA1 carriers' tumors and 18 (39%) sporadic tumors. Having a TP53 mutation did not increase the likelihood of having other pathogenic mutations in either BRCA1 carriers or sporadic tumors; 74% of all tumors with p53 mutations had no additional pathogenic mutations overall. PIK3CA pathogenic/likely pathogenic mutations were significantly more common in sporadic tumors (26%) than BRCA1 carrier tumors (8%). PIK3CA mutation did not increase the likelihood of other gene mutations and did not correlate with TP53 mutations. BRCA1 pathogenic mutations were identified in four cases with no germline testing and likely represent somatic mutations. No pathogenic mutations were found in 12 (46%) of the BRCA1 carriers' tumors and 10 (22%) sporadic tumors. There were four BRCA1 carriers with bilateral BCs; two pairs had the same mutations, one pair had different TP53 pathogenic mutations and another pair had different PIK3CA pathogenic mutations. A total of twenty-four cases were triple negative, 13 sporadic and 11 BRCA1 carriers (see table below). As expected, BRCA1 carriers were diagnosed with BC at a younger age with 21 (81%) cases diagnosed at age < 60 years while 22 (48%) of sporadic cases were in this age group.
**Conclusion**
TP53 is the most commonly mutated gene in BCs, even though more common in BRCA1 carriers' tumors; however, they are not required for tumor development as seen in the 57% of cases in our study with normal TP53 (50% of BRCA1 carriers). No specific additional pathogenic mutation was commonly seen in BRCA1 tumors with TP53 mutations. PIK3CA was frequently mutated in sporadic cases and not in BRCA1 carriers. BRCA1 tumors were less likely to have other pathogenic mutations than sporadic tumors in this study of 44 genes. Additional studies will help further elucidate the molecular basis of BRCA1 tumor carcinogenesis.

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**Publication Number:** PS12-25

Patterns of treatment and outcomes in real world patients with advanced estrogen receptor positive breast cancer receiving palbociclib and endocrine therapy

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**Background:** Advancement in the treatment of metastatic estrogen receptor positive (ER+) breast cancer has led to the introduction of CDK4/6 inhibitors such as Palbociclib, which are associated with reversal of endocrine resistance and delayed requirement for chemotherapy. Clinical trials to date have demonstrated improved survival outcomes for patients on these agents. The objective of this study was to evaluate their role in a real-world setting.
**Methods:** We performed a retrospective multicentre analysis of patients (pts) with metastatic ER+ breast cancer who were commenced on Palbociclib (PAL) between January 2010 and September 2019. Data extracted included demographics, disease characteristics, treatments, toxicities, response rates and survival outcomes. Statistical analysis was performed using Cox proportional hazard model for univariate analysis and Kaplan Meier curves for survival data.
**Results:** We identified 271 pts. The median age was 60 years (31-88) and 18% (n=48) pts were premenopausal. PAL was combined with the following ET partners: Aromatase inhibitor (AI) (38%, n=103), Fulvestrant (FUL) (38%; n=103), Tamoxifen (4%, n=10), FUL & AI combination (16%, n=44) and other (4%, n=11). Among 71 pts treated in the 1$^{st}$ line, overall response rate (ORR) was 56% (n=40). The median PFS (progression free survival) was 35 months (95% confidence interval [CI], 17.2-52.7) in all pts and 25 months (mo) in those not treated with FUL. In 1$^{st}$ line pts with de novo disease (37%, n=26), there appeared to be a trend towards improved PFS in the FUL vs non FUL group - not reached vs 25 mo (HR 0.21; 95% CI 0.02-1.79, p=0.15). There was no significant difference in PFS between the FUL vs non FUL group in relapsed pts (63%, n=45) treated in the 1$^{st}$ line - 22 vs 20 mo (HR 1.0, 95%CI 0.35-2.9; p=0.96). The median OS was 59 mo (95% CI, 9.5 to 108). Of 74 pts treated in the 2$^{nd}$ line, ORR was 24% (n=18), median PFS was 10 mo (95% CI, 5.8-14.1) & OS was 25 mo (95% CI, 18.3-31.6). Among 126 3$^{rd}$ line pts, ORR was 16% (n=20), median PFS was 5 mo (95% CI, 3.5-6.4) and OS was 20 mo (95% CI, 12.8-27.1). 3 of 9 pts achieved >6 mo of stable disease after switching ET and continuing Palbociclib beyond progression. The most frequent grade 3 toxicities were neutropenia (40%), anaemia (4%), fatigue (3%) & thrombocytopenia (2.5%). The rate of febrile neutropenia was 2.5%. Dose reductions occurred in 40%, with the most common reason being neutropenia. Treatment was discontinued in 3% due to toxicity. Premenopausal status or dose reductions were not associated with poorer survival outcomes.
**Conclusions:** Palbociclib appears to be safe and tolerable in a real-world population and is associated with favourable survival outcomes comparable to that seen in a clinical trial setting. Combining Palbociclib with Fulvestrant as opposed to other endocrine therapies may delay progression in the 1$^{st}$ line setting in patients with de novo metastatic ER+ breast cancer but larger studies are needed to explore this hypothesis further.

**Publication Number:** PS1-26

Sentinel lymph node biopsy alone in locally advanced breast cancer after neoadjuvant chemotherapy: Turkish multicentric neosenti-turk MF-18-02-study

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**BACKGROUND:** Omitting axillary lymph node dissection (ALND) following sentinel lymph node biopsy (SLNB) in patients with locally advanced breast cancer (LABC) after neoadjuvant chemotherapy (NAC) is still controversial. In this study, we evaluated factors affecting local recurrence and outcome in patients with LABC, who underwent SLNB alone after NAC. **METHODS:** Between 2004 to 2018, 320 patients with clinically node-positive LABC who received NAC and underwent SLNB alone after negative axillary staging were analyzed. All patients had breast and/or regional nodal irradiation. **RESULTS:** Median age was 46 (23-70). Of those, 228 patients had ypN0 disease (71.25%), whereas 92 patients had ypN(+) disease including 19 (20.6%) isolated tumor cells (ITC), 33 micrometastasis (35.9%) and 40 macrometastases (43.5%). At a median follow-up of 37 months (24-172), one patient (0.3%) with macrometastatic SLN having extracapsular extension was found to have locoregional recurrence at the 60th month. Five-year disease-free survival (DFS) and disease specific survival (DSS) rates were found as 87% and 95%, respectively. Patients with cT3&4 (HR=2.22, 95% CI; 1.07-4.62), non-luminal molecular pathology (HR=2.71, 95% CI, 1.23-5.97), and non-pCR in the breast (HR=2.21, 95% CI, 0.94-5.17) were found to have an increased HR compared to others in 5-year DFS. However, no significant differences could be found between patients ypN0, ypN-ITC&micrometastasis and ypN-macrometastasis regarding 5-year DFS and DSS rates. **CONCLUSIONS:** ALND could be safely avoided in selected patients with LABC who underwent SLNB after NAC having cT1-2, luminal pathology, breast and/or nodal pCR or low volume nodal disease, as long as axillary radiotherapy is provided.

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# Tolerability and efficacy of palbociclib in combination with an aromatase inhibitor (AI) in older women (≥75 years) with ER +ve, HER2-ve metastatic breast cancer. A large 'real world' UK multi-centre study

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IntroductionThe management of metastatic oestrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative advanced breast cancer has evolved with the introduction of CDK4/6 inhibitors improving disease outcomes when added to an AI in the first line setting. The FDA evaluated toxicity of all CDK4/6 inhibitors in women ≥75 years (n=198), and found increased toxicity and dose modifications [1], however, toxicity profiles differ between the CDK4/6 inhibitors. Palbociclib has been shown to be well tolerated in patients ≥75 years (n=83) [2] and ≥ 70 years (n=92) [3], however, more real-world data is essential to inform prescribing practices in larger datasets.MethodsWe undertook a national multi-centre retrospective study with 15 cancer centres participating. All patients aged ≥75 years with ER+/HER2- advanced breast cancer who had received at least 1 cycle of Palbociclib + AI as part of a patient access scheme or NICE approved by 1st December 2019 were included. Data collected included baseline characteristics, comorbidities, disease characteristics, toxicities with palbociclib, dose modifications, dose delays, discontinuation and response to treatment.ResultsData from 123 patients aged ≥75 years are included in this analysis from 3 UK cancer centres. Median age was 79 years (range 75 - 90). 98% had an ECOG performance status of 0-2. Co-morbidities were scored using Charlston comorbidity index (CCI - higher score signifies more co-morbidities). 102 patients had a CCI of ≤10 and 18 had a CCI >10. The starting dose of palbociclib was 125mg in 115 patients, but 8 (6.5%) patients started at a lower dose, a third of whom had a CCI of >10. The average number of concurrent medications was 4 (range 0-12). Visceral metastases were present in 52% of patients, and 33 patients (26.8%) had bone only metastases. The median number of cycles received was 10 (range 1 -36). 60 (48.8%) patients required one dose reduction, 18 patients required a 2nd dose reduction and 2 patients required a 3rd dose reduction. The most common cause for dose reductions was neutropenia G3-4 (n=31) and fatigue G1-3 (n=12). 75 patients (61%) required a dose delay and 9% of patients discontinued treatment due to toxicity. The rate of all grade neutropenia was 88.6% with only 1 patient (0.8%) developing febrile neutropenia. Other all grade common toxicities were fatigue (62.6%), anaemia (61.8%) and thrombocytopaenia (57.7%). 12 (9.7%) patients required hospital admission due to side effects of treatment. At the time of data analysis, 111 patients had had a radiological response assessment and the best response was stable disease in 57.7%, partial response in 32.4% and complete response in 0.9% (1 patient) with a clinical benefit rate (CR+PR+SD ≥24 weeks) of 83.8%. 10 patients (9%) had disease progression. The median progression free survival is immature, but at the time of this analysis was 13 months (range 1-36 months).ConclusionOur real world data contributes to the existing smaller published datasets in the over 75s to reassure clinicians that palbociclib is an effective and manageable treatment choice in older women. Compared to published data in older patients [2, 3], febrile neutropenia rates from palbociclib were lower. Despite a higher dose reduction and delay rate than published data [3], the clinical benefit rate was not adversely affected and the early PFS signal is reassuring.

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# Outcomes of metastatic male breast cancer

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**Background:** Breast cancer is rare in men. The prognosis of male breast cancer (MBC) is poor than female breast cancer. The study aims to evaluate the clinical features and prognosis in metastatic male breast cancer (mMBC).
**Method:** The data of 28 patients were retrospectively reviewed. The clinical and histopathological features of the patients were recorded. Overall survival (OS) and prognostic factors evaluated with Kaplan-Meier analysis and Cox-regression analysis.
**Results:** The median follow-up period was 55.1 months (range, 6.6-205.6). The median age at diagnosis was 57 years (range, 26-86). Seven (27%) of the patients were de-novo metastatic. Invasive ductal carcinoma (92.6%) was the most common pathological subtype. The ratio of HER2 positivity in patients was 21.6%, and estrogen and progesterone receptor's positivity were 96.4% and 71.4%, respectively. The most common metastatic locations of disease were bone-75%, lung-39.3%, brain-21.4%, and surrenal-10.7%. Six of the patients received trastuzumab-based chemotherapy. A total of 14 (50%) patients deceased during the study period. The median OS was 42.6±10.7 months (range, 21.6-63.7) for all patients. One-, three- and five-years overall survival ratios were 95.7%, 54.2%, and 36.6%, respectively. In univariate analysis, Brain metastasis (p=0.033), the number of metastatic sites (p=0.045), and the history of regular alcohol consumption (p=0.008) were a statistically significant factor on OS. However, the results were not confirmed in multivariate analysis. Also, we found that trastuzumab-based treatment and de-novo metastasis were not affecting on OS in mMBC.
**Conclusions:** Due to the rarity, the data of mMBC is limited. In this study, we observed that the prognosis of mMBC was poor. Despite the low number of patients, we detected that having brain metastasis, the number of metastatic sites, and history of alcohol consumption may be a prognostic factor in univariate analysis.

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# Pd-l1 mRNA expression in plasma-derived exosomes predicts prognosis and response to anti-pd-l1 antibodies in unresectable locally advanced triple negative breast cancer (TNBC) treated with atezolizumab-paclitaxel

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**Background**
Despite modern therapies have improved outcomes of patients with non-TNBC cancers, patients diagnosed with unresectable locally advanced TNBC usually have poor outcome for its aggressive clinical behaviour. Over time for cancer management, predicting and monitoring response to treatments is crucial, better if through easy non-invasive procedures. Atezolizumab plus nanoparticle albumin-bound (nab)-Paclitaxel prolonged progression-free survival (PFS) and overall survival (OS) among patients with TNBC, as demonstrated by phase III IMpassion130 trial. Despite this, there is a dire need for biomarkers reflecting treatment response. In our study, we correlated plasma PD-L1 mRNA levels with prognosis and response to anti -PD-L1 antibodies in unresectable locally advanced TNBC in the era of Atezolizumab.

**Methods**
We assessed 30 consecutive patients with unresectable locally advanced TNBC treated with Atezolizumab plus nab-Paclitaxel. Blood samples were collected at time point 0 (at baseline) and after 2 months and we assessed the association between PD-L1 mRNA copies per ml in plasma-derived exosomes and response to treatment. Exosomal PD-L1 mRNA in plasma was determined using Bio-Rad QX100 digital droplet PCR system and exoRNeasy kit. Objective responses were defined following the RECIST criteria v.1.1

**Results**
At baseline, patients with complete and partial response (CR+PR, n=11) displayed a significantly higher number of PD-L1 mRNA copies per ml compared to ones with stable or progressive disease (SD+PD, n=19) (mean value: 745.6±131.1 vs 124.7±34.4, $p<0.001$). In patients with CR and PR mean PD-L1 copies/ml were 745.6±131.1 and 175.4 at baseline vs 2 months, respectively ($p=0.001$).In patients with stable disease the mean ± s.e.m. values were 270±71.1 vs 217.5±17.3 copies per ml ($p=0.614$) while in progressive disease PD-L1 mRNA levels were 112.1±31.2 vs 454.3±46.2 copies per ml at baseline vs 2 months, respectively ($p<0.001$).Two months after the start of Atezolizumab plus nab-Paclitaxel decrease of PD-L1 mRNA copies per ml relative to pre-treatment PD-L1 mRNA copies per ml, was positively correlated with an objective response to treatment.Increase of PD-L1 mRNA copies per ml was significantly associated with worse and shorter OS: median OS in patients with increase of PD-L1 mRNA copies/ml was 5 months (range 2-7 months, 95%CI 1.1-6.1); on the other side median OS in patients with decrease of PD-L1 mRNA copies/ml was more than double (range 8-15 months) ($p<0.001$).Moreover, prolonged survival outcomes ($p<0.001$) were recorded in cases with low baseline circulating $Lox1^+$ Myeloid-derived suppressor cells (MDSC) (r=0.62, $p<0.001$) and high Natural Killer cells (NK) (r=0.66, $p<0.001$): the NK-to-MDSC ratio (NMr) was significantly higher in patients with higher number of PD-L1 mRNA copies per ml at baseline ($p=0.002$). During PD-L1 blockade, 2 months after starting treatment, NK progressively raised in clinical benefit group while declined in non-responders ($p=0.001$)

**Conclusions**
Despite the study's limitations, our data suggest exosomal PD-L1 is significantly associated with outcome and response to treatment.

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Comparison of clinicopathological features in BRCA-wild type and -mutated male breast cancer patients

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**Background:** BRCA mutations result in a variety of cancer types such as breast, ovarian, and prostate. 4-40% of the patients with male breast cancer have BRCA mutations, and BRCA 2 mutation is more commonly detected. In this study, we compared the clinicopathological characteristics of BRCA-wild type and -mutated male breast cancer (MBC).
**Methods:** The data of 43 patients were retrospectively reviewed. Clinical and histopathological data of the patients were recorded. The characteristics of the patients were compared by the chi-square test and Fisher exact test. Survival analysis evaluated with Kaplan-Meier analysis.
**Results:** The median follow-up period was 35.8 months (range, 2.2-225.8). The median age at diagnosis was 58 years (range, 25-81) and not statistically different between groups (p=0.753). 11 (25.6%) of the patients had BRCA mutations. Four (9.3%) patients had BRCA1 mutations, six (14%) patients BRCA2 mutations, and one (2.3%) patients had both BRCA 1 and 2 mutations. Among BRCA- wild type and - mutated patients: estrogen receptor positivity (p=0.055), progesterone receptor positivity (p=0.698), HER2 overexpression (p=0.542), tumor localization (p=0.305), tumor histology (p=0.069), lymph node involvement (p=0.589), tumor stage (p=0.892), and recurrence status (p=0.698) were comparable. The median overall survival was 115.6 months (range, 76.0-155.3), and similar between groups (p=0.647).
**Conclusions:** MBC is rare. In literature, the data of MBC and BRCA mutation is limited, and studies included a low number of patients**.** In a result, we found that clinicopathological characteristic and prognosis of BRCA-mutated and-wild type MBC was similar.

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Characterizing errors in perfusion model parameters derived from retrospectively abbreviated quantitative DCE-MRI data

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**Introduction.** X-ray mammography is the standard-of-care screening protocol for breast cancer due to its low cost, widespread availability, and greater specificity. While magnetic resonance imaging (MRI) has lower specificity, it has superior tissue contrast, and dynamic contrast-enhanced (DCE) MRI has been shown to increase MRI specificity due to its ability to estimate tissue vascular properties. Because of the increased expense and scan time for MRI, there is an ongoing effort to develop abbreviated breast MRI scans for screening high-risk patients at a lower cost without compromising quantitative information. Here we investigate the effects of the limited dynamic time course afforded by an abbreviated breast MRI exam on the quantitative tissue information computed from retrospectively abbreviated DCE-MRI data. **Methods.** *Data acquisition*. We evaluate the error in perfusion model parameters computed using DCE-MRI time courses sourced from three datasets acquired with very different temporal resolutions (*dt*). These datasets are the ACRIN 6883 multi-site breast trial (*dt* = 15 s), The University of Texas at Austin (UTA) neoadjuvant therapy study (*dt* = 7.3 s), and The University of Chicago (UC) ultra-fast breast DCE-MRI study (*dt* = 3.4 s). Ten representative patients are chosen from each of these datasets for a total of 30 DCE-MRI patient datasets. All 30 full-time courses (FTCs) are retrospectively truncated into a series of abbreviated-time courses (ATCs). An ATC containing the first *n* post-contrast injection time points of a DCE-MRI time course is referred to as "ATC *n*." For the ACRIN dataset, *n* is the inclusive set of integers from 7 to 18; and, similarly, for the UC data, *n* is the inclusive set of integers from 12 to 23. For the UTA dataset, *n* is the inclusive set ranging from 13 through 53, incrementing by eight. *Data Analysis.* The groups of FTCs and ATCs are analyzed by one of three models, determined by the specifics of the acquisition details of each dataset. The standard Kety-Tofts (SKT) model is fit to the UTA time courses, the reference-region (RR) model is fit to the ACRIN time courses, and the Patlak model is fit to the UC time courses. The volume transfer constant ($K^{trans}$) characterizes tissue enhancement in all three models; whereas, the extravascular/extracellular volume fraction ($v_e$) is specific to the SKT and RR models, and the plasma volume fraction ($v_p$) is specific to the Patlak model. Due to the absence of an arterial input function (AIF) for the ACRIN dataset, the RR model was most appropriate with the pectoral muscle serving as the reference region. The UTA dataset has a population AIF and is thus able to be modeled by the SKT. Lastly, the UC dataset does not capture the tissue washout necessary for $v_e$ estimation, so the Patlak model was chosen for analyzing tissue enhancement. **Results and Conclusion.** The longest ATCs of 4.5, 6.4, and 1.3 min. yielded average errors of 9.1%, 7%, and 3.6% in $K^{trans}$ for the ACRIN, UTA, and UC datasets, respectively; and the shortest ATCs of 2, 1.6, and 0.6 min. yielded higher average errors of 24.2%, 22.8%, and 65% in $K^{trans}$, respectively. This is expected from simulations as even the most aggressive ATCs did not substantially exclude the tissue enhancement, characterized by $K^{trans}$. Errors in $v_e$ were higher overall since shorter ATCs exclude much of the washout phase. As $K^{trans}$ has been shown to discriminate between malignant and benign lesions in full length DCE-MRI scans, it is promising that tolerable errors are observed in the abbreviated MRI setting. There is potential for implementing quantitative abbreviated DCE-MRI scans in the clinic for enhanced diagnostic specificity while freeing up scan time for additional imaging sequences without interfering with standard-of-care image acquisition.

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# Recurindex® predicts local regional recurrence for n1 breast cancer after mastectomy

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**Background**: Post-mastectomy radiation therapy (PMRT) is part of standard regimen in the management of breast cancer. It has been shown to decrease the incidence of local regional recurrence (LRR) and improve breast cancer survival. Yet, its role in patients with 1-3 positive lymph nodes (N1) remains unclear. The lack of biological markers to evaluate the efficacy of PMRT for N1 patients leads to excessive treatment of low-risk patients and ignore of those at high risk. A clinical-genomic model RecurIndex® (RI-LR), based on a genomic database from mRNA expression as well as clinical factors (lymph node involvement, ER status,age at diagnosis, and lymphovascular invasion), is mainly developed for predicting the LRR in early stage breast cancer patients.
**Method**: The preliminary result enrolled 107 breast cancer patients with N1 involvement in a retrospective study atthe fourth hospital of Hebei Medical University. Kaplan Meier method is used to calculate the survival rates in terms of LRR-free interval (LRFI). The log rank test and cox regression model are applied for the survival difference between two independent groups, and for investigating prognostic factors related to high-risk patients. The primary endpoint is LRFI.
**Results**: With a median follow-up of 84 [IQR 64-84] months, RI-LR partitioned these N1 patients into 70% high-risk group and 30% low-risk group. LRR rate was 14.7% in the high-risk group whereas only 3.1% in the low-risk group. The survival curve clearly showed a partitioned trend of two groups (5-year LRFI 87.5%vs 100%, p = 0.085). Patients identified in the RI-LR high-risk group showed significantly higher LRFI if they had PMRT compared to those without PMRT (5-year LRFI 94% vs 70%, p =0.043), suggesting that higher radiosensitive patients could be identified by RI-LR. Multivariate analysis revealed that high-risk patients treated with PMRT has a 71 % reduction of LRR compared to those without PMRT (HR 0.29, 95%CI: 0.08-1.00, p = 0.051).
**Conclusions**:The present study provided robust evidence that RI-LR could partition N1 breast cancer patients into good and poor prognosis of LRR. RI-LR is capable of identifying high-risk patients who would benefit from PMRT. This observation warrants to validate in a larger cohort.
**Key words**: Early breast cancer, genomic assay, recurrence index (RI), local-regional recurrence (LRR), post mastectomy radiotherapy (PMRT)

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# Effect of an outpatient pharmacy team to improve management and adherence to oral chemotherapy

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***Introduction*** Oral chemotherapy agents have become increasingly common for the treatment of various malignancies, specifically in the metastatic setting. In metastatic breast cancer, oral chemotherapy is now considered the standard of care for first-line treatment due to progression-free survival and overall survival benefits. Oral agents are also considered to be a convenient and less toxic therapy option, improving quality of life. However, these benefits are offset by challenges in the delay to initiation of therapy, adherence, and toxicity management which may lead to high co-pays, delays in treatment, increased clinic visits, and non-adherence. These issues can be augmented at a safety net hospital charged to care for the most vulnerable patients. Close monitoring and follow-up are critical but can be complex and pose an additional burden on the treating oncologist. Pharmacists can serve as an extender to the oncologist and may help mitigate many of these clinical and operational barriers through adherence strategies, toxicity management, care coordination, and optimization of dosing schedules and regimens. ***Methods/Materials*** We conducted a quality improvement (QI) initiative aimed to decrease the average number of treatment day delays experienced by patients receiving oral chemotherapy for the treatment of MBC during the first six cycles of chemotherapy. A secondary aim was to improve adherence and patient-provider satisfaction. A protocol was designed and implemented utilizing pharmacists to provide assistance with obtaining the medications through a specialty pharmacy, oral chemotherapy counseling, toxicity assessments, and strategies to help optimize oral adherence (OPTIMAL protocol). Pharmacists conducted live in-person visits and telemedicine visits at weekly to monthly intervals to supplement the ongoing routine care of the oncology provider. All treatment and supportive care recommendations, in addition to any identified barriers, were communicated to the provider. ***Results*** A baseline assessment of 63 patients receiving oral oncolytic therapy from December 1$^{st}$, 2018 through November 26$^{th}$, 2019 was completed. Patients experienced most delays during cycle 1, with an average of 14.5 days of delay (range 1 - 34 days). The most common reasons for delay throughout the first six cycles of therapy were toxicity development, receipt of medication from the pharmacy, and patient adherence. A separate analysis of patients on CDK4/6 inhibitors (n=8) identified an average treatment day delay of 7.7 days (range 3.2 - 15.3 days) during the first six cycles of chemotherapy. Over a 7-month period, fifteen patients were enrolled in the OPTIMAL protocol and experienced an average treatment day delay of 2.9 days (range 0 - 6.8 days) during the first six cycles. Pharmacists made 206 documented interventions amongst the patients on the protocol, encompassing medication reconciliations, therapy counseling, and clinical recommendations. Eleven patients reported treatment-related toxicities, resulting in six therapy modifications and two-dose modifications. Four patients experienced progression on oral oncolytic therapy and subsequently went on to other treatment options. ***Conclusion*** Our protocol to incorporate pharmacists in initial and follow-up clinic visits at an outpatient breast cancer clinic within a safety net hospital was associated with decreased treatment day delays. Pharmacists performed a large number of meaningful clinical and operational interventions to facilitate medication treatment in a, particularly vulnerable population. This intervention supports the valuable and versatile role pharmacists can play in co-managing patients with the rest of the healthcare team.

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# A novel technology for uniform post-lumpectomy radio-frequency ablation for margin extension and local control tested in IRB-approved pilot mastectomy study

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**Background:** Radio-frequency ablation (RfA) of post-lumpectomy breast cavities has been shown to extend the surgical margin to reduce the need for re-operations and to provide local control without radiation therapy in many Breast Conservation Surgery (BCS) patients. However, all studies to-date have had to use adapted RfA needle electrodes designed for inoperable solid liver/kidney tumor ablation as no devices had been specifically developed for breast lumpectomy application. The SIRA™ device (Innoblative Designs Inc., Chicago, IL) is a first-in-class Saline-coupled Intra-cavitary RfA device specifically designed to fit the post-lumpectomy breast cavity and deliver uniform post-lumpectomy cavity ablation for margin extension and local control. We aimed to evaluate the SIRA device's ablation performance in human breasts of patients undergoing prophylactic mastectomy. The device settings and ablation dose (i.e., power and duration) were previously optimized within this same model to target a ~1cm ablation depth, where residual cancer cells are most likely to be located. The study was designed to evaluate the repeatability and uniformity of the optimized settings across multiple patients. **Methods:** This study was approved by the Northwestern University IRB. Immediately following the prophylactic mastectomy, simulated lumpectomies 3-4cm in diameter were removed from the breast specimen by a surgeon. The SIRA device was then inserted and secured in place within the cavity with suture by the surgeon. Once secured, the ablation procedure was performed using the optimized modelled ablation dose (80W for 22min). Following each procedure, 18 representative tissue blocks were taken around each ablation cavity, H&E slides were made, and the resulting ablation zones were analyzed histologically by a board-certified pathologist, including the percent fat per slide. **Results:** In the 10 procedures performed, a mean ablation depth across all margins of 8mm (SD = 1.3mm) was achieved. The standard deviation within each individual procedure ranges between 0.3mm and 2.8mm, indicating the ablation is relatively uniform around the cavity. 70% of the patients had calculated BIRADs scores of either Heterogeneously Dense or Extremely Dense. **Conclusions:** The results of this study confirmed the feasibility of the SIRA device to create consistent and effective creating uniform ablations to targeted depth of ~1cm around a lumpectomy cavity in fresh human breasts undergoing mastectomy. The prophylactic mastectomy model allows for analysis of the SIRA in freshly excised *ex vivo* tissue to provide nearly identical electrical conductivity, thermal conductive, and mechanical stress-strain properties as *in vivo* breast tissue. Future studies will provide more statistical clarity on the effect of breast density on ablation depth. Most patients in the study had Heterogeneously Dense or Extremely Dense breasts, which was expected due to the nature of the younger patients receiving prophylactic mastectomy; however, the performance here was consistent across densities and supplemented with a parallel study in older, fattier breasts in a cadaveric model. Ultimately, these data show proof-of-concept for the SIRA device to provide margin extension and local control, which may ultimately reduce the need for reoperations and for adjunctive radiation in select BCS patients.

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# A phase 1 study of D-0502, an orally bioavailable SERD, for advanced or metastatic HR-positive and HER2-negative breast cancer

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**Background:** Targeting the estrogen receptor (ER) has proven to be one of the most successful strategies in treating $HR^+$ ($ER^+$ and $PR^+$) and $HER2^-$ breast cancer. Selective estrogen receptor degraders (SERD) can be used as single agents or in combination with CDK4/6 inhibitors such as palbociclib. Fulvestrant is currently the only approved agent in its class and is limited by poor oral bioavailability necessitating monthly intramuscular injections. D-0502 is an orally bioavailable SERD with potent activity in various $HR^+$ and $HER2^-$ breast cancer cell lines and xenograft models. Its combination with palbociclib in both MCF-7 xenograft models and ESR-1 mutated (Y537S) patient derived breast cancer xenograft models resulted in further tumor growth inhibition or regression. Drug metabolism and pharmacokinetic studies both in vitro and in vivo demonstrated that D-0502 exhibits favorable PK profiles suitable for clinical development. **Methods:** A first-in-human phase 1 study was conducted to evaluate D-0502 in women with advanced or metastatic $HR^+$, $HER2^-$ breast cancer (MBC) (NCT03471663). The primary objective is to characterize the safety and tolerability of D-0502 and D-0502 in combination with palbociclib, to identify an MTD and/or RP2D. The secondary objectives are to evaluate the PK properties and the preliminary anti-tumor activities. Patients received D-0502 orally once daily in 28-day cycles. The study has completed dose escalation (phase 1a), and dose expansion and combination studies (phase 1b) are ongoing. In phase Ia, patients were enrolled and evaluated using conventional 3+3 dose-escalation to identify the MTD of D-0502 as a single agent. The phase 1b was divided into 2 stages. In Stage 1, D-0502 was evaluated with palbociclib at a dose below the MTD first before escalating to the MTD. Stage 1 also included patients in China treated at a dose below and at the MTD as single agent as well as in combination with palbociclib. Stage 2 will further evaluate the MTD for both single agent and combination of D-0502 with palbociclib. **Results:** At the time of this abstract submission, phase 1a dose escalation is completed, R2PD has been identified, and no DLTs were observed. PK analysis of D-0502 indicates a dose proportional increase in exposure as the dose increases, and the exposure has exceeded the potential therapeutic exposure level based on preclinical studies. The Phase Ib Stage 1 portion has also completed enrollment and the study is currently enrolling patients into phase Ib Stage 2. D-0502 as a single agent or in combination has been well tolerated with radiological tumor response and clinical benefit response (CBR) observed. Safety, PK and preliminary efficacy data will be reported at the meeting presentation. **Conclusion:** A first-in-human phase 1 study of D-0502 has been initiated in women with advanced or metastatic HR-positive and HER2-negative breast cancer. D-0502 has been well tolerated and achieved significant exposure and preliminary clinical activity in patients. Further results will be presented at the meeting.

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# The prognostic role of MMP 9 in early breast cancer

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**Background:** Matrix metalloproteinase 9 (MMP9) is involved in the extracellular matrix degradation during physiological and pathological conditions including tumorigenesis. This translational study was aimed to evaluate the prognostic role of the intratumoral MMP9 expression and correlate it with presence of CTCs in early breast cancer. **Methods:** A total of 318 primary breast cancer (PBC) patients were enrolled into this study. Surgical specimens were processed by the tissue microarray method and subjected to immunohistochemistry using the MMP9 monoclonal antibody. The MMP9 expression was evaluated in tumor cell as well as in tumor associated stroma. Quantitative real-time polymerase chain reaction -based assays was applied for identification of CTCs. **Results:** Significantly increased expression of MMP9 was found in breast cancer cells when compared to tumor associated stroma. A positive correlation was determined between MMP9 expression and hormone positive status as well as low proliferation index of analysed breast cancer tumour cells. Additionally, in tumor associated stroma was confirmed only the association with hormone receptor status. The univariate survival analysis of whole tested population detected no prognostic role of MMP9 expression neither in tumor cells (HR = 0.96, 95% CI 0.58-1.59, P = 0.864) nor in tumor associated stroma (HR = 1.29, 95% CI 0.60-2.78, P = 0.547). However, the subgroup of in hormone receptor negative and triple negative patients with absence of MMP9 expression in tumor cells and stroma had significantly better disease-free survival (DFS) (HR = 0.33, 95% CI 0.12-0.93, P = 0.025, and (HR = 0.14, 95% CI 0.00-4.81, P = 0.002, respectively) and (HR = 0.17, 95% CI 0.05-0.57, P = 0.003); (HR = 0.12, 95% CI 0.00-4.89, P = 0.001) compared with patients with presence of MMP9. Moreover, while tumor MMP9 was prognostic in CTC_EMT positive subgroup (HR = 0.40, 95% CI 0.16-0.95, P = 0.047), absence of stromal MMP9 had protective role in CTC_EP positive patients (HR = 0.18, 95% CI 0.01-2.75, P = 0.053). **Conclusions**: Our data suggest that the increased expression of MMP9 in PBC was related with favorable tumor characteristics. However, it´s prognostic value was limited only to hormone receptor negative, triple negative, CTC_EMT and CTC_EP positive subgroups. Therefore, we can suppose that evaluating of MMP9 tumor expression could help identify patients with increased risk of disease recurrence in these subgroups of patients.

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Trigonella foenum (fenugreek) extract and ectopic miR-34a inhibit stemness characteristics and enhance sensitivity of (CD44+/CD24−/ALDH1+) breast cancer stem cells subpopulation to doxorubicin by targeting notch1/ALDH1signaling pathways

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Breast cancer stem cells (BCSCs) have been implicated as the root of tumorinitiation, therapeutic resistance, relapse, and metastasis due to their uniqueabilities of self-renew, differentiation potentials and resistance to mostconventional therapies.Signaling pathways of stemness markers, Notch-1, ALDH1 andmicroRNAs, a class of emerging small non-coding RNAs, are importantregulators of BCSC functions and self-renewal capacity by modulatingmultiple biological processes via the post-transcriptional regulation of geneexpression and cellular signaling pathways. Understanding the earlymolecular mechanisms and identifying the miRNAs that are involved inchemo-resistance, and their crosstalk with Notch-1 and ALDH1, could be apotential therapeutic option for breast cancer drug resistant.Previously, we showed that Trigonella foenum (Fenugreek) extract (FCE),a traditional herbal plant, has an anti-tumor activity against HepG2 cell line.In the present study, we evaluated and screened a panel of aberrant expressedmiRNAs (i.e. miR-142, let-7a, let-7b and miR-34a) that might have a crosstalkwith Notch-1 and ALDH1 in isolated (CD44+/CD24−/ALDH1+)subpopulation treated with or without FCE extract alone or in combinationwith Doxorubicin for different time intervals.Our results revealed that FCE treatment alone for 48 h showed a significantdecrease in cell viability, clonogenicity and invasion capacity of(CD44+/CD24−/ALDH1+) BCSCs subpopulation compared to untreatedcells. Furthermore, FCE-inhibited Notch-1 and ALDH1 expression that wasassociated with a significant decrease in miR-142 by 4.6-folds and an increasein expression levels of let-7a, let-7b and miR-34a by 4.5, 7.7 and 15.4 foldsrespectively. Moreover, ectopic miR-34a expression significantly reduce cellproliferation and increase apoptotic induction consistent with downregulationof Notch-1 and ALDH1 expression in treated cells extract alone or incombination with Doxorubicin for 24h, suggesting that miR-34a expressionmight play a role in the breast cancer potential.Furthermore, FCE treated (CD44+/CD24−/ALDH1+) subpopulationectopically expressing miR-34a showed an increase in chemosensitivity todoxorubicin at low doses after 24 h compared to the controls. In initiated(CD44+/CD24−/ALDH1+) BCSC tumor xenografts ectopically expressingmiR-34a, FCE/Doxorubicin combined treatment showed a significant regression in tumor size by 62% after 72h compared to untreated controls orDoxorubicin alone.All in all, the aberrant expression of selected miRNAs, such as of miR-34a, might regulate a crosstalk with stemness characteristic markers, Notch-1and ALDH1, that are involved in the pathogenesis of breast cancer.

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# Fatty acid synthase inhibition targets ERα in tamoxifen-resistant breast cancer

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**INTRODUCTION:** Estrogen receptor-positive (ER+) breast cancer accounts for nearly 70% of all cases. Common targeted anti-estrogen therapies such tamoxifen, fulvestrant and aromatase inhibitors have shown success in the clinic, but unfortunately, often lead to resistance. The fatty acid synthase enzyme (FASN) is responsible for endogenously synthesizing long-chain fatty acids, such as palmitate, which can contribute to protein modification, phospholipid biosynthesis for membranes, and lipid raft signaling that favors tumorigenesis. The depletion of intracellular palmitate leads to an alteration of lipid composition within lipid rafts of the plasma membrane as well as lipids within the endoplasmic reticulum membrane. Endoplasmic reticulum stress elicits an inhibition of protein translation through the phosphorylation of eukaryotic initiating factor 2-α (p-eIF2α) and is activated by various stimuli including altered phospholipid composition within the membrane. Our preliminary findings illustrated a degradation of the ERα upon treatment with the FASN inhibitor, TVB-3166, in tamoxifen-resistant breast cancer both *in vivo* and *in vitro*. Moreover, previous studies have illustrated FASN inhibition to induce endoplasmic reticulum stress concomitant with a loss of the androgen receptor (AR) in castration-resistant prostate cancer. Additionally, palmitate treatment rescued AR expression that was accompanied by an attenuation in endoplasmic reticulum stress. **HYPOTHESIS:** We hypothesize FASN inhibition leads to a degradation of ERα in tamoxifen-resistant breast cancer through the induction of endoplasmic reticulum stress. **METHODS:** Patient tumor explants were incubated for 72h on gelatin sponges in culture medium in the absence or presence of 200nM TVB-3166. Tissue were fixed in 10% formalin and processed into paraffin blocks and stained for ERα and Ki67. To investigate TVB induced endoplasmic reticulum stress, tamoxifen-Resistant (TamR) MCF-7 and MCF-7 cells were treated with TVB-3166 or vehicle control followed by treatment with either palmitate or ER stress inhibitor, 1,2-Bis(2-Aminophenoxy)ethane-*N,N,N′,N′*-tetraacetic acid (BAPTA). Expression of ERα, p-eIF2α, eIF2α were measured by western blot. **RESULTS:** TVB-3166 treatment of primary tumor explants decreased their proliferation (Ki67) compared to untreated controls (14% vs 36%, $p<0.01$). Both IHC and Western blotting demonstrated a reduction in ERα upon treatment with TVB-3166. In addition to the decreased expression of ERα, there was an increase in the phosphorylation of eukaryotic initiation factor 2α (p-eIF2α). The expression of ERα was rescued upon palmitate treatment while resulting in decreased p-eIF2α. Inhibition of endoplasmic stress using BAPTA also rescued ERα expression after TVB-3166 treatment. **CONCLUSION:** FASN is a potentially viable target in tamoxifen-resistant breast cancer.

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# “Bridge” neoadjuvant endocrine therapy for early stage breast cancer patients during COVID-19 at an academic hospital in NYC: Lessons learned

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**Background:** Neoadjuvant endocrine therapy has traditionally been considered a treatment option for locally advanced and/or surgically high-risk women with hormone positive disease. Early stage hormone-positive breast cancer, on the other hand, is usually managed with upfront surgery, with post-operative hormone therapy as a risk-reducing adjunct. During the COVID-19 pandemic, however, widespread closures of operating rooms throughout the country resulted in many breast cancer patients being offered presurgical endocrine therapy as a bridge to surgery. We explored the demographic and clinicopathologic characteristics of these patients and quantified their rate of uptake. **Methods:** The Institutional Breast Cancer Database was queried for all patients who were diagnosed with ER+ stage 0, I, or II breast cancer and were offered presurgical endocrine therapy (tamoxifen or aromatase inhibitor) by a medical oncologist from 3/12/2020 to 4/30/2020. Variables of interest included demographics, tumor characteristics, and rate of medication uptake and compliance. **Results:** Of 192 newly diagnosed breast cancer patients seen at NYU Perlmutter Cancer Center during this time period, 136 patients had early stage ER+ breast cancer. Forty-five patients had not yet undergone surgery, and were recommended to receive presurgical hormonal therapy as a bridge given the COVID-19 pandemic (Table 1). The average age was 60.5 years old (SD=13.8 years, range 31-89), and all were female. Thirty-four of 44 patients were post-menopausal (75.6%), while 10 were premenopausal (22.2%), and one was perimenopausal (2.2%). Twenty-six patients were white (57.8%), 12 were black (26.7%) 3 were Asian (6.7%), and 4 were other (8.9%). Thirty-four patients (75.6%) had invasive disease, while 8 had ductal carcinoma in situ (DCIS, 17.8%), and 3 had DCIS with microinvasion (6.7%). Nine patients (20%) did not take the medication for various reasons: 1 contracted COVID-19, 1 refused any treatment, 1 decided to transfer care out of state, 1 preferred to take a homeopathic remedy instead of endocrine therapy, 1 preferred to wait for surgery without medication, and 4 were scheduled for surgery sooner than anticipated and did not start the medication. The remaining 36 patients (80%) took medication for an average of 43.6 days (SD=27.3 days, range 9-101 days) prior to surgery. Twenty-eight patients (77.8%) took an aromatase inhibitor, and 8 (22.2%) took tamoxifen. Forty-two patients have now undergone surgery (93.3%); the remainder include the patient who is refusing all treatment, the patient who transferred out of state, and one patient who has not yet scheduled surgery, but is reportedly still taking an aromatase inhibitor. **Conclusion:** Improving adherence to long-term adjuvant endocrine therapy is an urgent need as patient acceptance is low. Reported completion rates range around 50%, and have not been improved by educational or technology-based interventions. The unique situation posed by the current COVID-19 pandemic has temporarily changed the management of early-stage breast cancer, and resulted in a high initial acceptance of endocrine therapy (80%), although duration is shorter in this presurgical setting. Further investigations will evaluate length of use, the psychosocial and behavioral factors that influence willingness to take endocrine therapy, and apply these lessons to management of early-stage hormone-positive breast cancer.

Patient Demographics and Tumor Characteristics

| **Variables** | **Total (N=45)** | **%** |
|---|---|---|
| **Median Age (years)** | 60.5 (31-89) | |
| **Race** | | |
| White | 26 | 57.8 |
| Black | 12 | 26.7 |
| Asian | 3 | 6.7 |
| Other | 4 | 8.9 |
| **Menopause Status** | | |
| Pre-menopausal | 10 | 22.2 |
| Peri-menopausal | 1 | 2.2 |
| Post-menopausal | 34 | 75.6 |
| **Mean BMI (kg/m$^2$)** | 28.3 (17.8-46.5) | |
| **Palpability** | | |
| Non-palpable | 30 | 66.7 |
| Palpable | 15 | 33.3 |
| **Mammographic Breast Density** | | |
| Entirely Fatty | 2 | 4.4 |
| Scattered Fibroglandular | 17 | 37.8 |
| Heterogeneously Dense | 24 | 53.3 |
| Extremely Dense | 2 | 4.4 |
| **Histology** | | |
| DCIS | 8 | 17.8 |
| DCIS with microinvasion | 3 | 6.7 |
| Invasive carcinoma | 34 | 75.6 |
| **Clinical Stage** | | |
| 0 | 8 | 17.8 |
| I | 27 | 60 |
| II | 10 | 22.2 |
| **Endocrine Therapy** | (N=36) | |
| Tamoxifen | 8 | 22.2 |
| Aromatase Inhibitor | 28 | 77.8 |
| **Mean Duration of Endocrine Therapy (days)** | 43.6 (9-101) | |

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# Acute myocardial infarction prevalence and trends in females with active breast cancer

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Introduction:Breast cancer is among the three most common malignancies worldwide, and a better understanding of the epidemiology of the cardiovascular disease in females with breast cancer is needed Methods:Females with active breast cancer diagnosis hospitalized from January 2010 to December2017 were identified in the Nationwide Readmissions Database. Outcomes of interest were the prevalence of acute myocardial infarction (AMI), non-ST-segment myocardial infarction (NSTEMI), cardiac complications, and in-hospital mortality.Results:1,424,102 females with breast cancer were identified. Of whom, 17,578 (1.23%) were hospitalized for AMI. AMI patients were older with a mean age of 72.51 (11.73) vs. 62.22 (14.29), p<0.001. AMI patients had a higher prevalence of hypertension; 65.3% vs. 47.3%, p<0.001, known coronary artery disease; 51.1% vs. 8.2%, p<0.001, hyperlipidemia; 46.6% vs. 24.2%, p<0.001, known heart failure; 42.6% vs. 8.8%, p<0.001, smoking; 26.7% vs. 21.6%, p<0.001, history of stroke; 6.2% vs. 3.2%, p<0.001, history of prior AMI; 9.5% vs. 2.3%, p<0.001, and diabetes with chronic complications; 11.0% vs. 4.2%, p<0.001, and diabetes without complications; 25.2% vs. 15.8%, p<0.001. Over the 8 years, the prevalence of cardiovascular risk factors increased in breast cancer patients including; diabetes with chronic complications; from 2.3% in 2010 to 10.4% in 2017, p-trend<0.001, obesity; 7.8% in 2010 to 13.3% in 2017, p-trend<0.001, coronary artery disease; 8.1% in 2010 to 10.2% in 2017, p-trend<0.001, hyperlipidemia; 20.7% in 2010 to 29.7% in 2017, p-trend<0.001, and smoking; 16.8% in 2010 to 28.2% in 2017, p-trend<0.001. AMI increased over the study duration from 1.0% in 2010 to 1.8% in 2017, p-trend<0.001, and NSTEMI increased from 0.8% in 2010 to 1.5% in 2017, p-trend<0.001. The observed increase was persistent when patients with localized malignancies were examined with AMI inclining from 2.1% in 2010 to 2.4% in 2017, p-trend<0.001, and NSTEMI from 1.6% in 2010 to 2.0% in 2017, p-trend<0.001. Breast cancer patients with AMI had a higher hospital mortality rate; 14.7% vs. 4.2%, OR: 3.96, 95% CI (3.80-4.13), p<0.001, cardiac arrest; 3.9% vs. 0.5%, OR: 8.53, 95% CI (7.87-9.24), p<0.001, and cardiogenic shock, 5.1% vs. 0.1%, OR: 42.03, 95% CI (38.73-45.60), p<0.001.Conclusion:Females with breast cancer have a concerning prevalence of cardiovascular disease with stern worse outcomes, and the prevalence is shown to be increasing over the study duration. Known cardiovascular risk factors are also increasing in breast cancer patients. Further efforts should be directed to aggressively reduce the prevalence of modifiable risk factors in order to improve the outcomes of breast cancer patients.

| | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | P-trend |
|---|---|---|---|---|---|---|---|---|---|
| Coronary Artery Disease | 8.1% | 8.3% | 8.0% | 8.5% | 8.9% | 8.1% | 9.7% | 10.2% | <0.001 |
| Diabetes with chronic complications | 2.3% | 2.5% | 2.5% | 2.9% | 3.3% | 3.9% | 7.2% | 10.4% | <0.001 |
| Heart Failure | 7.8% | 7.8% | 7.9% | 8.5% | 9.5% | 9.0% | 11.3% | 12.5% | <0.001 |
| Hyperlipidemia | 20.7% | 21.9% | 22.8% | 24.6% | 25.8% | 23.1% | 28.0% | 29.7% | <0.001 |
| Obesity | 7.8% | 8.7% | 9.8% | 11.2% | 12.2% | 12.2% | 12.2% | 13.3% | <0.001 |
| Smoking | 16.8% | 17.2% | 19.0% | 20.7% | 23.2% | 22.2% | 27.6% | 28.2% | <0.001 |
| Outcomes | | | | | | | | | |
| AMI | | | | | | | | | |
| Overall | 1.0% | 1.0% | 1.1% | 1.1% | 1.3% | 1.2% | 1.5% | 1.8% | <0.001 |
| Localized Malignancies | 2.1% | 1.9% | 2.0% | 2.0% | 2.1% | 1.8% | 2.0% | 2.4% | <0.001 |
| Patients with History of Radiation Therapy | 1.2% | 0.7% | 1.1% | 0.7% | 1.2% | 1.2% | 1.6% | 1.6% | <0.001 |
| History of prior AMI | 3.5% | 3.6% | 4.2% | 4.7% | 5.5% | 4.3% | 6.6% | 6.5% | <0.001 |
| NSTEMI | | | | | | | | | |
| Overall | 0.8% | 0.8% | 0.9% | 0.9% | 1.0% | 1.0% | 1.3% | 1.5% | <0.001 |
| Localized Malignancies | 1.6% | 1.5% | 1.6% | 1.6% | 1.7% | 1.5% | 1.7% | 2.0% | <0.001 |
| Patients with History of Radiation Therapy | 0.9% | 0.6% | 0.9% | 0.6% | 0.9% | 1.0% | 1.5% | 1.3% | <0.001 |
| History of prior AMI | 3.0% | 2.5% | 3.8% | 3.7% | 4.5% | 3.9% | 5.7% | 5.6% | <0.001 |

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Men1611 promotes immune activating myeloid cell polarization

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MEN1611 is a PI3K inhibitor currently in clinical development targeting the p110 α, β and γ isoforms, while sparing the δ subunit. In preclinical models, MEN1611 has demonstrated a long lasting antitumor activity when combined with trastuzumab in HER2+/PiK3CA mutated breast cancer. Aim of this work is to characterize the effects of MEN1611 on the PI3Kγ isoform, highly expressed in tumor-associated macrophages (TAMs), in order to understand whether the anti-tumor activity of MEN1611 might be also mediated by the inflammatory microenvironment. Previous evidences have shown that selective targeting of PI3Kγ by IPI-549 can reshape the inflammatory cells infiltrating tumors towards a less immunosuppressive phenotype and promote cytotoxic T cell-mediated tumor regression. In order to evaluate the effect of MEN1611 on TAMs, we established an *in vitro* model by differentiating murine and human macrophages from bone marrow-derived monocytes or buffy coats-isolated monocytes respectively. Pro-inflammatory M1 macrophages have been differentiated by treatment with Lipopolysaccharide (LPS) and interferon γ (IFNγ), while pro-tumoral M2 macrophages by interleukin 4 (IL-4) stimulation. The cells, thus obtained, have been incubated with MEN1611 or IPI-549 (positive control) and the effects on their phenotype, gene and protein expression, evaluated through confocal microscopy, RNASeq and flow cytometry respectively. A syngeneic xenograft model of breast cancer based on 4T1 cells has been also established in order to investigate *in vivo* the activity of MEN1611 on the inflammatory environment (TAMs and T cells). *In vitro* data showed MEN1611 and IPI-549 ability to repolarize murine and human macrophages towards a pro-inflammatory phenotype. Confocal analysis revealed a shape remodeling from an elongated M2-like towards a round M1-like; gene and protein expression analysis revealed a significant increase of immuno-stimulating factors mRNA and M1 chemokines and cytokines secretion, respectively. A modulation of the inflammatory infiltrate was also observed *in vivo* where RNASeq and flow cytometry analysis on dissociated treated tumors highlighted an increase of pro-inflammatory markers. The in-silico ingenuity pathway analysis (IPA) performed on genes modulated by MEN1611 revealed the enhancement of some processes related to an immune activating switch, such as the recruitment of myeloid cells or the cytotoxicity of lymphocytes and natural killer cells. In conclusion, we demonstrated *in* a cellular context that MEN1611 activity on PI3Kγ isoform is responsible for macrophages reprogramming from an immune-suppressive to an immune-activating phenotype. Moreover, we observed that in 4T1 murine breast cancer model, tumor regression induced by MEN1611 was also
sustained by a modulation of the inflammatory microenvironment, characterized by an increased recruitment and cytotoxicity of T cells.

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# Pelvic floor disorders and quality of life among breast cancer survivors

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Introduction: Approximately 25% of women in the United States experience a symptomatic pelvic floor disorder such as urinary incontinence, pelvic organ prolapse, anal incontinence, and sexual dysfunction. Aspects associated with breast cancer treatment such a chemotherapy, oophorectomy/ovarian suppression, and endocrine therapy may predispose women to pelvic floor disorders. The prevalence of pelvic floor disorders among breast cancer survivors has been cited at 18%, but unpublished cross-sectional data suggests the prevalence may be much higher. In this study, 8.5% - 11.5% of participants experienced prolapse symptoms, 56.2% experienced anal incontinence symptoms, and 43.3% - 51.2% experience urinary incontinence symptoms. While pelvic floor dysfunction is associated with lower quality of life, it is unknown if breast cancer survivors with pelvic floor disorders experience decreased quality of life. The primary aim of this study was to assess if breast cancer survivors with pelvic floor disorders experience lower quality of life.
Methods: Women 18 years or older who were previously treated for breast cancer and who were enrolled in a cancer research registry were invited to complete the Pelvic Floor Distress Inventory 20 (PFDI-20), the Female Sexual Function Index (FSFI), and the Short Form 12. Demographic and clinical data were abstracted from the research registry. A participant was considered eligible for the study if she had enrolled in the cancer registry and completed all core questions (i.e. demographics, cancer diagnosis, cancer treatment, endocrine therapy, medical/surgical history, and risk factors). As per standard PFDI-20 reporting, presence of a symptom was defined as answering a 1, 2, 3, or 4 to a question, while presence of a bothersome symptom was defined as answering a 2, 3, or 4. A score of 26 or less on the FSFI was considered indicative of sexual dysfunction.
Results: A total of 634 women were considered eligible for enrollment in the study. 445 were able to be contacted, and 410 women agreed to participate in the study. Of those, 303 returned the PFDI-20 questionnaire and FSFI questionnaire, and 264 returned the SF-12 for response rates of 74% and 64%, respectively. Overall, higher scores on the PFDI-20 was associated with lower scores on both the physical and mental components of the SF-12 (Rho = -0.298, p = <.0001; Rho = -0.202, p = .0009, respectively). When the PFDI-20 was broken into subscores, higher POPDI scores (prolapse) was associated with lower physical component scores but not lower mental component scores. Higher CRADI scores (anal incontinence) and UDI-6 scores (urinary incontinence) were associated with lower physical and mental scores. Neither overall FSFI scores or subset domain scores were associated with lower physical or mental component scores of the SF-12. In linear regression analysis, PFDI summary score remained statistically significantly related to both mental and physical component subscores after controlling for age, race, stage of breast cancer, time since diagnosis, and use of adjuvant endocrine therapy. FSFI scores were related to age and endocrine therapy use, but were not related to SF-12 scores.
Conclusion: Among a subset of breast cancer survivors, pelvic disorders including pelvic organ prolapse, urinary incontinence, and anal incontinence exist, and these disorders are associated with decreased mental wellbeing. All pelvic floor disorders except pelvic organ prolapse were associated with decreased physical wellbeing. None of the domains of female sexual dysfunction were associated with decreased physical or mental wellbeing among breast cancer survivors. A subset of breast cancer survivors experiences bothersome pelvic floor disorders and thus screening for these disorders can increase referrals to appropriate treatment and complement survivorship care to enhance overall quality of life.

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# An initial safety study of gedatolisib plus cofetuzumab pelidotin for metastatic triple-negative breast cancer

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**Background:** The PI3K pathway is dysregulated in the majority of triple-negative breast cancer (TNBCs), yet single agent inhibition of PI3K in TNBC has minimal clinical activity. We previously reported that PI3K inhibition leads to an immediate compensatory up-regulation of the Wnt pathway. Dual targeting of both pathways is highly synergistic against TNBC models *in vitro* and *in vivo*. We initiated a Phase I clinical trial of gedatolisib, a pan-class I isoform PI3K/mTOR inhibitor, and cofetuzumab pelidotin, an antibody-drug conjugate against the cell-surface PTK7 protein (Wnt pathway co-receptor) with an auristatin payload. PTK7 is up-regulated after PI3K inhibition and auristatin is in itself synergistic with gedatolisib providing the potential for a dual mechanism of synergy.
**Methods:** Dose escalation proceeded using a traditional 3+3 schema with a small expansion cohort at the final dose level to better characterize safety. Participants had metastatic TNBC or ER low (ER and PgR <5%, HER2 negative) breast cancer, and had received at least one prior line of chemotherapy. The primary objective was safety. Secondary endpoints included objective response (ORR), clinical benefit at 18 weeks ($CB_{18}$), and progression-free survival (PFS). Exploratory analyses probed the association of tumor DNA, RNA, and IHC with clinical efficacy to identify putative biomarkers.
**Results:** Between January 2018 and January 2020, 18 patients were enrolled in 3 dose cohorts: gedatolisib (qw) & cofetuzumab pelidotin (q3w) 110mg+1.4mg/kg (n=4), 180mg+1.4mg/kg (n=3), and 180mg+2.8mg/kg dose levels (n=11). The median age was 53 years (32-77). Nausea (n=16), anorexia (n=13), fatigue (n=12), and mucositis (n=12) were common but rarely reached ≥Grade 3 severity (nausea, n=1; fatigue, n=2). Myelosuppression was uncommon (Grade ≥3 neutropenia, n=2). 16 participants were evaluable for response. 3 achieved a confirmed partial response (PR), and 3 had stable disease (SD). ORR=18.8%. All 3 PRs lasted ≥ 6 months. $CB_{18}$=31.3%. Median PFS was 2.0 months (95% CI for PFS:1.2-6.2); median OS was 9.5 months (95% CI for OS:4.3-not reached). Correlative analyses of genomic, transcriptomic, and protein biomarkers with response are currently ongoing.
**Conclusions:** The combination of gedatolisib + cofetuzumab pelidotin for the treatment of metastatic TNBC was found to be well tolerated and demonstrated promising clinical activity. Further investigation of this drug combination in metastatic TNBC is warranted.
**Trial Registration:** NCT03243331

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# The new normal; adjusting to remote ways of providing bespoke weight management support to breast cancer survivors during the COVID-19 global pandemic

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**Purpose**NEWDAY-ABC (North England Women's Diet and ActivitY After Breast Cancer) trial is a bespoke weight management and behaviour change intervention for women treated for early-stage estrogen-receptor positive breast cancer (BC) with a body mass index (BMI) of ≥25 kg/m$^2$. Many women are overweight or report further weight gain during and after BC-treatment. Due to the complex nature of weight management, NEWDAY-ABC was co-designed with BC-survivors and health care professionals (HCPs) prior to the COVID-19 outbreak. However, because of the COVID-19 pandemic, refinements had to be made to the intervention to enable remote (virtual) delivery options, allowing the trial to proceed while adhering to government social distancing and shielding guidance.
**Methods**Prior to the COVID-19 outbreak, initial focus groups (FG) were conducted with n=16 BC-survivors and n=21 HCPs. Framework analysis was used to categorise what BC-survivors want from a weight management intervention. Participants (n=9) subsequently attended a two-stage successive interactive co-design workshop. Workshop 1 explored: i) techniques to motivate change; ii) approaches to overcome challenges to intervention adherence; iii) core components of the intervention. Workshop 2 explored: i) language and graphics used for the support and educational materials; ii) delivery mechanisms; iii) refinement of workshop 1 ideas.
**Results / findings**Co-design revealed the intervention should address: i) self-confidence and self-esteem; ii) reassurance of safe physical activity (PA) and dietary guidance for BC-survivors; iii) knowledge about what happens to the body after treatment. In terms of intervention delivery: i) self-monitoring of weight should be optional; ii) content should be as visual as possible iii) emotional needs are as important to address as PA and dietary recommendations; iv) one-to-one facilitator support is as important as group peer-support.
To integrate all these elements, the NEWDAY-ABC intervention included face-to-face group support sessions. However, due to the COVID-19 pandemic, remote delivery options had to be embedded into the intervention design to enable this support to be provided via means that are accessible to all eligible participants, whilst adhering to the guidance on social distancing and shielding of vulnerable populations.
Key considerations include:•Participant and session leader's ability to access and engage with remote delivery•Creating a peer supportive environment remotely•Remote platform security•Effectiveness of remote delivery in achieving clinically meaningful weight loss
**Conclusions**The COVID-19 pandemic has forced cancer care to quickly adapt to ways of providing remote support to meet the needs of cancer patients and survivors. While this presents many challenges, including issues of accessibility, privacy and accessing peer support, use of virtual delivery platforms and new technologies means that BC-survivors can still access this bespoke weight management intervention during an extended period of post-pandemic social distancing. The effectiveness of the NEWDAY-ABC intervention in providing the required level of peer support, guidance and self-confidence needed for clinically meaningful weight loss with virtual delivery options will be tested in a randomised controlled trial.

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# A randomized, pre-surgical study to investigate the biological effects of AZD9833 doses in women with ER-positive HER2-negative primary breast cancer (SERENA-3)

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**Background** AZD9833 is an orally bioavailable selective estrogen receptor (ER) antagonist and degrader (SERD) that has shown anti-tumor efficacy in a range of preclinical breast cancer models. SERENA-1, an ongoing first-in-human study assessing AZD9833 as a monotherapy and in combination with palbociclib, established dose-dependent tolerability in pre- and post-menopausal women at doses of 25-450 mg once daily (QD), with clinical benefit and target engagement at all dose levels. Two randomized, open-label Phase 2 trials are also ongoing in women with ER+ HER2- breast cancer. SERENA-2 compares the efficacy of AZD9833 with fulvestrant in post-menopausal women with advanced breast cancer following treatment with ≤1 endocrine therapy. SERENA-3 will examine the biological effects of different doses of AZD9833 in treatment-naïve women with primary breast cancer. **Methods** SERENA-3 is a randomized, open-label, parallel-group, pre-surgical study to investigate the biological effects of different doses of AZD9833 in ER+, HER2- primary breast cancer. Eligible patients will be post-menopausal (and potentially pre-menopausal) women awaiting curative-intent surgery for newly diagnosed, ER+ HER2- primary breast cancer. The study is designed in two stages. In Stage 1, 24 post-menopausal women will be randomized 1:1 to receive either 75 mg or 150 mg oral AZD9833 QD for 5-7 days, followed by a minimum 5-day pre-surgery washout period; Stage 2 gives provision for additional groups depending on emerging data from Stage 1. The primary objective of this study is to explore the effect of AZD9833 on ER expression in pre- and on-treatment tumor samples from women with primary breast cancer, as assessed by immunohistochemistry and H-score. Safety and tolerability will be assessed as secondary endpoints, along with the pharmacokinetic and pharmacodynamic effects of AZD9833 on other biomarkers. Blood will be collected at screening, on the day of biopsy and the day of surgery to assess circulating tumor DNA and exploratory biomarkers. Primary endpoint analysis will be performed on the pharmacodynamic analysis set. The study will be conducted in 20 centers across 3 countries. For more information please contact Professor John Robertson at: john.robertson@nottingham.ac.uk.

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# Impact of TAILORx data on chemotherapy prescribing in British Columbia

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**Background:** Developed with retrospective data, the 21-gene recurrence score assay (RS) reduces adjuvant chemotherapy (CTx) use in hormone-positive (HR+), HER2-negative, node-negative breast cancer, justifying the assay's cost. The TAILORx trial prospectively confirmed the predictive value of RS and established thresholds for CTx benefit in younger and older patients. We examined CTx use in British Columbia (BC) following TAILORx publication, as a prelude to exploring age-adjusted cost effectiveness of the assay.
**Methods:** We assembled 3 cohorts of patients with HR+, HER2-negative, node-negative breast cancer: diagnosed before RS funding (cohort 1: January 1, 2013-December 31, 2013), after introduction of public funding (cohort 2: July 1, 2015-June 30, 2016), and after TAILORx results (cohort 3: July 1, 2018-June 30, 2019). Patients aged 18-80 years with tumors that were grade 3, grade 2 T1b or larger, or any T size and grade if ≤ 40 years of age were included, matching BC funding criteria. Previous in situ or invasive breast cancer cases were excluded. CTx use by age and RS was compared between cohorts using univariate analyses.
**Results:** 2,066 patients met inclusion criteria (Table 1). CTx use in cohorts 1, 2, and 3 was 21%, 17%, and 13%, respectively. In cohorts 2 plus 3, CTx use was 30% for patients up to 50 years of age and 11% for patients over 50 years of age. Baseline characteristics were balanced, except grade 3 histology (24%, 25%, 17% in cohorts 1, 2, 3, respectively; p=0.01). RS was ≥ 26 in 33% of grade 3 and 34% of PR negative tumors. CTx use declined by 19% after RS funding was introduced and by another 23% after TAILORx publication (p=0.001). Reduction in CTx use was significant for RS 11-20 tumors (cohort 3 vs. 2, p=0.004). A 7.5% nonsignificant increase in CTx was seen for RS 26-30 tumors (cohort 2 vs. 3, p=0.55). There was no significant change in CTx use in patients aged > 50 years (12% in cohort 2 vs. 10% in cohort 3, p=0.22). Among patients aged 70-80 years in cohort 3 with RS, 5% had RS ≥ 26, and of these, 40% had CTx (9% of patients in this age group), compared with 92% CTx use for patients aged ≤ 50 years with RS ≥ 26 (15% of patients in this age group).
**Conclusions:** CTx use decreased after TAILORx publication, particularly for RS 11-20 tumors. CTx use changed less in patients over 50 years old, suggesting that trial results confirmed pre-existing prescribing practices. CTx use increased in patients with RS 26-30 tumors, reflecting acceptance of the new threshold for CTx benefit established by TAILORx. CTx use was low overall in patients aged > 50 years, especially in those aged 70-80 years, in part due to the very low frequency of high RS tumors. Given these findings, we conclude that cost effectiveness modelling for publicly funded RS should take age into consideration.

**Table 1:** Receipt of adjuvant chemotherapy (CTx) by 21-gene recurrence score (RS) result before assay availability (cohort 1), after assay availability (cohort 2), and after TAILORx publication (cohort 3) in patients (pts) aged ≤ 50 (a) and 51-80 years (b).

**a)**

| Age | | ≤ 50, n = 423 | | |
|---|---|---|---|---|
| Cohort | | 1 | 2 | 3 |
| No. of pts who received CTx / No. of pts in group (%) | RS not done | 51/105 (48.6) | 28/56 (50) | 1/6 (16.7) |
| | RS ≤ 10 | 1/5 (20.0) | 0/17 (0) | 1/25 (4.0) |
| | RS 11-20 | 1/8 (12.5) | 4/52 (7.7) | 2/67 (3.0) |
| | RS 21-25 | 1/3 (33.3) | 8/17 (47.1) | 10/20 (50.0) |
| | RS 26-30 | 0/0 (0) | 5/5 (100) | 5/5 (100) |
| | RS ≥ 31 | 2/2 (100) | 10/11 (90.9) | 17/19 (89.5) |
| | **Entire cohort** | **56/123 (45.5)** | **55/158 (34.8)** | **36/142 (25.4)** |

**b)**

| Age | | 51-80, n = 1643 | | |
|---|---|---|---|---|
| Cohort | | 1 | 2 | 3 |
| No. of pts who received CTx / No. of pts in group (%) | RS not done | 72/494 (14.6) | 25/279 (9.0) | 2/86 (2.3) |
| | RS ≤ 10 | 0/6 (0) | 0/60 (0) | 0/110 (0) |
| | RS 11-20 | 2/11 (18.2) | 5/126 (4.0) | 0/198 (0) |
| | RS 21-25 | 2/5 (40.0) | 6/56 (10.7) | 2/64 (3.1) |
| | RS 26-30 | 2/3 (66.7) | 5/20 (25.0) | 14/35 (40.0) |
| | RS ≥ 31 | 2/2 (100) | 31/40 (77.5) | 37/48 (77.1) |
| | **Entire cohort** | **80/521 (15.4)** | **72/581 (12.4)** | **55/541 (10.2)** |

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# Evaluating the pathogenicity of emerging genomic aberrations detected by circulating tumor DNA over the course of metastatic breast cancer

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**Introduction:** Previously reported data from our group and others have demonstrated an increase in genomic complexity and number of alterations over the course of treatment in MBC. Our study aims to categorize the pathogenicity of genomic aberrations found on serial ctDNA evaluations in MBC to explore the relevance of emerging mutations. **Methods:** Patients with MBC and ctDNA next-generation sequencing (NGS) analysis by Guardant360 (Guardant Health, Redwood City, CA) completed from 2015 to 2019 were retrospectively identified with an IRB-approved protocol. Clinical-pathologic features and time point for progression of disease were abstracted from review of the electronic medical record. Among the 255 patients with ctDNA analysis, 85 patients had serial ctDNA analysis from baseline and at subsequent progression of disease (PD1) and 27 had repeat ctDNA analysis at next progression (PD2). Genomic alterations were classified as oncogenic, likely oncogenic, predictive oncogenic, likely benign, inconclusive, unknown significance, and synonymous based on categorization by OncoKB.org (Chakravarty et al, JCO PO 2017). Oncogenic, likely oncogenic, and predicted oncogenic were considered ‘pathogenic’ while the remainder were ‘not known pathogenic’. Two-sample t-tests for difference of means ($\alpha = 0.05$) was used for analysis of changes in pathogenic proportions and mutant allele frequencies (MAF). **Results:** The median age was 53.8 years, 41 patients had hormone receptor positive (HR+) HER2-negative, 22 had HER2+, and 22 had triple negative (TN) MBC. The median and interquartile range (IQR) of the time of MBC diagnosis to first ctDNA collection was 10 mo (0.3-23.1 mo), from baseline ctDNA to analysis at the time of disease progression (PD1) was 6.7 mo (3.6-12.5 mo), and from PD1 to second progression (PD2) was 4.6 mo (3.1-8.5 mo). At baseline 66% of alterations were pathogenic (38.4% oncogenic, 27.6% likely oncogenic, 26.5% unknown significance). The proportion of pathogenic variants did not significantly change over time: 62% at PD1 (p=0.41) and 56% at PD2 (p=0.19). The percent of pathogenic alterations by disease subtype at baseline and PD1 was 66% and 60% in HR+ HER2-, 73% and 57% in HER2+, and 62% and 71% in TN. 57% and 70% of patients had a new pathogenic alteration at PD1 and PD2, respectively. The most frequently detected new pathogenic alterations at the time of disease progression were *TP53*, *PIK3CA*, *ESR1*, *FGFR1*, and *MYC*, which occurred in 28%, 18%, 15%, 12%, and 11% of patients, respectively. Among genes that were altered in at least 10% of patients, the aberrations were very likely to be pathogenic (>75% of alterations pathogenic) for *TP53*, *PIK3CA*, *ESR1*, *MYC*, *BRAF*, *FGFR1*, often pathogenic (50-75% of alterations pathogenic) for *NF1*, *KIT*, *GATA3*, *ERBB2*, *EGFR*, *CCNE1*, *PDGFRA*, and often not known pathogenic (<50% of alterations pathogenic) for *MET*, *AR*, *ARID1A*, and *BRCA2*. When comparing the mean MAF of pathogenic and not known pathogenic alterations, paired by gene, the MAF was not significantly different for pathogenic alterations except for *GATA3* (p=0.03). **Conclusion**: The continued emergence of pathogenic mutations at times of progression without a corresponding increase in the proportion of pathogenic variants suggests that new pathogenic mutations may arise as a result of increased tumor genomic instability over time, although these findings require confirmation in larger datasets. The large proportion of patients who present with new pathogenic variants at disease progression supports the utility of ctDNA to track tumor evolution. Additionally, this study highlights the importance of considering the pathogenicity of genomic alterations, as over one-third of aberrations in MBC were not known to be pathogenic.

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# Upregulation of SLC26A9 resulted in the development and progression of HER2 positive breast cancer via activating TGFβ signaling pathway

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**Background:** Slc26a9 (Solute carrier family 26 member 9) is a member of Slc26a family of multifunctional anion transporters, which functions as $Cl^-$ channel (*Liu et al., Front Physiol 2018*). Our previous study showed that SLC26A9 deficiency results in the development and progression of gastric cancer, which demonstrated that the key role of SLC26A9 in the tumorigenesis first time (*Liu et al., Gastroenterology 2018*). However, what's the role of SLC26A9 in the breast cancer (BC) onset is not clear. We therefore wondered whether Slc26a9 gene is involved in promoting breast carcinogenesis and its mechanisms.
**Methods:** The tissue microarrays and IHC assay were used to detect the expression and clinic relevance of SLC26A9 in the human BC. Different BC cell lines were used to investigate the expression and function of SLC26A9 in the BC. SLC26A9 gene transfect and knockout experiment were performed to detect the regulator role of SLC26A9 in BC cell behaviors.
**Results:** Compared with adjacent normal tissues, SLC26A9 expression was significantly increased in the BC tissue, SLC26A9 expression level in BC correlated with the differentiated state of BC and patient's clinical outcome, indicating that SLC26A9 may be involved in BC pathogenesis and progression in humans and it might be a novel poor prognosis marker for BC. Moreover, HER2 positive BC tissues exhibited high SLC26A9 expression than HER2 negative BC tissues. Compared with normal mammary cell line, SLC26A9 was significantly upregulated in the all BC cell lines, with highest expression in HER2 enriched cell line SKBR3. Deletion of SLC26A9 in SKBR3 resulted in inhibition of BC cell proliferation, migration and invasion, but promotion of cell apoptosis, which were investigated by different cell function assays, including cell counting Kit-8, cell proliferation curve, Annexin VFITC/PI double staining, Wound-healing and transwell assays respectively. Moreover,
SLC26A9 deficiency in SKBR3 caused alteration of epithelial mesenchymal transition (EMT) markers, including downregulation of N-cadherin, Snail1, Fibronectin and Vimentin, but increasement of E-cadherin and ZO-1, accompany with disrupting TGFβ signaling pathways, including downregulation of TGF-β1, p-Smad2 and p-Smad3. However, overexpression of SLC26A9 in SKBR3 resulted in inhibition of cell proliferation, migration and invasion, but promotion of cell apoptosis. Accompanying with activation of TGFβ pathway mediate EMT.
**Conclusions:** Upregulation of SLC26A9 resulted in the development and progression of HER2 positive BC via activation of TGFβ signaling pathways. SLC26A9 might be a novel prognosis marker and therapeutic target for BC.

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18F-FDG-PET/CT and MRI in the assessment of neoadjuvant chemotherapy treatment response in breast cancer. Correlation with pathological response

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**Introduction:** Residual cancer burden (RCB) after neoadjuvant chemotherapy (NAC) can accurately predict disease recurrence and survival in breast cancer. In this context, end of treatment (EOT) image-guided response assessment could be useful to adapt treatment for individual patients. Our main objective was to assess the effectiveness of 18F-FDG PET/CT and MRI in determining NAC response. **Methods**: Patients with surgically resectable breast cancer (stages II-III) were prospectively included and evaluated with 18F-FDG-PET/CT and MRI before and after standard-of-care neoadjuvant chemotherapy (NAC). Ultrasound guided breast biopsy was performed before NAC and pathologic examination with residual cancer burden (RCB) scoring was performed after surgery. Standard uptake values (SUVmax and SUVmean) from baseline PET scans were measured. EOT images results were compared with RCB scores to assess the sensitivity and specificity of (EOT) 18F-FDG-PET/CT and MRI images. A multinomial logistic regression was performed to assess predictors of pathological response. A p-value of 0.05 was considered significant. **Results:** 30 patients were included, with 25% showing complete pathological response. EOT 18F-FDG-PET/CT images had a sensitivity of 55% and specificity of 100% to predict RCB > 0, while EOT MRI had a sensitivity of 65% and specificity of 66,6%. Luminal tumors showed significant lower baseline SUVmean and SUVmax values than triple-negative tumors. Ki67 expression didn´t correlate with treatment outcome. High estrogen receptor expression level was significantly associated with non-complete pathological response and higher false negative rates in both EOT 18F-FDG-PET and MRI images (7/8 in PET and 6/7 in MRI). **Conclusions:** 18F-FDG-PET / CT could be a useful diagnostic tool to assess neoadjuvant chemotherapy treatment response in breast cancer, showing greater specificity than MRI to predict pathological response. A high expression of estrogen receptors could lead to a high rate of false negative findings, both in PET and MRI. A greater number of cases is required to validate these findings.

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Secondary invasive breast events (SIBE) among patients with oncotype DX recurrence scores (RS) 26-30 and >31: Results from a large oncotype database

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**Background:** Oncotype RS is a 21-gene assay used to predict the likelihood of distant recurrence and benefit of chemotherapy in patients with lymph node negative (LN-), hormone positive (HR+) breast cancer (BC). The Oncotype RS is used to identify patients who may be spared chemotherapy in the adjuvant setting without adverse impact on survival or secondary invasive breast events (SIBE). Results of the TAILORx trial (Sparano et al, 2018) provided evidence that chemotherapy can likely be spared for most patients with oncotype RS≤25, with chemotherapy benefit potentially related to chemotherapy-induced menopause. More aggressive endocrine therapy with concurrent ovarian suppression in pre-menopausal women may mitigate the need for chemotherapy among patients with higher RS. We developed a large oncotype database to determine rates of SIBE (ipsilateral recurrence, contralateral breast cancer or metastatic recurrence) among patients with higher genomic risk (Oncotype RS 26-30 and ≥ 31) to determine the benefit of chemotherapy among these groups. **Methods:**We identified 887 patients with early-stage, HR+ BC treated between 2006-2018. Among these patients, 515 had treatment and follow-up data available for SIBE analysis. Median follow-up for SIBE was 62 months with 41 SIBE (8%) including both LN+ and LN- patients. When stratified by RS using conservative cutoffs (Sparano et al, 2018): low risk (≤10), intermediate risk (11-25), and high risk (≥26), 5 year rates of SIBE were 4%, 6% and 16% respectively. The Kaplan Meier method was used to estimate the time to SIBE distributions overall and among different RS groups with the log rank test used to compare distributions between groups. **Results:** Among 887 patients, 616 (69%) were post-menopausal. A total of 654 (74%) patients had surgical management, of which 226 underwent mastectomy (35%) and 428 underwent lumpectomy (65%). Among the 630 patients who received adjuvant therapy, 14 (2%) received chemotherapy alone, 143 (23%) received a combination of chemotherapy/endocrine therapy and 473 (75%) received endocrine therapy alone. Twenty-four patients (3%) refused one or more recommended therapies. Three hundred fourteen patients (50%) also received radiation therapy. Rates of chemotherapy administration were 8% among low RS, 16% among intermediate RS and 82% among high RS patients (73% for RS 26-30 and 90% for RS ≥31). One-hundred eighty six of 887 patients were missing chemotherapy administration data as they were likely treated at another center. Patients with treatment data available and adequate follow up were included in the SIBE analysis (n=515). Among the 27 LN- patients with RS 26-30, twenty (74%) received chemotherapy and the remaining seven (26%) did not. The five year rate of SIBE was 25% among patients who received chemotherapy and 33% among those who did not receive chemotherapy; p=0.5489. Among the 23 LN negative patients with RS ≥31, twenty-one (91%) patients received chemotherapy and the remaining two (9%) did not. The five year rate of SIBE was 0% in both patients who received chemotherapy and in patients who did not receive chemotherapy; p-value not estimable in this subgroup due to no SIBE in either group. **Conclusion**: In this large oncotype database, there was no statistically significant difference in SIBE for patients with higher genomic risk (RS 26-30 and ≥31) whether or not they received chemotherapy. This data was limited by small numbers of patients in these sub-groups. More aggressive endocrine therapy with ovarian suppression has become an alternative option to spare chemotherapy in intermediate risk patients (RS 11-25). This approach may be useful among patients with even higher risk oncotype scores. Prospective randomized studies may be useful to determine utility of chemotherapy among patients with RS ≥26.

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# Phase II neoadjuvant study of GDC-9545 + palbociclib (palbo) vs anastrozole (A) + palbo in postmenopausal women with estrogen receptor-positive, HER2-negative, untreated early breast cancer (ER+/HER2- eBC)

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**Background**

Endocrine therapies (ETs) are the mainstay of ER+ BC management; however, many patients (pts) have disease relapse or develop therapeutic resistance. CDK4/6 and aromatase inhibitors decrease Ki67 expression significantly and are potent in arresting the cell cycle in the neoadjuvant eBC setting. Ki67 is a proliferation biomarker with prognostic value in ER+ BC. Efficacy of ETs relies on induction of cell cycle arrest, and during neoadjuvant treatment, Ki67 scores reflect the ability of ETs to suppress proliferation. Selective ER degraders have also shown efficacy against these tumors. The highly potent, non-steroidal, oral selective ER degrader GDC-9545 has therefore been developed as a monotherapy or in combination with CDK4/6 inhibitors for ER+ BC. Preliminary phase Ib data in postmenopausal women with metastatic BC have shown that oral 100 mg once daily (PO QD) GDC-9545 is well tolerated as a monotherapy and with palbo, with encouraging antitumor activity (clinical benefit rates: 55% without palbo/81% with palbo; clinical benefit observed in pts with prior fulvestrant treatment and in pts with detectable *ESR1* mutations at enrollment) (Lim et al. ASCO 2020; abstract 1023).

We present a phase II, randomized, open-label, two-arm, neoadjuvant study of GDC-9545 vs A in a window of opportunity (WoO) phase, followed by GDC-9545 + palbo vs A + palbo in a neoadjuvant phase, for postmenopausal women with ER+/HER2- untreated eBC (NCT04436744).

**Trial design**

Pts are randomized 1:1 to GDC-9545 or A. The WoO phase will last 14 days; and the neoadjuvant phase, 16 weeks (4 x 28-day cycles) before surgery. GDC-9545 will be given at 30 mg PO QD; A, at 1 mg PO QD. 30 mg GDC-9545 was selected as it is well tolerated with promising anti-tumor activity (Jhaveri et al. SABCS 2019; abstract PD7-05), and no improvement in efficacy is expected at doses > 30 mg. During the neoadjuvant phase, pts will receive 4 x 28-day cycles of GDC-9545 + palbo (125 mg PO QD on days 1-21 of each cycle) or A + palbo.

**Eligibility**

Female pts ≥ 18 years with ECOG performance status 0-1, histologically confirmed invasive breast carcinoma, measurable disease (modified RECIST v1.1), primary tumor ≥ 1.5 cm in its longest diameter (tumor size category at presentation: cT1c [≥ 1.5 cm]-cT4a-c), and Ki67 score ≥ 5% stained nuclei.

**Aims**

The primary efficacy endpoint is mean relative Ki67 score change from baseline to week 2 during the WoO phase. Secondary efficacy endpoints are objective response rate and complete cell cycle arrest (CCCA) rate (proportion of patients with centrally assessed Ki67 scores ≤ 2.7% stained nuclei upon treatment at week 2) in the neoadjuvant phase. Exploratory efficacy endpoints are changes in Ki67 scores from baseline to surgery and from week 2 to surgery, CCCA rate (upon treatment at surgery or post-treatment biopsy), and pathologic complete response rate in the neoadjuvant phase. Safety and tolerability, pharmacokinetics, and biomarkers will also be assessed.

**Statistical methods**

Randomization is stratified by T status (cT1c-cT2 vs cT3-cT4 a-c), Ki67 score (< 20% vs ≥ 20%), and progesterone receptor status (positive vs negative). Ki67 scores will be centrally assessed and measured in percentage scores. Mean relative change at week 2 will be summarized in original percentage scales for each arm, and corresponding 95% confidence intervals will be calculated by normal approximation. Change in mean score between arms will be compared via z-test. Patients with missing central scores at baseline and/or week 2 will be excluded.

**Accrual**

Target enrollment is 215 patients at ~90 sites globally once the study is open for enrollment.

**Contact information**

For more information or to refer a patient, email global.rochegenentechtrials@roche.com or call 1-888-662-6728 (USA only).

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS11-27

# A phase I/II clinical trial of EDP1503 with pembrolizumab for triple-negative breast cancer

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**Background:** Systemic immunity can be regulated via transient interactions of non-colonizing bacteria and immune cells in the small intestinal mucosa. The potential to harness these interactions for IO treatment was first described by Sivan in 2015. EDP1503 is a non-colonizing preparation of a single strain of *Bifidobacterium animalis lactis* that, when administered orally, in preclinical models, invokes an anti-tumor immune response by activation of innate and adaptive immune mechanisms. The pleiotropic effects of EDP1503 are initiated in the small intestine and mediated by interactions with multiple pattern-recognition receptors inducing a proinflammatory signature in human PBMCs, activating CD8 and NK cell IFNγ production and cytolytic activity. Preclinically, EDP1503 inhibits tumor growth as a monotherapy and in combination with anti-PD-1/L1. Single agent PD-1/L1 therapies have showed limited clinical benefit in previously treated triple-negative breast cancer (TNBC) patients. Here, we report the safety, tolerability, and efficacy of EDP1503 in combination with pembrolizumab in patients with TNBC (NCT03775850).
**Methods:** EDP1503-101 is an open label Phase 1/2 study of EDP1503 in combination with pembrolizumab. TNBC subjects who had received ≥ 1 treatment regimen for metastatic disease were enrolled. Prior anti-PD-1/L1 treatment was permitted. Subjects initially receive 14 days of EDP1503 monotherapy orally twice a day (b.i.d) and then EDP1503 b.i.d. in combination with pembrolizumab 200 mg iv every 3 weeks. The initial 3 subjects received 2 capsules of EDP1503 b.i.d. All other subjects received 4 capsules b.i.d. Safety and tolerability were assessed using CTCAE v5.0. Evidence of anti-tumor activity was based on investigator-assessed objective response (OR), by RECIST v1.1 and iRECIST, and disease control rate defined as OR and/or stable disease (SD) after 4 cycles of therapy. Paired biopsies at baseline and day 14 were used to establish PD-L1 status and investigate pharmacodynamic biomarker changes.
**Results:** As of 1 October 2020, 15 TNBC subjects had been treated (median age of 52, median of 2 prior lines of therapy and ECOG of 0-1). Additional subjects are being recruited, up to a maximum of 30. EDP1503 was well-tolerated as monotherapy and in combination with pembrolizumab. 53% of subjects experienced treatment-related adverse events (TRAEs). Most common TRAEs were GI-related: abdominal distension (20%), decreased appetite (20%), diarrhea (13%), flatulence (13%). No Grade 4-5 TRAEs were observed. 1 Grade 3 TRAE (diarrhea) leading to treatment discontinuation was reported. In 12 subjects receiving the 4 capsules b.i.d dose, 2 partial responses (PR) and 1 SD were observed, giving an objective response rate (ORR) of 18% and a disease control rate (DCR) of 27% in evaluable patients (n=11). Both responders had tumor burden reductions of >65% by RECIST. One responder had 4 prior lines of therapy for metastatic disease, including a PD-L1 inhibitor combination, has a PD-L1 combined positive score (CPS) of 30 and has been on study treatment for 192 days with a 66% reduction in target lesions. The only residual lesion is 6 mm which is PET-negative. The other responder had 2 prior lines of therapy for metastatic disease, was checkpoint inhibitor naive, has a PD-L1 CPS of 2 and remained on study treatment for 275 days with a 73% reduction in target lesions before discontinuing due to treatment-related AEs. The patient with SD had also previously relapsed on a PD-L1 inhibitor and was on study treatment for 226 days before progressing.
**Conclusions:** EDP1503 administered with pembrolizumab is safe and well-tolerated with no Grade 4-5 TRAEs or SAEs. Clinical benefit was observed in a subset of TNBC patients treated with the combination of EDP1503 and pembrolizumab. This study is continuing to recruit TNBC patients at the high dose of EDP1503.

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# Duration of chemotherapy-induced nausea and vomiting (CINV) as a predictor of later-cycle CINV

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**Background**: CINV remains a challenging chemotherapy toxicity, particularly for anthracyclines + cyclophosphamide (AC) for breast cancer. Complete response (CR), defined as no vomiting or use of rescue medication over 5 days after chemotherapy, has been the standard endpoint for successful antiemetic prophylaxis, yet duration of prophylaxis treatment failure (i.e., breakthrough CINV) is rarely assessed. Previous work demonstrated that initial cycle breakthrough CINV is associated with at least one subsequent cycle with CINV (Schwartzberg 2011), and that longer duration CINV is associated with more lost work time and impaired activity (Schwartzberg ASCO 2020). We sought to evaluate the duration of breakthrough CINV in cycle one and its association with individual patients' repeat breakthrough CINV in subsequent cycles. **Methods**: Days of CINV was a prespecified endpoint in a prospective, 4-cycle CINV prophylaxis trial of combination netupitant/palonosetron (NEPA) + dexamethasone (Dex) for patients with breast cancer receiving AC; the primary endpoint was CR. Patients without CR were classified as prophylaxis treatment failure (TF) and categorized as short TF (sTF, 1-2 days) or extended TF (xTF, ≥3 days), consistent with work by Ballatori [2006] and Roeland [2019]. We analyzed patients' sequences of CR, sTF, and xTF for cycles 1-4 and assessed likelihood of CR for cycles 2-4 based on cycle 1 TF duration, using chi-square statistics. **Results**: Of 402 patients in cycle 1, 303 had CR and 99 (24.6%) had TF. Duration of TF in cycle 1 was sTF for 48 patients while 51 patients had xTF. Patients with sTF in cycle 1 often experienced CR in cycle 2 (32/46 remaining patients; 69.6%) while patients with xTF in cycle 1 often had TF in cycle 2 (38/49; 77.6%). Patients had >84% likelihood of repeating their cycle 2 outcome (CR or TF) in cycles 3 and 4. Over all cycles, those with sTF in cycle 1 had CR in 75/108 later cycles (69.4%) while xTF in cycle 1 led to CR in 32/105 later cycles (29.0%), p<0.001) (see Table). Duration of later-cycle TF was typically consistent with initial cycle TF duration (p=0.046). As a predictor of later cycle TF, xTF had a positive predictive value of 0.695, with sensitivity of 0.689 and specificity of 0.701. Those with xTF in cycle 1 had 2.28 times the relative risk of later TF (CI 1.67-3.11; p<0.001) vs those with sTF. The absolute increase in risk from xTF was 40.4%. **Conclusions**: Although the majority of patients receiving NEPA + Dex as prophylaxis for AC in breast cancer successfully avoided breakthrough CINV, for patients with prophylaxis treatment failure, CINV duration in cycle 1 strongly predicted their future likelihood of CINV. Patients with extended (≥3 days) breakthrough CINV in cycle 1 had CINV again in over 2/3 of later cycles; conversely those with short breakthrough CINV in cycle 1 avoided CINV entirely in over 2/3 of later cycles. The markedly higher risk faced by patients with initial-cycle extended CINV is both statistically significant and clinically meaningful, due not only to its longer duration and risk-prediction but also to previously demonstrated worsening of work loss and impaired activity. Clinicians should monitor breakthrough CINV duration, seek to avoid extended CINV, and consider changing antiemetic prophylaxis when extended CINV does occur. Further study is needed to confirm this finding in other chemotherapy regimens and with other triple prophylaxis regimens.

Impact of Extended CINV in Cycle 1 on CINV in Later Cycles

| | **TF1** | | | | | **P value** |
|---|---|---|---|---|---|---|
| **Initial Cycle Result** (n/total initial cycles) | **Total TF1** (99/402) | **Short TF1** (48/99) | | **Extended TF1** (51/99) | | **Short vs Extended TF1** |
| **Later CR cycles** (n, % of total later cycles) | 107 (50.2%) | 75 (69.4%) | | 32 (29.0%) | | <0.0001 |
| **Later TF** (n, % of total later cycles) | 106 (49.8%) | 33 (30.6%) | | 73 (71.0%) | | |
| **Duration of Later TF** (n, % of all later TF) | | **Later sTF** | **Later xTF** | **Later sTF** | **Later xTF** | 0.046 |
| | | 20 (60.6%) | 13 (39.4%) | 29 (39.7%) | 44 (60.3%) | |
| **Total later cycles** (n, %) | 213 (100%) | 108 (100%) | | 105 (100%) | | |
| TF: prophylaxis Treatment Failure; TF1: TF in cycle 1; CR: Complete Response (0 days TF); CR1: CR in cycle 1; sTF: Short (1-2 days) TF; xTF: Extended (≥3 days) TF | | | | | | |

**2020 San Antonio Breast Cancer Symposium®**

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# Integrated immuno-genomic analyses in early breast cancer: Results from the Scandinavian breast group 2004-1 (SBG-2004-1) randomized phase II trial

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**Background:** Given the emerging role of immune-related biomarkers in breast cancer (BC), little is known about specific immune cell composition patterns and genomic alterations and how these could interact in early BC setting. The aim of this proof-of-principle study is to describe immuno-genomic correlates within the tumor microenvironment using newly developed techniques for multiplexed fluorescent immunohistochemistry (mfIHC, Mezheyeuski et al., J Pathol. 2018) and high-throughput low-input genome sequencing (CUTseq, Zhang et al., Nat Commun 2019). **Methods**: The randomized SBG-2004-1 phase II trial evaluated the feasibility of tailored and dose-dense epirubicin and cyclophosphamide followed by docetaxel (EC→T) as adjuvant chemotherapy for early BC, enrolling a total of 124 patients. CUTseq was applied to gDNA extracted from archival low-input formalin-fixed paraffin-embedded (FFPE) tissue as well as peripheral blood samples of BC patients. mfIHC was performed on FFPE tissue microarrays, allowing simultaneous detection of six immune markers (CD4, CD8, PD-L1, PD-1, FoxP3, CD68) and quantification in an automated and tissue-compartment manner (Vectra® Polaris™ automated quantitative pathology imaging system and inForm® software, Akoya Biosciences). Patient characteristics and 10-year follow-up data were also available. Associations of different immune cell patterns and DNA copy number alterations (CNAs) with clinicopathological parameters and survival outcomes were evaluated using standard statistical methods.**Results:** 69**/**124 (55.6%) and 82**/**124 (66.1%) FFPE samples were available for CNA profiling (blood gDNA for normalization, n=33) and mfIHC, respectively. *MYC* gene was the most commonly amplified cancer-associated gene (*n*=44, 63.8%), and other frequent alterations included *ERBB2* (*n*=31, 44.9%) and *PIK3CA* (*n*=14, 20.3%) amplification as well as *TP53* (n=29, 42%) and *PTEN* (n=16, 23.2%) deletion. CNA burden (*i.e.*, the percentage of the genome either amplified or deleted) was significantly correlated with higher tumor grade (p=0.013) but was not prognostic for relapse-free survival. CD4+ T-cells were the most abundant immune cell subpopulation, followed by CD68+ macrophages. The immune checkpoint markers PD-L1 and PD-1 were mostly expressed in CD4+ T-cells in both tumor and stroma compartments**,** while stromal PD-1+CD8+ and PD-1+CD68+ cell subsets were also among the ones with the higher cell density. CD4+ T-cell density was significantly correlated with tumor size, whereas the different immune cell infiltration patterns were not found to be prognostic. Combined immuno-genomic analyses revealed that high CNA burden was inversely associated with intra-tumoral CD4+ (Spearman's r=-0.33, *p*=0.01) and CD8+ infiltration (Spearman's r=-0.37, *p*=0.004). **Conclusions:** The present study indicates the feasibility of CNA profiling by CUTseq and immuno-profiling by mfIHC in FFPE samples obtained from BC patients. Moreover, our data provide a link between genomic alterations and the immune landscape in early BC and set the basis for further application of CUTseq and mfIHC in larger patient cohorts.

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# Molecular evaluation of immunogenicity and genomic alterations in invasive lobular breast cancer

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**Background:** Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer and accounts for 10-15% of all cases. Though ILC has distinct clinical, prognostic and molecular features, studies are limited and include few patients. ILCs show a decreased response to neoadjuvant chemotherapy and an increased resistance to endocrine therapy. Thus, there is a great need to identify alternative therapies, such as immunotherapy, that could improve overall survival. Success of immunotherapy largely depends on tumor immunogenicity which varies with histologic type. Determination of predictive and prognostic biomarkers for ILC will help determine who can benefit the most. Our study investigates canonical markers of immunogenicity - PD-L1 expression and Tumor Mutational Burden (TMB) - in patients with ILC compared to invasive ductal carcinoma (IDC). We further correlate these markers in different subtypes i.e. hormone receptor positive (HR+), HER2 positive (HER2+), and in triple negative breast cancers (TNBC). We also analyze differences in immune cell profiles constituting the tumor microenvironment (TME) and differences in genomic alterations between ILC and IDC. **Methods:** A retrospective data analysis was performed to identify breast cancer tumors with ILC or IDC histology profiled at Caris Life Sciences (Phoenix, AZ) that were tested for PD-L1 by SP142 assay and had whole transcriptome sequencing data available. ILC and IDC cases were further subtyped as HR+ and HER2+ and TNBC. PD-L1 expression in immune cell was assessed using Ventana PD-L1 (SP142) histochemical assay and PD-L1 expression in tumor cell was assessed by laboratory developed test using SP142 clone with staining higher than 2+ considered positive. TMB was measured by counting somatic non-synonymous missense mutations on the 592 gene panel (Nextseq) next generation sequencing (NGS) assay, and ≥ 10 mutations/megabase (mut/Mb) was considered high. Using the whole transcriptome RNA sequencing (NovaSeq) data we analyzed the difference in immune cell profiles constituting the TME using a computational RNA deconvolution approach. NGS was used to identify significant differences in genomic alterations between ILC and IDC. **Results:** We identified 1,359 breast cancer patients (ILC: 194 vs IDC: 1,165). Among ILC, 79% were HR +, 11% TNBC, <2% HER2+ and the rest were of unclear subtype, compared to 55% HR +, 31% TNBC, 10% HER2+ in the IDC group. PD-L1 expression in immune cells was lower in ILC (PD-L1≥ 1% ILC: 13% vs. IDC: 35% p <0.0001; PD-L1>10% ILC: 1% vs. IDC: 5% p=0.017). PD-L1 expression in tumor cells was also lower in ILC (ILC 1% vs
IDC 5%; p =0.0136). All subtypes of ILC had lower PD-L1 expression in immune and tumor cells when compared to IDC. TMB was similar and comparable in IDC and ILC (median TMB 7 mut/Mb). Assessment of TME showed a significantly increased abundance of cytotoxic lymphocytes and monocytic cells in IDC, and stromal endothelial cells in ILC. Androgen receptor (AR) expression, and mutations in CDH1 (ILC 76% vs IDC 2%) and PIK3CA (ILC 44% vs IDC 30%) were more common in ILC. CDH1 mutation was significantly higher in both TN ILC (ILC 60% vs IDC 1%; p<0.05) and HR+ ILC (77% vs IDC 2%; p<0.05) subtypes of ILC. TP53 mutation was lower in ILC (ILC 26% vs IDC 65%) irrespective of subtype. **Conclusion:** In summary, PD-L1 expression in immune cells and tumor cells was lower in ILC, however TMB was comparable between ILC and IDC. Immune cell profiling supports a cold or less immunogenic TME for ILC. A composite immune biomarker may be able to better characterize immunogenicity of ILC.

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Oncogenetic caracterization and imunohistochemistry patterns of male cancer breast diagnosticated in Haroldo JuaÇaba hospital, Northeast of Brazil

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**INTRODUCTION:** The male breast cancer (MBC) is a rare disease, responsible for about 0.2% of all cancers and 0.1% of deaths for male cancer. Despite the rarity of the disease, statistics indicate that the incidence of MBC has been increasing significantly. The main risk factors for the development of MBC include old age, hormonal imbalance, radiation exposure, and family history of breast cancer. Hereditary breast and ovarian cancer (HBOC) is a syndrome associated with mutations in the BRCA1 and BRCA2 genes that have been related to MBC that as a rare disease, still poorly understood.
**METHODOLOGY:** Family history analyzes, type and tumor staging, molecular markers expression, hormone receptors (RE, RP, and HER2), and cell proliferation marker (KI67) analysis were performed by immunohistochemistry. The presence of genetic mutations and the frequency of these mutations were evaluated in 31 genes of HBOC suspected patients treated at the Haroldo Juaçaba Hospital between the years 2009 to 2020.
**RESULTS:** A total of 236 patients were diagnosed with breast cancer and submitted to a genetic test. Six of them were male patients aged between 54 and 73 years. His family history indicated that 83.3% had first-degree relatives affected by breast cancer. Different pathological staging was founded after tumors evaluation with the presence of micrometastases (P3) and higher levels of invasion in the lymph nodes. The expression of the cell proliferation marker (KI67) indicated low levels of expression except for patient P5. All patients presented expression of two hormone receptors (ER and RP) and no expression for HER2, except for one patient (P1), who had bilateral breast cancer, with HER2 expression (+2) on the right breast (first tumor) and no RP and HER2 expression in the left breast (second tumor), besides a moderate expression of KI67 (40%) (Table 1). The oncogenetic evaluation indicated that 83.33% of the patients had mutations described in the clinical database (ClinVar) 60% of them were pathogenic. The variants founded were in the PALB2 (16.66%), BRCA1 (33.33%), and BRCA2 (33.33%) genes (Table 1). The pathogenic mutations founded were located in the BRCA 1 and BRCA2 genes. One patient (P5) did not present mutations or VUS. The patient without the mutation (P5) presented a tumor with T3N1 pathological staging, low expression of estrogen (10%) and progesterone (10%) receptors, absence of HER2 expression, and high capacity of proliferation, indicated by the expression of KI67 (80%). The results indicate heterogeneity in the histological and molecular patterns of the patients evaluated, besides the oncogenetic patterns that may be associated with HBOC, especially those whose variants founded were pathogenic.**CONCLUSION:** Due to the low frequency of male breast cancer, the oncological data of these patients are relevant for epidemiological, pathological, and oncogenetic characterization, improving the characterization and identification of patterns for this pathology.Research Sponsor: Ministerio da Saude, Brasil (PRONON)

**Table 1.** Histopathologic molecular markers and variation gene characterization of male breast cancer evaluated in Hospital Haroldo Juaçaba, Northest of Brazil, between 2009 and 2020. *VUS #Pathogenic variation.

| | **Age** | | **Familiar history** | | | | **Molecular markers** | | | | **Variation** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient** | **Diagnostic** | **Last clinical evaluation** | **BC** | **Other** | **Subtype tumor** | **Pathological staging** | **RE** | **RP** | **HER2** | **KI67** | **Gene** | **Specificity** |
| P1 | 48 | 57 | Yes | Pancreas; CCP | LUMINAL A | (R) pT1cpN1a(L) pT1B | (R) 80% (L) 80% | (R) 20%(L) negative | (R) +2(L) negative | (R) 18% (L) 40% | PALB2* | c. 3257G>A:Arg1086Gln |
| P2 | 72 | 74 | Yes | No | LUMINAL B | (L)pT2 pN3a | 90% | 100% | Negative | 20% | BRCA1* | c. 754C>T:Arg252Cys |
| P3 | 64 | 66 | No | No | LUMINAL A | pT2pN1mic | 90% | 70% | Negative | 10% | BRCA1# | c. 5266dupC: p.Gln1756Pro fs74 |
| P4 | 54 | 57 | Yes | No | LUMINAL A | (L)T4bN2 | 90% | 90% | Negative | 10% | BRCA2# | c. 4808delA: pAsn1603Thr fs14 |
| P5 | 58 | 58 | Yes | Prostatic | LUMINAL A | (R) T3N1 | 10% | 10% | Negative | 80% | Not detected | Not detected |
| P6 | 58 | 58 | Yes | Prostatic | LUMINAL B | (R) T4dN0 | 60% | 60% | Negative | 30% | BRCA2# | c. 4808delA: pAsn1603Thr fs14 |

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# Benefits of a rapid diagnostic centre for breast cancer care during the COVID-19 pandemic

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**BACKGROUND**: Changes in access to breast imaging and suspension of mammographic screening during the COVID-19 pandemic had the potential to significantly delay breast cancer diagnostic pathways. The Gattuso Rapid Diagnostic Centre (GRDC) is an innovative clinic that provides a patient-centered approach for investigation of suspicious breast abnormalities and sees approximately 1200 patients per year. The aim of this study was to assess the impact of the pandemic on patient volumes and imaging at this high-volume breast rapid diagnostic centre.
**METHODS**: A retrospective review of consecutive patients who presented to the GRDC from the start of the pandemic (March 12, 2020) until May 31, 2020 was performed. The number of patients, reason for referral, cancer detection rate (CDR), and waiting time from appointment to diagnosis were evaluated and compared to a corresponding time period in 2019.
**RESULTS**: A total of 168 new patients presented to the GRDC during the study period, corresponding to a 32.3% decrease in the number of patients compared to 2019 (n=248). Seventy-eight patients (46.4%) were referred due to the presence of a clinical palpable abnormality, which represented an increase of 13.8% (n=81 [32.7%] in 2019; p=0.005). Out of 168 patients, 69 were diagnosed with a breast malignancy, yielding a CDR of 41.1% during the pandemic versus 111 patients in 2019 (CDR of 44.8%; p= 0.456). The average time from appointment at GRDC to diagnosis was lower at 0.76 days vs 1.21 days in 2019. The rate of same day diagnosis was significantly higher at 39.5% vs 27.0% in 2019 (p=0.008). Twenty-five patients (14.9%) received neoadjuvant systemic therapy compared to 16 patients (6.5%) in 2019 (p=0.005). **CONCLUSION**: There were fewer patients presenting for breast investigations during the pandemic period and a significant increase in the percentage of patients with palpable masses as the cause for referral with no appreciable change in the CDR. The presence of a rapid diagnostic breast center enabled patients with concerning breast symptoms to access and receive expedited assessment. This ensured patients did not undergo diagnostic delays despite the health care restrictions that emerged during the COVID-19 pandemic.

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Small extracellular vesicle-mediated intercellular TGF-β1 transferring promotes adriamycin-resistant transmission in breast cancer cells

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Chemotherapeutic resistance is a major obstacle to control of advanced breast cancer (BCa). We have previously shown that small extracellular vesicles (sEVs) can transmit adriamycin resistance between BCa cells. Here, we demonstrate that sEV-TGF-involves in intercellular drug-resistant transmission from adriamycin-resistant cells to adriamycin-sensitive cells. sEVs were isolated and characterized form the both sensitive and resistant cells. sEVs derived from the resistant cells were incubated with the sensitive cells and resulted in transmitting the resistant phenotype to the recipient cells. Cytokine antibody microarray revealed that most metastasis associated cytokines present at the high levels in sEVs from the resistant cells compared to their levels in sEVs from the sensitive cells, particularly TGF-β1. The sEV-TGF-β1 led to phosphorylation of Smad2/3 and remarkably changed the phenotypes of the recipient cells by suppressing apoptosis and enhancing cell movability. Finally, the sEV-TGF-mediated drug-resistance transmission was validated using a zebrafish xenograft tumor model. The results from this study elaborated that sEV-TGF-β1 intercellular transfer contributes to adriamycin resistance in BCa.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS9-27

# Estimation of clinical benefit and economic burden for using a commercial 70-gene signature test for Brazilian breast cancer patients in the public health system

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**Background**
The clinical benefit of adjuvant chemotherapy (CT) for breast cancer (BC) depends on several factors, like menopausal status, stage and molecular subtype. Commercial available gene signatures make possible a more accurate selection of the patients who could benefit more with adjuvant chemotherapy. In Brazil, gene signatures are not available to public health system users, nor even reimbursed for privately insured patients, making this matter a major cause of frustration for patients and oncologists. MINDACT trial evaluated 70-gene signature MammaPrint (70-GS) as predictive test for chemotherapy benefit. Long-term follow up showed premenopausal patients who had not received CT and were in in the high clinical risk/ low genomic risk group presented unfavorable outcomes. We aimed to estimate clinical impact and economic burden that a hypothetical access to 70-GS may result based on a Brazilian BC population treated in a university hospital.

**Methods**
Medical records from BC patients who received neo/adjuvant chemotherapy from January/2018 to June/2020 at the Hospital das Clínicas de Ribeirão Preto - USP (HCRP-USP) were retrospectively analyzed. The following inclusion criteria were considered to select patients who could benefit most with 70-GS: stage I or II invasive BC, tumors smaller than 5 cm, up to three positive lymph nodes (LN+), postmenopausal status and HR+/HER2- (hormone receptor-positive, HER2-negative) tumors. Online search for costs and reimbursed values. The Brazilian public health system reimburses clinics R$ 571 (US$ 107) (US$ 1=R$ 5.32; July 1, 2020) each month a patient receives adjuvant CT for stage I BC and R$ 800 (US$ 150) each month for stage II BC. The 70-GS test, purchased privately, costs R$ 15,000 (US$ 2,820). The study was approved by the local ethics committee (HCFMRPUSP no 4.078.614).

**Results**
From Jan/2018 to June/2020, 311 patients were treated with neo/adjuvant chemotherapy. Mainly 4 cycles of AC (doxorubicin-cyclophosphamide), 8 cycles of ACT (AC + docetaxel or paclitaxel) or 4 cycles of TC (docetaxel-cyclophosphamide) regimens were delivered, which lasted from 3 to 6 months. For an entire CT period, we estimate the maximum reimbursement amount of R$ 4,800 (US$ 752) (6 months for stage II BC). In our population, patient who received CT, according to subtypes, were 174 (56%) HR+/HER2-, 30 (10%) HR+/HER2+, 38 (12%) HR-/HER2+ and 69 (22%) triple-negative. Among RH+/HER2-, 96 (55%) were postmenopausal BC, 77 (44%) were premenopausal BC and one was male BC (1%). Taking in accountpostmenopausal stage I and II BC, tumors <5 cm and ≤3 LN+, a total of 54 patients who received CT (17%) would be candidates to 70-GS testing. For this group, the maximum reimbursement with CT would be R$ 259,200 (US$ 48,722) while the costs with 70-GS would be R$ 810,000 (US$ 152,280).

**Conclusions**
Among 311 patients who received CT at our institution, 54 met the inclusion criteria we chose as the most beneficial to perform 70-GS test. Considering that MINDACT trial found that 46% of high clinical risk may not require CT, approximately 25 patients (8%) could have avoided CT, saving R$ 120,000 (USS$ 22,556). The 70-GS test valuation for the public health system, considering only savings from chemotherapy, would be R$ 2,222 (US$ 418) and the current cost of 70-GS is 6.75 times higher than the money saved. Additional pharmacoeconomic analyses should include the estimated costs of early and late toxicities (i.e. febrile neutropenia, leukemia and cardiotoxicity) for this population, which can reduce the difference between the cost of 70-GS test and the amount saved. A national agreement between the company and the government could also contribute to increase access and make treatment de-escalation a reality also in lower-middle-income countries.

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Consumption of a high-fat diet rich in linoleic acid promotes mammary tumor growth

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**Consumption of high-fat diets rich in linoleic acid promotes mammary tumor growth**

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**AbstractBackground:** The most recent Dietary Guidelines in 2015-2020 for Americans from the U.S. Department of Health and Human Services (DHH) and U.S. Department of Agriculture (USDA) recommends a healthy eating pattern with more oils but less saturated fats. Oils predominantly consist of unsaturated fats with either monounsaturated or polyunsaturated fatty acids (FAs). As high fat diets (HFDs) contribute to obesity, which increases the risk of breast cancer, in this report we evaluate whether the consumption of HFDs rich in different unsaturated fatty acids induces similar degrees of obesity and further determines the impact of different oils on mammary tumor growth using our unique murine mouse models. **Hypothesis:** Consumption of different oils impacts obesity-associated mammary tumor development. **Methods:** Weaned C57BL/6 wild type (WT) mice and epidermal fatty acid binding protein (E-FABP)-deficient (genetically depleted E-FABP) female mice were randomly grouped and fed either a safflower oil HFD (45% fat, rich in 18:2 polyunsaturated FAs) or an olive oil HFD (45% fat, rich in 18:1 monounsaturated FAs), or a control low fat diet (LFD). After 5 months on the diets, E0771 mammary tumor cells ($0.5x10^6$/mouse) were injected into the mammary fat pad and tumor volume was measured at 3-day intervals for tumor growth. Immune cell phenotype and functions were evaluated before and after tumor injection. The student's t-test and/or ANOVA were used to compare immune cell function, obesity and tumor sizes in WT and E-FABP-/- mice, respectively. **Results:** Compared to the LFD diet, consumption of either safflower oil HFD or olive oil HFD was able to induce a similar degree of mouse obesity in WT mice. E-FABP deficiency has no obvious impact on HFD-induced mouse weight increase. Interestingly, while safflower oil-induced obesity significantly increased mammary tumor growth, olive oil-induced obesity did not
promote mammary tumor growth when compared to LFD-fed lean mice. Immunophenotypic and functional analyses showed that mice on the safflower oil diet exhibited lower numbers of CD8+ T cells with reduced production of TNFa than mice on the olive oil diet or LFD. Moreover, safflower oil-associated tumor growth was compromised in mice genetically lacking of E-FABP expression. Mechanistically, E-FABP expression in T cells, especially in CD8+ T cells, mediated 18:2 linoleic acid-induced ROS production and T cell death, thus leading to impaired anti-tumor immunity in safflower oil-fed obese mice.**Impact:** Although oils are healthy dietary components as recommended by DHH and USDA, different oils exhibit diverse immunoregulatory effects *in vivo*. Overconsumption of oils with 18:2 FAs may cause obesity-associated breast cancer development.

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# From theory to practice: Impact of aromatase inhibitors in the bone health of women with early breast cancer

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**Background**: Aromatase inhibitors (AI) are extensively used as adjuvant endocrine therapy in post-menopausal women with hormone receptor positive early breast cancer (HR+ EBC), but their impact on bone health is not negligible. They decrease bone mineral density, accelerate osteoporosis and lead to increased risk of fractures, thus impairing quality of life. Identification of patients at higher risk would be helpful for best treatment decisions. Recommendations have been published for bone health preservation but real-world data regarding implementation and adherence to these recommendations is scarce. This work aimed to assess bone loss, fracture incidence and risk factors associated with these events, as well as the prognostic influence of fractures in women undertaking adjuvant AI.
**Materials and Methods:** In this retrospective cohort study, we have evaluated women with HR+ EBC under adjuvant therapy with AI, during a 3-year period. A minimum of 3 months under AI and 3 years of follow-up after AI start were necessary for inclusion. Statistical analysis of collected data was performed using R 3.5.2, R-Studio 1.1.456 and Stata 15.1 software.
**Results:** 451 eligible women were reviewed (median age 68 years, 30-98 min-max). Median time under AI was 40 months (3-114). Baseline bone densitometry, carried out in only 69% patients, showed abnormal results in 75%, but only 69% and 16% started calcium/vitD supplementation and bisphosphonates therapy, respectively. A fracture event occurred in 8.4%, mostly in the radium and femoral neck and in women with higher age (p=0.006). This group also showed lower T-scores at lumbar spine and femoral neck (p=0.067). On multivariate analysis, age (OR 1.04, 95% CI 1.01-1.07, p=0.016) and time under AI (OR 1.02, 95% CI 1.00-1.03, p=0.045) were independent predictors of fracture events, with a fair discrimination (AUC 0.71). Analysis of disease-free survival according to fracture event varied between groups disfavouring the fracture cohort (at 73 months, survival 78.6%, 95% CI, 47.6-92.4 vs. 95.6%, 95% CI, 91.2-97.8, p=0.027). The multivariate model confirmed the prognostic impact of fracture occurrence (adjusted-HR of 3.17, 95% CI 1.10-9.11; p=0.032).
**Conclusion**: Bone health is often forgotten, despite its great impact in survivorship. Our results suggest a pathophysiologic link between EBC and bone metabolism, potentially estrogen-mediated, which translates into EBC recurrence. Further research in this area may help refining these findings. Moreover, early identification of women at higher risk with individualized treatment plans comprising shorter duration of AI is warranted. Poor adherence to existing guidelines is a crucial barrier to effective approaches to bone health.

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# Trends in breast cancer mortality in Brazil - a 14-year registry-based study

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**Background:** Breast cancer (BC) is the leading cause of cancer-related deaths among women worldwide. BC mortality rates have been decreasing over the past decades in the developed countries. In the United States, BC mortality declined on average 1.5% each year over 2008-2017. Given the paucity of BC mortality data in Brazil, we sought to characterize BC mortality trends in southeastern Brazil and its relationship with demographic variables.
**Methods:** A cross-sectional registry-based analysis was conducted to describe BC mortality trends in the State of Sao Paulo (Brazil) from 2004 to 2017. Sao Paulo is the most populous state in Brazil, with 45.5 million inhabitants, corresponding to 21.8% of the country's total population. BC-related death records, including gender and age were collected from SEADE Foundation's database, an official entity charged with generating statistical data for the State of Sao Paulo. Mortality rates are expressed in units of deaths per 100,000 individuals per year. The annual percentage change (APC) was calculated to identify mortality trends over the period. Trend analysis was carried out by linear regression and an increase or decrease in trend was considered statistically significant when p-value < 0.05.
**Results:** From 2004 to 2017, 52,005 deaths from BC were recorded in the State of São Paulo, Brazil. Average annual mortality was 8.96/100,000 (17.38/100,000 for females and 0.11/100,000 for males). Average mortality rates were higher in the age group over 65 years-old (46.47/100,000). BC mortality rates remained stable during the period analyzed (APC 0, 95%CI -0.2% to +0.3%, P = 0.9) for both females (APC 0, 95%CI -0.3% to +0.2%, P = 0.7) and males (APC +2.4%, 95%CI -1.7% to +6.6%, P = 0.2). Among females, an increasing BC mortality trend was detected for patients under 40 years-old (APC +2.4%, 95%CI +1.6% to +3.2%, P < 0.0001) and remained stable for the age groups between 40 - 65 years-old (APC -0.3%, 95%CI -0.7% to +0.1%, P = 0.1) and over 65 years-old (APC -0.1%, 95%CI -0.4% to +0.2%, P 0.5).
**Conclusion:** In contrast with data from other developing countries, a stable BC mortality has been demonstrated in southeastern Brazil over a 14-year period for the general population. However, a significant increase in BC mortality rates has been demonstrated among patients under 40 years-old.

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# A phase II proof-of-concept study of palbociclib (P) rechallenge in patients (pts) with hormone receptor (HR)[+]/HER2[-] metastatic breast cancer (MBC) and clinical benefit to prior P-based treatment (BIOPER)

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**Background:** The addition of a cyclin-dependent kinase 4-6 inhibitor (CDK4/6i) to letrozole or fulvestrant significantly improves progression-free survival (PFS) and overall survival (OS) in HR[+]/HER2[-] MBC pts. At present, the optimal endocrine treatment (ET) after progression on a CDK4/6i remains unknown. However, preliminary findings revealed drivers of adaptive resistance more frequently related to ET than to CDK4/6i. BIOPER explored the efficacy and safety of continuing the same CDK4/6i in combination with a different ET agent beyond progression on prior P-based regimen in HR[+]/HER2[-] MBC and assessed predictive biomarkers to identify those pts who are more likely to benefit from this strategy. **Methods:** BIOPER (NCT03184090) is a multicenter, non-controlled, phase II trial. Eligible pts included pre- and post-menopausal women aged ≥18 years with HR[+]/HER2[-] MBC that showed a confirmed progressive disease (PD) after having achieved clinical benefit (response or stable disease ≥24 weeks) on immediately prior P plus ET-based regimen. Up to two prior ET lines and not more than one line of prior chemotherapy for MBC were allowed. Pts received P (oral, 75/100/125 mg/day 3 weeks on/1 week off) combined with ET of physician's choice (including tamoxifen, exemestane, fulvestrant, anastrozole, or letrozole) until PD or unacceptable toxicity. Co-primary endpoints were clinical benefit rate (CBR) -in terms of complete or partial response [PR] and stable disease lasting ≥24 weeks as per RECIST 1.1 (H0: CBR≤5% versus H1: CBR≥20%)- and tumor molecular alterations in the cyclin D-CDK 4/6-retinoblastoma pathway detected at baseline as markers of resistance and sensitivity to P rechallenge. Secondary endpoints included investigator-assessed PFS, objective response rate (ORR), OS, and safety using the Common Terminology Criteria for Adverse Events (AEs) 4.03. **Results:** Between June 15, 2017 and April 25, 2019, a total of 33 pts from 21 centers in 2 countries were enrolled. Among the 33 pts who were included in the safety set, 1 patient who did not achieve clinical benefit on prior P-based regimen was excluded from the efficacy analysis (n=32). The median age was 59.5 years (range 42-80 years) and all pts were post-menopausal. A total of 25 (78.1%) pts had visceral disease (56.3% of whom with liver metastases), 16 (50%) had ECOG 0, and 19 (59.4%) presented ≥3 metastatic sites. Of 32 pts, 15 (46.9%) received letrozole, 14 (43.8%) received fulvestrant, and 3 (9.4%) exemestane. The median PFS for the prior P-based regimen was 13.8 months (mo) (95% confidence interval [CI] 5.6-47.1 mo). The median number of prior ET and chemotherapy lines for MBC was 2 (range 1-4). By the data cutoff date, 26 PFS events occurred, 5 pts were still on treatment, and 1 patient discontinued treatment because of investigator's decision. The CBR was 34.4% (95% CI 18.6-53.2%) reaching the prespecified primary endpoint. The ORR was 3.1% (95% CI 0.1-16.2%) with 1 patient with PR. The median PFS was 2.6 mo (95% CI 1.8-5.5 mo). With a median follow-up of 11.8 mo, the OS data were immature with a total of 8 deaths (25%). The incidence of all grade (G) and G 3 or 4 (G3-4) AEs were 90.9% and 48.5%, respectively. The most common G3-4 AEs were neutropenia (42.4%) and leukopenia (6.1%). No discontinuations due to AEs and treatment-related deaths occurred. A comprehensive molecular tumor profiling will be presented during the symposium. **Conclusions:** Prolonging CDK4/6 blockade beyond progression on prior P-based treatment achieved the prespecified clinical benefit among pts with HR[+]/HER2[-] MBC. This strategy is currently being evaluated in the randomized phase II PALMIRA trial. Further research is ongoing to identify patient subgroups who could benefit from this treatment strategy.

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# A prospective multicenter study evaluating the impact of the 21-Gene Breast Recurrence Score® upon physician treatment decision and cost in lymph node-positive breast cancer patients in Quebec

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**Background**: Locoregional lymph node involvement has historically been used as the most important deciding factor for the administration of chemotherapy in the adjuvant setting of breast cancer patients. The 21-gene Breast Recurrence Score® assay (the assay) is emerging as an important tool to assist with chemotherapy decisions amongst hormone receptor (HR)-positive, node-positive breast cancer (BC) patients. Previous studies have suggested that node-positive patients with low Recurrence Score (RS) results do not benefit from chemotherapy. We wanted to better understand the impact of the assay upon physician treatment decisions and treatment cost in this patient cohort.

**Methods:** We conducted a multicenter prospective observational trial for ER/PR-positive HER2-negative BC patients that have undergone surgical treatment for T1-T3 disease and 1-3 positive lymph nodes. Physicians were required to complete a questionnaire indicating treatment choice prior to and post availability of Recurrence Score results. Patients were enrolled in the study from the time of consent to 6 months after the start of adjuvant therapy. The primary endpoint was change in the physician's recommendation for chemotherapy prior to and post assay results. Secondary endpoints include the change in recommendation for additional growth factor (GF) supportive therapy, change in physician's expressed level of confidence, and changes in estimated cost of recommended treatments prior to and post assay results.

**Results:** 70 patients were enrolled between March 2018 and September 2019 at five hospital centers, as part of the McPeak Sirois Group of Quebec. The median age of the cohort was 61 years (range, 38 to 82 years). 18.5% (n=13) of the cohort consisted of patients < 50 years, and 81.4% (n=57) were > or = to 50 years. 64.3% (n=45) of the patients had one positive lymph node and 35.7% (n=25) of the patients had 2 or 3 positive lymph nodes. 25.7% (n=18) of the patients had a RS < 11 and 68.6% (n=48) had a RS result between 11-25. For the entire cohort, we found that the proportion of patients for whom chemo-hormonal therapy was recommended was reduced by an absolute 67.1% by knowledge of the RS result (OR (odds of having chemo-hormonal therapy post-RS recommendation versus pre-RS recommendation) = 0.03 [95% CI: 0.01-0.08]; P<0.0001). The RS results led to an absolute reduction in physician recommendation in chemo-hormonal therapy by 38.5% for patients < 50 years, and by 73.7% of patients (OR=0.02 [95% CI: 0.01-0.06]; P <0.0001) for patients > or = to 50 years. Changes in treatment recommendation were identified for patients with one positive node, 73.3% (OR=0.02 [95% CI: 0.01-0.07]; P<0.0001); and for patients with two or three positive nodes, 56.0% (OR=0.06 [95% CI: 0.02-0.23]; P<0.0001). Recommendations for GF supportive therapy due to RS results decreased by 42.6% (OR=0.16 [95% CI: 0.07-0.34]; P <0.0001). Moreover, RS results led to an increase in confidence in physician treatment decisions for 68.6% of patients (OR=18.3 [95% CI: 7.90-42.28]; P <0.0001). We found that the cost of chemotherapy, in addition to anti-emetics and GF supportive therapy, decreased by 69.9% per patient (pre-RS mean, $3,968 CAN; versus post-RS mean, $1,196 CAN) (P <0.0001).

**Conclusions:** Overall, we found that the 21-gene Breast Recurrence Score® assay changed physician treatment decisions in about two-thirds of all patients with hormone receptor-positive, node-positive BC, regardless of the number of positive nodes (up to 3). The assay increased physician confidence and was associated with an important decrease in treatment cost. Taken together, the assay is a cost-effective approach that can decrease the use of chemotherapy amongst HR-positive, node-positive BC patients in Quebec.

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# The predictive value of tumor-infiltrating lymphocytes and PD-L1 expression on the efficacy of neoadjuvant trastuzumab plus chemotherapy in HER2-positive breast cancer

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**Background:**Many studies have explored the predictive factors for the efficacy of neoadjuvant therapy in HER2 + breast cancer. However, no reliable and widely used biomarker was found till now except several clinicalpathologic factors including HER2. HER2 oncogene can regulate the recruitment and activation of tumor-infiltrating immune cells (TILs) and trastuzumab therapeutic effects by inducing programmed death ligand 1 (PD-L1), suggesting that TILs and the expression of PD-L1 may be associated with the efficacy of trastuzumab. Several studies have verified certain predictive value of TILs and PD-L1 in HER2 + breast cancer patients, but controversy remains. Besides, most of them focus on the expression of PD-L1 or TILs before neoadjuvant therapy, but not the change in the paired tissues before and after neoadjuvant therapy. This study aimed to investigate the change of TILs and the expression of PD-L1 in the paired tissues before and after neoadjuvant therapy and the correlation to the efficacy of neoadjuvant trastuzumab plus chemotherapy and disease-free survival (DFS) in HER2+ breast cancer patients.**Methods:**HER2+ breast cancer cases receiving neoadjuvant therapy (n=115) were retrospectively collected between July 2013 and November 2018. The expression of PD-L1 was detected by immunohistochemistry using SP142 antibody and the percentage of positive membranous staining in tumor cells (TC-PD-L1) and TILs (TILs-PD-L1) was scored respectively. TIL percentile score for full sections were assessed by two pathologists independently. **Results:**In our study, 87 patients receiving neoadjuvant chemotherapy alone, and 68 patients receiving neoadjuvant trastuzumab plus chemotherapy. Among them, 39 patients achieved pCR and 116 patients were non-pCR. Univariate analysis confirmed that the pCR was positively correlated with high TILs and TILs-PD-L1 expression before neoadjuvant therapy ($P< 0.05$). Multivariate logistic regression analysis confirmed that pre-treatment TILs-PD-L1 expression but no other clinicalpathologic factors,was independent predictor of pCR in neoadjuvant therapy ($P<0.05$).Among all patients, TILs increased in breast cancer tissues after neoadjuvant therapy ($P<0.001$). Consistent results were found in subgroup analysis of trastuzumab plus chemotherapy group and chemotherapy alone group ($P<0.05$). In 116 non-pCR patients, TC-PD-L1 was down-regulated in breast cancer tissues after neoadjuvant therapy ($P=0.0219$). Consistent results were found in 43 non-pCR patients receiving neoadjuvant trastuzumab plus chemotherapy($P=0.0437$). While in 73 non-pCR patients receiving neoadjuvant chemotherapy, there was no significant difference in TC-PD-L1 expression before and after neoadjuvant therapy ($P=0.1465$). On the other hand, in the general population, neoadjuvant trastuzumab plus chemotherapy group and neoadjuvant chemotherapy group, TILs-PD-L1 were all down-regulated after treatment($P<0.05$).Kaplan-Meier analysis showed that the changes of TILs, TC-PD-L1, TILs-PD-L1 between pre and post neoadjuvant therapy have no correlations with DFS. In multivariate Cox regression analysis, lymph node status and distant metastasis were independent prognostic factors for DFS.**Conclusions**:1. Pre-treatment high TILs-PD-L1 was an independent predictor of PCR in patients with HER2+ breast cancer treated with neoadjuvant therapy.2. Trastuzumab maybe relate to the down-regulation of TC-PD-L1 and TILs-PD-L1 expression. 3. Lymph node status and distant metastasis were independent prognostic factors.4. Both TILs-PD-L1 and TILs change before and after neoadjuvant therapy for HER2-positive breast cancer, which may suggest that the immune microenvironment plays a role in neoadjuvant therapy.

**Publication Number:** PS14-28

Core−shell structured gold nanorods@iron-based metal-organic framework for magnetic resonance imaging guided photothermal therapy in triple-negative breast cancer

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Background/Objective: As the most aggressive subtype of breast cancer, triple-negative breast cancer (TNBC) with high mortality lacks effective treatment options and results in poor prognosis. Photothermal therapy (PTT) has emerged as a potential anticancer strategy. Until now, the construction of multifunctional photothermal agents is vital importance for effective PTT generally. In this work, the novel core-shell gold nanorods (GNs)@iron-based metal-organic framework (Fe-MOF) was firstly successfully fabricated for magnetic resonance imaging (MRI) guided PTT in TNBC. The inner GNs have excellent photothermal properties and the outer Fe-MOF shell endow the nanocomposite with superior T2 MRI property.Methods: The GNs @ Fe-MOF was firstly prepared by a layer-by-layer technique. Prepared nanocomposite was characterized by measuring measuring measuring transmission electron microscope (TEM), UV-Vis-NIR absorption spectra, powder X-radiffraction (XRD) patterns. MR imaging of nanocomposite was assessed in vitro and in vivo. The biocompatibility and photothermal cytotoxicity of the nanocomposite was assessed by a CCK-8 assay. The photothermal effect of nanocomposite in vivo was evaluated by monitoring tumor growth. The tumor tissues were analyzed by Hematoxylin and eosin (H&E) to further analyze photothermal effect. The toxicity of the materials in major organs was also investigated by H&E.Result: The core-shell GNs @ Fe-MOF was successfully prepared and displayed excellent dispersion. The nanocomposite possessed good biocompatibility and effectively killed tumor cells under laser irradiation. Meanwhile, the nanocomposite showed clear signal contrast in T2-weighted images in vitro and in vivo. Moreover, the nanocomposite significantly inhibited tumor growth under laser irradiation in vivo. H&E showed that the nanocomposite caused serious damage to tumor tissue under laser irradiation.Conclusion: The current work developed a novel multifunctional core-shell GNs @ Fe-MOF with good biocompatibility for MRI guided PTT in TNBC.Keywords : Magnetic resonance imaging, Photothermal therapy,gold nanorods@iron-based metal-organic Framework

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# Genomic heterogeneity and associated clinical outcomes of breast cancers treated with CDK4/6 inhibitors: Insights from real-world clinical genomic data

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**Background:** The CDK4/6 inhibitors (palbociclib, abemaciclib, and ribociclib) have heralded a paradigm shift in the management of people with metastatic ER+/ HER2- breast cancer. Traditionally assessment of genomic status has relied on tumor testing from a solid tumor biopsy, however, circulating tumor DNA (ctDNA) has demonstrated strong concordance proving the viability of ctDNA as a diagnostic alternative to tissue testing. Using a real-world clinical-genomic dataset, we aimed to describe the clinical outcomes of patients who underwent ctDNA testing and were treated with an FDA approved CDK4/6 inhibitor and report on the genomic diversity observed following disease progression.

**Methods:** The GuardantINFORM™ clinical-genomic database was interrogated for women aged 18 or over with a confirmed diagnosis of breast cancer, at least one instance of a claim for one of palbociclib, abemaciclib, or ribociclib monotherapy, and at least one resulted comprehensive ctDNA genomic profile (Guardant360®, Guardant Health). Time to next treatment, defined as discontinuation of CDK4/6 inhibitor therapy or treatment with an additional therapy, and time to death was calculated for first- and second- line treatment through a proprietary algorithmic approach. A subset of patients with a Guardant360 test completed both pre and post CDK4/6 inhibitor monotherapy was analyzed to determine changes in genomic profile following treatment.

**Results:** In total 1,616 patients who matched inclusion and exclusion criteria were identified in the GuardantINFORM database, of these 79% were not known to have died as of the most recent data cut. All three major CDK 4/6 inhibitors were represented in the dataset.

Table 1. Comparison of First and Second Line CDK4/6i Monotherapy

| | First Line CDK4/6i monotherapy | Second Line CDK4/6i monotherapy |
|---|---|---|
| Not Known to be Deceased | 81% | 74% |
| Record of a subsequent therapy following CDK4/6 treatment | 62% | 85% |
| Median Time to Next Treatment (months) | 11.9 | 5.2 |
| Median Time to Death (months) | 26.6 | 26.6 |

150 patients had a Guardant360 test completed pre and post CDK4/6 inhibitor monotherapy. Somatic alterations more commonly observed in post-treatment tests included those in TP53 (16% pre-treatment vs. 24% post-treatment), ESR1 (8% vs. 15%), CCND1 (7% vs. 11%), ERBB2 (5% vs. 11%), AR (4% vs. 6%), BRCA2 (3% vs. 7%), TERT (2% 5%), and MYC (4% vs. 9%). Alterations in ARID1A were more commonly observed pre-treatment (8% vs 6%). There was no difference in the occurrence of alterations in FGFR1.

**Conclusions:** The results presented here demonstrate clinical outcomes similar to those previously reported for CDK4/6 inhibitor monotherapy demonstrating the ability to use this real-world database to generate clinically meaningful treatment data. Incorporation of genomic data pre and post treatment identified changes in the genomic profile of several genes indicating the impact of therapy on the cancer molecular pathogenesis. The ability to simultaneously query the somatic genomic profile and the therapeutic regimen provides novel clinical information to aid in understanding of treatment optimization, disease mechanism, and future drug development for metastatic breast cancer.

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Pre-treating TNBC with docetaxel and il-12 enhances anti-PD1 efficacy

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**Introduction:** Amongst all breast cancers, Triple Negative Breast Cancer (TNBC) account for 15-20% of all the cases. TNBC affect younger patients, and is more prevalent in African-American women. The poor prognosis for this very aggressive tumor subtype is exacerbated by the lack of specific targeted therapy against the disease. Although TNBC initially respond very well to chemotherapy, paradoxically the disease-free survival is very short. It has been showed that TNBC have higher rates of CD8+ T-cells infiltration, and express high level of PD-L1. Together, these data provide a strong rationale for the combination of chemotherapy and immunotherapy to treat TNBC patients. In this study, we investigated the response to pre-priming the tumor with one round of docetaxel and IL-12, followed by anti-PD1 maintenance in mouse E0771 and 4T1 TNBC syngeneic models. We hypothesized that docetaxel will promote the release of neo-antigens, while IL-12 will activate immunity specific to these antigens and anti-PD1 therapy prevent the exhaustion of those T-cells. **Materials/Methods:** Mouse TNBC E0771 and 4T1 cell lines were injected in the mammary fat pad of C57BL/6, and Balb/c mice respectively. On day 1, the mice received a single dose (20mg/kg) of docetaxel and one intratumoral injection ($1.25x10^9$) of mAdv.IL-12, a replication defective adenoviral vector containing mIL-12 (mouse) cDNA under the transcriptional control of Rous sarcoma virus long terminal repeat (provided by Dr. Chen, HMRI). Anti-PD1 (InVivoMab anti-mouse PD-1 CD279) was administered 3 times a week (2 cycles) starting 5 days post docetaxel and Il-12 treatment. At the end of the study, IFN-gamma levels were measured from blood and tumor samples; tumor sizes were compared between treatment groups (Control/mAdv.IL-12/anti-PD1/and various Combination), as well as survival curves. The metastatic burden to the lungs (H&E), as well as the apoptosis in the tumor (TUNNEL) were assessed by IHC. **Results:** In both 4T1 and E0771 tumor models, triple combination of docetaxel + IL-12 followed by anti-PD1 significantly reduced tumor size compared to both single agents, and double combination. In the Triple Combo group, 1 mice had lung metastasis vs all of them in the other treatment groups. IHC data indicate a higher level of TILs in the treatment groups, with a statistically significant difference in the combination groups compared to single agents. There was more apoptosis in the triple combo group as indicated by TUNNEL. **Conclusion:**Our preliminary data strongly supports that treating TNBC models with docetaxel and mAdv.IL-12 followed by anti-PD1 significantly slows down tumor growth, and decrease lung metastasis incidence. We are actively investigating the mechanism through which the response is achieved.

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Runx3 regulates emt during development lapatinib resistance

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RUNX3 regulates EMT during development lapatinib resistanceBackground: Lapatinib is a small molecular inhibitor of HER2 and EGFR tyrosine kinase, which is used for HER2 positive metastatic breast cancer patients. However, significant proportion of patients relapse due to acquired resistance. The epithelial to mesenchymal transition (EMT), which induces cell migration, invasion and cancer stem cell progression, was one of the mechanism that confers to drug resistance. We determined the correlation of lapatinib resistance and EMT, and identified a regulatory factor of EMT which associated with the development process of acquired lapatinib resistance.Methods: Acquired lapatinib resistant SK-BR-3 (SK-BR-3 LR) cells were established by continuously exposing to lapatinib for 7 months. The sensitivity of lapatinib was confirmed by MTT assay. Cell cycle progression was verified using flow cytometry analysis. Expression of signal transduction molecules were determined using quantitative PCR, western blotting and transcriptome data analysis. Cell migration and invasion ability were verified using wound healing assay and Boyden chamber assay. siRNA knock-down system were used for further analysis. Results: Lapatinib resistant (SK-BR-3 LR) cells showed aggressive morphology compared with parental cells. The growth rate and cell cycle progression were increased in SK-BR-3 LR cells. Expression of Snail, Vimentin, SOX2, Nanog, TGF-b1 and Smad proteins increased in SK-BR-3 LR cells. In SK-BR-3 LR cells, cell migration and invasion were significantly increased. Correlated with a promoter methylation of RUNX3, expression of RUNX3 was down-regulated in SK-BR-3 LR cells. In Runx3 knock-down cells TGF-b1, SOX2, smad molecules were up-regulated. Conclusion: SK-BR-3 LR cells showed aggressive phenotype. Expression of EMT markers, cancer stem cell markers, TGF-β pathway associated molecules and Smad proteins were increased in SK-BR-3 LR cells. Also, the increase of cell migration and invasion was observed in LR cells. RUNX3 affected to cell migration and invasion through regulation of EMT associated molecules. Therefore, RUNX3 might be a specified molecule, which partially contributes resistance to lapatinib through regulates EMT.

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Winpro: A window of opportunity study of endocrine therapy with and without prometrium in postmenopausal women with early stage hormone receptor-positive breast cancer

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**Background:** There is bidirectional interplay between PR and ER in human breast cancers (Lim, Endo Rel Can 2016). Evidence in breast cancer cell lines suggests that dual treatment with estrogen and progesterone compared to estrogen alone leads to reprogramming of ER chromatin binding sites via regulation of 470 genes (Mohammed, Nature 2015). Importantly, there was an additive anticancer effect in preclinical breast cancer models when natural progesterone was combined with standard endocrine therapy; we hypothesize that this combination has activity in women with breast cancer.**Trial design:** We are conducting a phase II multi-center, randomised, open-label, three-arm study in which 200 postmenopausal women with early-stage ER-positive (ER ≥10%), PR-positive (PR ≥10%), HER2-negative breast cancer will be randomised 1:1:1 to letrozole 2.5mg daily (arm 1); letrozole 2.5mg and prometrium 300mg PO daily (arm 2); or tamoxifen 20mg and prometrium 300mg PO daily (arm 3). Surgery will occur on day 14 after treatment initiation. Eligible subjects must have tumor size ≥10mm on imaging, no history of uterine cancer or venous thromboembolism, and no receipt of other preoperative therapies. The primary objective is to assess the reduction in proliferative marker Ki67 following treatment in either combination arm compared to letrozole alone.**Methods:** Blood will be collected at baseline and at end of treatment. Tissue samples will be collected from the diagnostic biopsy and at the time of surgery. The primary endpoint is geometric mean reduction of centrally assessed Ki67 expression after two weeks of treatment compared with baseline. Given the expected geometric mean reduction of 76% for aromatase inhibitor alone (Dowsett, J Natl Can Inst 2007) and allowing 4% dropouts, 200 patients provides 80% power to detect an improvement in Ki67 suppression to 92% in either experimental arm with p-value 0.025 for each comparison.The secondary endpoint of safety and tolerability will be assessed (NCI-CTCAE v4.0). Translational endpoints include definition of a predictive gene set biomarker for Ki67 reduction; tumor biomarkers after treatment, including apoptotic markers Bcl-2 and cleaved-caspase3, as well as protein and mRNA expression of ER, PR, AR, FoxA1, and CyclinD1; and levels of estrone, estradiol, E2, progesterone, testosterone, DHT, and DHEAS in serum and finger prick dried blood spot after treatment.**Accrual:** Enrolment commenced in February 2018 and 70 patients have been randomized from 7 sites to date (1 July 2020). Target accrual is 200 patients enrolled from 8 sites.**Contact information:** This study is led at The Kinghorn Cancer Centre, St Vincent’s Sydney Hospital Sydney, Australia, and funded by the Cancer Council of NSW and the NHMRC Translational Breast Cancer Project grant. Contact Elgene Lim MBBS FRACP PhD at e.lim@garvan.org.au.

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# Efficacy of adjuvant chemotherapy stratified by age and the 21 gene recurrence score in estrogen receptor positive breast cancer

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**Background:** The 21-gene recurrence score (RS) can predict chemotherapy benefit in estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative early breast cancer patients. The TAILORx showed that age would influence the interaction between RS and chemotherapy effect, and patients ≤50 years with RS >15 can benefit from chemotherapy. The current study aimed to determine the RS threshold that can predict chemotherapy benefit in both young and elder women. **Methods:** Patients diagnosed with pN0-1, ER+/HER2- breast cancer between 2009 and 2016 at Shanghai Ruijin hospital were retrospectively reviewed. A one-to-one propensity score matching (PSM) was performed between women receiving chemotherapy or not. Patients were then stratified by different cutoffs of age (range, 30-65 years). In each prespecified strata of age, cox proportional hazards models were used to determine the RS threshold which was predictive of chemotherapy benefit. **Results:** A total of 1227 patients were included. The median age was 58 years and the median RS was 24. After matching, the RS values that can manifest the chemotherapy benefit varied with age. For patients at 55 years of age or younger, apparent chemotherapy benefit was observed in those who had RS >25 (P = 0.03), with 4-year invasive disease-free survival (IDFS) rate of 97.0% and 89.3% in patients receiving chemotherapy or not. While patients derived no benefit from chemotherapy if they had RS ≤25 (P = 0.66, 4-year IDFS rate: 95.3% vs. 94.6%). However, for patients older than 55 years, adjuvant chemotherapy was associated with better prognosis in those with RS >36 (P = 0.014, 4-year IDFS rate: 94.7% vs. 76.2%), but not in those having RS ≤36 (P = 0.13, 4-year IDFS rate: 92.3% vs. 95.8%). **Conclusions:** The RS threshold to demonstrate the chemotherapy benefit differed with age. Young patients with RS >25 and old patients with RS >36 could benefit from adjuvant chemotherapy.

Survival of breast cancer patients receiving adjuvant chemotherapy or not stratified by age and the

| | | Chemoendocrine therapy | | Endocrine therapy | | P-value |
|---|---|---|---|---|---|---|
| | | 4-year IDFS rate (%) | 95% CI (%) | 4-year IDFS rate (%) | 95% CI (%) | |
| ≤55 years | | | | | | |
| | RS ≤25 | 95.3 | 90.7-100.0 | 94.6 | 89.6-100.0 | 0.66 |
| | RS >25 | 97.0 | 91.3-100.0 | 89.3 | 82.0-97.3 | 0.03 |
| >55 years | | | | | | |
| | RS ≤36 | 92.3 | 87.7-97.2 | 95.8 | 92.1-99.6 | 0.13 |
| | RS >36 | 94.7 | 87.9-100.0 | 76.2 | 52.1-100.0 | 0.014 |

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# Phase 1b study evaluating a triplet combination of ipatasertib (IPAT), atezolizumab, and a taxane as first-line therapy for locally advanced/metastatic triple-negative breast cancer (TNBC)

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**Background:** The combination of immune checkpoint modulators with chemotherapy improves efficacy compared with chemotherapy alone in PD-L1+ advanced TNBC (IMpassion130; KEYNOTE-355). The addition of IPAT to paclitaxel (PAC) improved efficacy in a phase 2 trial in advanced TNBC (LOTUS). Preliminary overall response rate (ORR) data from a multicenter phase 1b study (NCT03800836) evaluating a triplet combination of IPAT, atezolizumab, and taxane chemotherapy showed promising anti-tumor activity in a similar patient population, irrespective of PD-L1 status [Schmid, AACR 2019]. Here, we report follow-up results including progression-free survival (PFS) from this study. **Patients and Methods:** Eligible patients had measurable unresectable locally advanced/metastatic TNBC, ECOG performance status 0/1, and had received no prior systemic therapy for advanced disease (prior [neo]adjuvant chemotherapy and/or radiation permitted if all chemotherapy was completed ≥12 months before first dose). Patients with brain metastases were excluded. Patients received oral IPAT 400 mg/day on days 1–21 and IV atezolizumab 840 mg on days 1 & 15 in combination with PAC 80 mg/m$^2$ (Arm A) or nab-PAC 100 mg/m$^2$ (Arm B) on days 1, 8, & 15. Cycles were repeated every 28 days until loss of clinical benefit, unacceptable toxicity, or consent withdrawal. Arms C and D evaluated sequential regimens comprising a doublet induction therapy with the third agent added on day 15 (Arm C: IPAT + PAC, then + atezolizumab; Arm D: atezolizumab + PAC, then + IPAT). Tumors were assessed every 8 weeks. Key endpoints were confirmed ORR (per RECIST v1.1), duration of response (DoR), PFS, and safety. **Results:** At the data cut-off (26 Jul 2020), results were available from 114 patients (Arm A n=70, Arm B n=20, Arm C n=12, Arm D n=12). Median duration of follow-up was 11.1 months. Efficacy results are summarized in the table. Safety of the combination appeared to be consistent with the known safety profile of the individual drugs. Grade ≥3 adverse events (AEs) occurred in 55% of patients (including rash [13%], diarrhea [12%], and neutropenia [10%]) and serious AEs in 34%. AEs led to discontinuation of IPAT in 6% of patients and atezolizumab in 4%. No new safety signals were identified.

| **Population** | | **Confirmed ORR, n (%) [95% CI]** | **Median DoR, months (95% CI)[a]** | **Median PFS, months (95% CI)** |
|---|---|---|---|---|
| **All patients (n=114)** | | 61 (54) [44-63] | 7.3 (5.6-7.8) | 7.2 (5.5-7.4) |
| **PD-L1 status[b]** | **Positive (n=51)** | 32 (63) [48-76] | 7.4 (5.0-12.9) | 7.3 (5.4-7.4) |
| | **Negative (n=45)** | 20 (44) [30-60] | 5.6 (3.7-7.4) | 7.2 (5.4-9.1) |
| | **Unknown (n=18)** | 9 (50) [26-74] | 11.1 (5.8-NE) | 6.3 (4.9-11.0) |
| **Arm (taxane backbone)** | **A (PAC) (n=70)** | 36 (51) [39-64] | 7.4 (5.6-12.9) | 7.2 (5.3-7.4) |
| | **B (nab-PAC) (n=20)** | 13 (65) [41-85] | 7.3 (3.9-7.4) | 6.6 (3.4-9.0) |
| | **C+D (PAC) (n=12+12)** | 12 (50) [29-71] | 6.8 (3.9-14.7) | 7.5 (5.5-11.3) |
| ***PIK3CA/AKT1/PTEN* status[c]** | **Altered (n=36)[d]** | 19 (53) [35-70] | 6.8 (3.9-7.6) | 7.4 (5.5-9.1) |
| | **Non-altered (n=45)** | 28 (62) [47-76] | 7.3 (5.5-9.4) | 6.6 (5.2-9.0) |
| | **Unknown (n=33)** | 14 (42) [25-61] | 10.2 (5.8-NE) | 6.0 (5.1-9.1) |

[a]In responding patients. [b]Assessed by VENTANA SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ, USA); PD-L1+ defined as immune cell expression in ≥1% of the tumor area. [c]Assessed using FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA). [d]*PIK3CA/AKT* mutation (n=12) or *PTEN* alteration (n=24). CI = confidence interval; nab = nanoparticle albumin-bound; NE = not estimable.

**Conclusions:** Updated results demonstrate a lower ORR than in the preliminary report of the first 26 patients. Subgroup analyses according to PD-L1 or *PIK3CA/AKT1/PTEN* alteration status or taxane backbone show no consistent trend across endpoints, although small sample sizes limit interpretation. Further biomarker analyses focusing on subgroups and biology may identify subsets of patients deriving a benefit.

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# Abrupt involution of lactating mammary gland induces metabolic reprogramming conducive to pro-tumorigenic changes

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**Background:** Epidemiological studies indicate that prolonged breast feeding reduces the risk of triple negative breast cancer (TNBC), which carries the worst prognosis. Prolonged breastfeeding allows gradual involution (GI) of the breast while lack of or short-term breast feeding leads to abrupt involution (AI). We developed a novel murine model mimicking AI and GI of breast, and found that GI offers better protection to mammary glands from tissue remodeling associated injuries. Our data showed that AI leads to the development of pro-tumorigenic microenvironment and ductal hyperplasia[1]. Tissue remodeling involves orchestrated cell death and repopulation, and is closely associated with metabolic reprogramming from mitochondrial oxidative phosphorylation (OXPHOS) to glycolysis. Such metabolic alterations can contribute to cellular changes aiding malignant transformation[2]. We used our murine model to evaluate whether AI affects cellular metabolism differentially when compared to GI. **Methods:** Wild-type mice of FVB background were used in all our experiments. Twelve to fourteen week old uniparous mice were allowed to nurse (6 pups/dam) for 7 days postpartum. All pups were removed on day7 postpartum from the dams in AI cohort and three each on day28 and day31 from dams in GI cohort. Whole mammary glands and sorted luminal progenitor (LP) cells harvested on postpartum day28 were subjected to Affymetrix microarray analysis. Gene Set Enrichment Analysis (GSEA) was used to compute pathway enrichments in AI vs. GI glands. Differentially expressed genes were validated using qRT-PCR. Mammary glands harvested on day28 postpartum were subjected to mass spectrometry based untargeted metabolic profiling using Agilent QTOF. Raw data were analyzed using XCMS to assess key metabolic networks altered in AI vs GI glands. Targeted analysis for lactate, pyruvate, succinate and palmitic acid were performed using C13 labelled internal standards to compare OXPHOS vs glycolysis reliance in the AI and GI glands. **Results:** We observed enrichment of mitochondrial OXPHOS pathway, fatty acid metabolism and Myc target genes in both whole mammary gland and LP cells of AI vs. GI mice. Adipogenesis and hypoxia related genes were enriched in AI-glands. We observed significant upregulation of genes involved in glucose transport and fatty acid synthesis in AI glands, namely, *Glut-5, Cidea, Acss2, Acsm3, Acly, Atp6v0d2, Acot11*, and *Elvol3.* Several factors indicating a higher reliance on OXPHOS vs glycolysis, such as, *Ppar-ɣ, Pgc1α, Cpt-2, Srebp1c* and *Chrebp* were upregulated in AI glands. Upregulation of *Cpt-2* and *Srebp1c* in the AI glands indicate higher flux through fatty acid oxidation and reliance on cholesterol synthesis. Metabolomic profiling revealed significant alteration in L-carnitine, GMP and XMP in AI glands which reflect mitochondrial fatty acid transport and nucleotide biosynthesis via guanine-guanosine salvage pathway. Pyruvate and lactate associated with glycolysis were increased in GI vs. AI glands. **Conclusion:** We show for the first time that in the abruptly involuting (AI) mammary glands following short-term breast feeding, there is a significant shift in the metabolic pathways towards mitochondrial OXPHOS and fatty acid oxidation compared to GI glands. Studies are underway to determine the effect of this metabolic shift on cellular transformation and tumorigenesis and the potential to target these pathways to reverse the detrimental effects of AI. [1.] Basree MM, Shinde N, Koivisto C, et al. *Breast Cancer Res*. 2019; 21(1):80. [2.] Ward PS, Thompson CB. *Cancer Cell*. 2012; 21(3):297.

**Publication Number:** PS19-28

Thymoquinone and tamoxifen co-treatment synergistically inhibit proliferation, invasion and induce apoptosis in human breast cancer cell lines in vitro and in vivo

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Epidemiological studies and experimental analysis indicate that dietary factors influence thedevelopment of breast cancer, suggesting the role of natural products as modifying factors againstbreast cancer. Thymoquinone (TQ) (a dietary phytochemical compound) the main active ingredientof the volatile oil of black seed (*Nigella sativa*) has been used to be safe when administered to awide variety of normal cells. In addition, Tamoxifen (TAM), a nonsteroidal triphenylethylene derivateand selective ER modulator, has been used as a single agent in the treatment of ER positive breastcancer.In the present study, we report the possible chemo-sensitizing effect of TQ as a promisingconventional chemotherapeutic agent*,* using a panel of human breast cancer cell lines, MCF-7, ZR-75-1, T-47D and BT-20 respectively *in vitro* and *in vivo*.Our data revealed that TQ, TAM or combined treatments significantly inhibited cell viability of MCF-7, T-47D, ZR-75-1 but slightly of BT-20 cell lines consistently with down-regulation of signaltransducer and activator of transcription 3 (STAT 3), mTOR, cyclin D1, oncogenic β-catenin,signaling a specific transcription factor and PPAR-gamma in a dose dependent manner. Mostimportantly, combined treatment enhanced inhibition of cell viability, DNA fragmentation andapoptosis induction through Caspase-3 activation and Bcl-2 down regulation in all tested cell linesbut this effect was limited in BT-20 cells compared to controls. Moreover, our data was supported bymicroscopic examination using electron scanning microscopy that revealed many apoptoticalterations after combined treatment compared to each TQ or TAM. Furthermore, confocalfluorescence microscopy examination revealed that only combined treatment showed a significantinhibition of filopodia formation as a sign of invasion inhibition in both BT-20 and MCF-7 humanbreast cancer cell lines. *In vivo*, tumor xenotransplants of human ZR-75-1 cells revealed that onlycombined treatment showed a significant regression in tumor size by 53% after 72h and enhancedE-cadherin expression as analyzed by immunohistochemistry and confocal fluorescencemicroscopy.Taken together, our findings provide strong *in vitro* and *in vivo* molecular evidences in support ofour hypothesis that Thymoquinone synchronized as chemo-preventive agent with Tamoxifen to inhibithuman breast cancer cell lines proliferation, invasion and induce apoptosis that might have a potentialimplication in breast cancer prevention and treatment.

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# Neratinib as extended adjuvant therapy in patients with HER2-positive/HR-positive early breast cancer: HTA-driven analyses from the ExteNET study

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**Background:** Neratinib is indicated in Europe for the extended adjuvant treatment of patients with HER2-positive/HR-positive early breast cancer having completed trastuzumab-based therapy less than one year ago. Here we report post-hoc analyses of the HR-positive subgroup (N=1’631) from the ExteNET-trial (neratinib vs. placebo) performed for the German health technology assessment (HTA) procedure.
**Methods:** The study endpoints were re-analyzed according to local HTA requirements. For the evaluation of efficacy time-to-event endpoints, stratified Cox regression models were used. The evaluation of tolerability endpoints was performed in the same way based on non-stratified models and tests. Patient-reported endpoints were analyzed using a mixed model for repeated measures. Overall survival analyses have not been performed, as - in accordance with the study protocol - the required number of events (248 deaths) had not been reached at the time-point of HTA [Nov. 2019].
**Results:** Baseline characteristics in the analyzed population were well balanced between treatment arms, comparable with the overall ExteNET-population and consistent with the typical configuration of patients with early breast cancer. The median treatment duration at the time of the primary data cut was 11.5 months in the neratinib and 11.9 months in the placebo arm. After a median follow-up of 2 years and in-line with the overall ExteNET-results, time-to-event analyses revealed a significant advantage in disease-free survival (DFS) for neratinib vs. placebo (HR [95%-CI]: 0.45 [0.29; 0.69]; p=0.0002). The incidence based analysis confirmed this benefit (RR [95%-CI]: 0.44 [0.29; 0.68]; p=0.0002). These results were consistent with the analysis of distant disease-free survival (DDFS; HR [95%-CI): 0.52 [0.32; 0,84]; p=0.0082). The analysis after 5 years of follow-up based on the latest data cut confirmed the 2-year results, with 7.4% of patients in the neratinib and 13.0% of patients in the placebo arm having experienced at least one relapse event. The time-to-event analysis supported the significant advantage with regards to the DFS (HR [95%-CI]: 0.57 [0.41; 0.78]; p=0.0005), with a 5-year DFS-rate of 91.2 vs. 86.8%. These results were again consistent with the DDFS analysis (HR [95%-CI]: 0.60 [0.42; 0.85]; p=0.0037), with a 5-year DDFS-rate of 92.7 vs. 88.7%. The neratinib tolerability profile is consistent with class effects and thus predictable for the inhibition of HER-receptors, with domination of gastrointestinal (especially diarrhea; all grades: 94.4%; grade 3: 39.4%; cumulative duration all grades: 54.5 days; no systematic diarrhea prophylaxis), general (especially fatigue; all grades: 28.1%; grade 3: 1.9%) and cutaneous (especially rash; all grades: 14.3%; grade 3: 0.4%) events. No cumulative or irreversible toxicities have been observed. As shown in the CONTROL study and instituted via a risk management plan, adequate diarrhea prophylaxis and management can reduce the frequency (all grade: 79.6-96.7%), cumulative duration (all grades: 14.0-24.0 days) and severity of diarrhea (grade 3: 15.0-33.7%).
**Conclusion:** Extended adjuvant neratinib provides a clinically relevant benefit with further reduction of relapse risk in the curative situation of patients with HER2-positive/HR-positive early breast cancer. Accordingly, German HTA-authorities have granted an added benefit for this new treatment option.

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Association between epigenetic age acceleration and postmenopausal breast cancer risk in the Women's Health Initiative

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Earlier age of menopause and bilateral oophorectomy are associated with accelerated biologic aging based on epigenetic clocks. While these relationships suggest women with greater epigenetic age acceleration (AgeAccel) might be at a reduced risk of postmenopausal breast cancer, prior studies conflict with this theory. We hypothesized this paradox may be attributable to an interaction between epigenetic and reproductive aging on cancer risk. We evaluated this premise among 5,044 postmenopausal women in the Women's Health Initiative (WHI) Observational Study and Clinical Trial with AgeAccel estimated in whole blood. Among a subset of 1,135 of these women, estradiol (E2) and sex hormone-binding globulin were assayed in baseline serum samples. For WHI participants with DNA methylation assays, we modeled the log odds of incident postmenopausal breast cancer during follow-up as a function of AgeAccel, adjusting for age at menopause, race/ethnicity, age at WHI screening, bilateral oophorectomy, nulliparity, alcohol consumption, smoking, body mass index, duration of postmenopausal hormone therapy use, exercise, clinical trial arm, and hysterectomy status at baseline. We repeated this analysis among the subset of participants with DNA methylation and E2 assays, and appraised the degree to which bioavailable E2 levels contributed to the observed association between AgeAccel and incident postmenopausal breast cancer. Finally, we evaluated whether bioavailable E2 levels modified the relationship between AgeAccel and cancer risk. Generalized estimating equations were used to model associations with AgeAccel, integrating repeated measures among a subset of participants and using inverse probability weights to account for sample selection probabilities. Based on our fully adjusted models, increased extrinsic AgeAccel was associated with decreased odds of incident postmenopausal invasive breast cancer during follow-up. This association was consistent among the subset of participants with E2 assays, and robust to adjustment for bioavailable E2 concentration. We found the inverse relationship between extrinsic AgeAccel and incident breast cancer was strongest among white non-Hispanic women with low levels of bioavailable E2. This study represents the largest investigation of the association between AgeAccel and postmenopausal breast cancer risk, and the first evaluation of how bioavailable E2 levels may influence this relationship. Our analyses inform our understanding of the relationship between the epigenetic and reproductive aging process, and the potential implications for postmenopausal breast cancer risk.

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Predicting axillary pathologic response to neoadjuvant chemotherapy for node-positive breast cancer: Clinical predictive model by using MRI and ultrasound

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**Purpose:** Neoadjuvant chemotherapy (NAC) has been shown to eradicate axillary lymph node metastasis in approximately 40% of patients. Sentinel lymph node biopsy (SLNB) could be an alternative surgical approach for these patients to avoid morbidity from axillary lymph node dissection (ALND). However, high false-negative rates of SLNB for initially node-positive patients were reported in previous trials. The aim of this study was to evaluate clinicopathological factors and imaging characteristics by MRI and ultrasound (US) as predictors of axillary pathologic complete response (ypN0) after NAC, which enable to identify candidates for SLNB in patients with clinically node-positive disease.
**Patients and methods:** We identified 153 patients with clinically node-positive breast cancer who received NAC from May 2009 to December 2019. Clinicopathological data including age, clinical T/N status, nuclear grade, hormone receptor (HR) and HER2 status were collected. All patients underwent MRI and US before and after NAC. Patients were judged to be node-positive when they have cytologically-proven nodal disease by fine-needle aspiration (FNA) or suspicious lymph nodes by diagnostic imaging. Lymph nodes with cortical thickness (>3.5mm), loss of fatty hilum or round shape (short-axis/long-axis ratio > 0.5) were defined as suspicious lymph nodes. All imaging data were evaluated at baseline and after NAC. To develop a predictive model for ypN0, the association between ypN0 status and clinicopathological and imaging characteristics were assessed by multivariate logistic regression analysis. The area under the receiver operating characteristic (ROC) curve was used to evaluate discrimination by the model.
**Results:** The median age was 55.0 (range: 22-79) years and the mean tumor size was 3.86 ± 2.04 cm. Pretherapeutic lymph node status was assessed by FNA in 88 (57.5%) patients. Of 153 patients, 80 (52.3%) patients had luminal, 39 (25.5%) had HER2-positive, and 34 (22.2%) had triple negative disease. Sequential anthracycline and taxane were administered for 138 (90.2%) patients, and 37 (94.9%) patients with HER2-positive-disease received concomitant anti-HER2 agents preoperatively. Overall, 62 (40.5%) patients achieved ypN0. Independent predictors of ypN0 status were breast complete response by MRI (odds ratio [OR]: 9.01, p<0.001), clinical stage N1 (OR: 6.64 vs. cN2-3, p=0.009), absence of lymphadenopathy after NAC (OR: 6.09, p<0.001), HR negativity (OR: 3.10, p=0.02) and HER2 positivity (OR: 2.87, p=0.04). In a model using these predictors, the area under the ROC curve was 0.870 (95% confidence interval: 0.814-0.925, p<0.001). Sensitivity, specificity, positive predictive value and negative predictive value of the model were 72.6%, 86.8%, 78.9% and 82.3%, respectively. After a median follow-up of 49.7 months, 5-year disease-free survival (DFS) was significantly higher in patients who achieved ypN0 than patients with residual axillary disease (88.7% vs. 76.9%, p=0.046). Among 62 patients who achieved ypN0 after NAC, ALND was omitted in 24 (38.7%) patients and irradiation to regional lymph nodes was performed in 8 (33.3%) out of 24 patients. Five-year DFS was comparable between patients with or without ALND (86.8% vs. 91.7%, p=0.815).
**Conclusions:** Our predictive model based on imaging characteristics by MRI and US could help to identify good candidates for omission of ALND after NAC in patients with initially node-positive breast cancer.

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Multiomic advanced diagnostics for CDK 4/6 drug target activation mapping of HR+/HER2- metastatic breast cancer

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**Background:** Three CDK 4/6 inhibitors (inh) are FDA approved in combination with endocrine therapy (ET) for HR+/HER2- metastatic breast cancer (MBC), however, there are no validated predictive markers of response to this class of drugs. Approximately 30-40% of patients (pts) have little to no response to these agents, with disease progression occurring in weeks to a few months after therapy initiation. We conducted an open-label, multicenter clinical trial (NCT03195192) to utilize cutting edge proteomic technologies to map the functional activation of the signaling architecture of pre-treatment tumor tissue from HR+/HER2- MBC pts receiving first line CDK4/6 inh plus ET, and to correlate these functional phosphoprotein-based signaling patterns with 1-year progression-free survival (1-yr PFS). **Methods:** We enrolled 29 of 100 planned pts, then the study closed early due to slow accrual. All pts were followed up to 12 months from starting a CDK4/6 inhibitor or until disease progression if it occurred earlier. The primary objective of this trial is to assess the correlation between baseline phosphorylated Rb levels that indicate activated Rb in tumor tissue and 1-yr PFS. We hypothesized that high levels of activated Rb will identify pts who are more likely to respond to CDK4/6 inh. Secondary objective is to evaluate the correlation between 1-yr PFS and 8 pre-specified qualifying (protein/phosphoprotein CDK 4/6 kinase pathway biomarkers: total Rb, Rb (S780), total Cyclin D1, Cyclin D1 (S286), total p16INK, total p27, p27 (T187), FoxM1 (T600). **Results:** Pre-treatment diagnostic FFPE biopsy material available from 24 evaluable pts were analyzed by a Laser Capture Microdissection (LCM) Reverse Phase Protein Microarray (RPPA) workflow. Seventeen of 24 pts (71%) were White, 7 (29%) African American; median age 65 (range 36-79); 22 pts (92%) received an aromatase inh and 2 (8%) had fulvestrant. The primary analysis expressed the relationship between phospho-RB and 1-yr PFS as a 2x2 table of frequencies summarized either above or below the median values observed in all pt values using a Pearson chi-squared test. Similarly, we analyzed the qualified protein/phosphoprotein markers quantified by RPPA by median dichotomization. Univariate analysis showed that 1-yr PFS correlated with below median levels of phospho and total RB (Chi-sq = 8.71, p-value = 0.003); phospho-FoxM1 (Chi-sq = 4.44, p-value = 0.035); Cyclin D1 S286 (Chi-sq = 4.44, p-value = 0.035); total and phospho-p27 and Ki67 (Chi-sq = 4.44, p-value = 0.035). None of these biomarkers were individually significant as continuous variables on multivariate analysis by logistic regression. **Conclusions:** Functional CDK 4/6 drug target pathway mapping analysis is possible from the pre-treatment diagnostic FFPE material. Our results indicate that pts whose tumors had low inherent proliferative and CDK 4/6 kinase activity were more likely to respond to first line CDK4/6 inh plus ET indicating possible prognostic determinants of the biomarkers.

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Patient knowledge, attitudes and perceptions regarding breast cancer biomarkers, testing, and quality of life

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**Background:** Precision medicine and molecular testing for specific biomarkers to inform treatment selection has evolved to become the standard of care for advanced breast cancer. Although there is widespread education for health care practitioners, there is less education available for patients. Two surveys from the oncology literature (Pinheiro 2017, Ciardiello 2016), reported that 90% of physicians worldwide utilize biomarkers and patients would like to understand how testing informs treatment. The objective of this survey was to gain a greater understanding of patient familiarity with biomarker testing, specifically ESR1 mutation testing, and willingness to request information and testing. Patients were also surveyed about other areas of education of greatest interest, including quality of life (QOL) issues.
**Methods:** A 10 question on-line survey was sent to patients through 2 patient advocacy organizations: CURE's CURExtra e-newsletter, and METAvivor's social media channels; METAvivor's survey included 2 additional questions to determine if respondents had metastatic disease and were currently on treatment. The survey asked about side effects impacting quality of life, satisfaction with information received about QOL issues, and knowledge about biomarkers (specifically ESR1), as well as willingness to request ESR1 testing.
**Results:** A total of 343 completed responses were received: 177 from CURE and 166 from METAvivor, 82.5% from patients, 11% from patients who were patients and advocates, 2.3% from advocates, and 4.3% other. Disease subgroups included ER+/HER2- (53%), ER+/HER2+ (16%), TNBC (12%) and ER-/HER2+ (11%). The mean and median times from diagnosis were 8.25 and 6 years. 22% of patients surveyed were familiar with or aware of biomarker testing; only 12% were familiar with ESR1 mutations and biomarker testing. In contrast, 75% of respondents were very likely (52%) or likely (23%) to ask their provider about ESR1 mutations if this would aid in tailoring treatment, with METAvivor respondents more likely to than CURE respondents (78 vs 70%). 71% were very likely (49%) or likely (22%) to request ESR1 mutation testing. Survey respondents identified 3 areas of greatest interest: new treatments in development, QOL, and management of side effects. Joint (62%) and bone pain (48%) were identified as negatively impacting QOL followed by sexual intimacy and recurrent urinary tract infections (52%). 51% reported that GI disturbances were concerns. 55% were very satisfied or satisfied with the QOL information that they were receiving from their provider and 54% looked to their providers as their primary source of information, with 27% citing the internet and medical journals as additional sources of information.
**Conclusion:** The results of this survey indicate knowledge gaps in patients with breast cancer, specifically regarding genomic testing to tailor therapy, and the role of ESR1. In addition, QOL of life issues remain an area of unmet need. The results from this survey underscores breast cancer patients' desire for information related to new treatments in development, discussions with their provider specific to QOL, and how to manage side effects from therapy. Providing patient education tools for providers and patient advocacy organizations
that includes information on tumor genomics, treatment options, and side effect management is of utmost importance.
**Support:** Sermonix Pharmaceuticals

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# Development and external validation of a clinical nomogram for individually predicting survival of metaplastic breast carcinoma

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**Background:** Metaplastic breast cancer (MBC) is a rare subtype with distinct clinicopathological features, but few studies have concerned the prognosis of this rare and morphologically diverse malignancy. A prognostic index estimating the clinical outcomes for MBC would be attractive in current clinical practice. The aim of the present study was to develop and validate an effective nomogram for predicting survival of MBC. **Methods:** In current study, we retrospectively analyzed 1017 MBC patients between January 2005 and December 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. Prognostic factors were identified based on Cox regression analyses, and the final clinical nomogram was developed to predict the 1-, 3-, or 5-year overall survival (OS). The model was validated using bootstrap resampling of SEER validation set and a Chinese cohort for external validation. Calibration curves were provided to internally validate the performance of the nomogram and discriminative ability was appraised by concordance index (C-index). **Results:** A total of 1017 MBC patients were included for our analysis,whose clinical and tumor characteristics were shown in **Table 1**. Patients diagnosed between 2005 and 2015 were assigned into 3:1 as training set (n=763) and SEER validation set (n=254). An external validation was performed by an individual set of 94 MBC patients from National Cancer Center in China from 2005 to 2018. The nomogram finally consisted of seven independent prognostic factors including age, tumor grade, tumor size, AJCC Node stage, surgery, chemotherapy and radiotherapy. The nomogram presented a good accuracy for predicting the OS with the C-index of 0.77. Interestingly, the nomogram based on the western (including 92.5 %non-Asian) SEER validation population(C-index of nomogram: 0.76)also had an optimal discrimination in Asian population (C-index of nomogram: 0.70).The calibration plots of the nomogram predictions was also accurate and corresponded closely with the actual survival rates. **Conclusions:** In conclusion, this novel nomogram was accurate enough to predict the OS by using readily available clinicopathologic factors in MBC general population. This prognostic index proposed here could provide individualized recommendations for patients and clinical decisions for physicians.

Table 1. Characteristic of primary metaplastic breast carcinoma cohort from SEER database

| **Characteristics** | **Patient with MBC (N=1017)** | **%** | **Univariable Analysis *P*** |
|---|---|---|---|
| **Age, years** | 59.9?13.2 | | **0.001** |
| <60 | 494 | 48.6 | |
| ≥60 | 523 | 51.4 | |
| **Race** | | | 0.331 |
| White | 719 | 70.7 | |
| Black | 222 | 21.8 | |
| Others | 76 | 7.5 | |
| **Laterality** | | | 0.374 |
| Left | 518 | 50.9 | |
| Right | 499 | 49.1 | |
| **Tumor grade** | | | **0.001** |
| Grade I, II | 150 | 14.7 | |
| Grade III, IV | 867 | 85.3 | |
| **Primary tumor size** | | | **0.001** |
| <5cm | 802 | 78.9 | |
| ≥5cm | 215 | 21.1 | |
| **Pathological type** | | | 0.753 |
| Metaplastic carcinoma | 915 | 90.0 | |
| Squamous cell carcinoma | 48 | 4.7 | |
| Spindle cell carcinoma | 25 | 2.5 | |
| Malignant myoepithelioma | 7 | 0.7 | |
| Adenocarcinoma mixed | 22 | 2.1 | |
| **Molecular Subtype** | | | 0.696 |
| Non-TNBC | 311 | 30.6 | |
| TNBC | 706 | 69.4 | |
| **AJCC N stage** | | | **0.001** |
| N0 | 757 | 74.4 | |
| N1 | 174 | 17.1 | |
| N2,N3 | 86 | 8.5 | |
| **Primary tumor resection** | | | **0.001** |
| No | 52 | 5.1 | |
| Yes | 965 | 94.9 | |
| **Radiotherapy** | | | **0.001** |
| No | 532 | 52.3 | |
| Yes | 485 | 47.7 | |
| **Chemotherapy** | | | **0.003** |
| No | 286 | 28.1 | |
| Yes | 731 | 71.9 | |

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Efficacy and safety of entrectinib in *NTRK* fusion-positive (*NTRK*-fp) breast cancer

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Neurotrophic tyrosine receptor kinase genes (NTRK1/2/3) act as oncogenic drivers across a range of tumors. NTRK fusions occur at low frequency (<5%) in all breast cancer types, including >90% of secretory breast carcinomas. Furthermore, up to 30% of patients (pts) with breast cancer will develop central nervous system (CNS) metastases (mets). Entrectinib is a potent, oral TRKA/B/C, ROS1 and ALK inhibitor, specifically selected for its CNS penetration properties. Entrectinib was evaluated in 3 global phase 1/2 clinical trials (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], and STARTRK-2 [NCT02568267]), where it demonstrated strong and durable systemic and intracranial efficacy in pts with NTRK-fp solid tumors, including those with breast cancer. We present updated data from this integrated analysis (data cut-off: 31 October 2018) focusing on pts with breast cancer.

The entrectinib trials were conducted at >150 sites in 15 countries, and enrolled pts with locally advanced/metastatic NTRK-fp tumors (with or without baseline CNS mets) confirmed by nucleic acid-based methods. Tumor assessments were performed at the end of cycle 1 (4 weeks) and every 8 weeks thereafter, and evaluated by blinded independent central review (BICR) using RECIST v1.1. Primary endpoints were objective response rate (ORR) and duration of response (DoR) by BICR. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

At clinical cut-off, the overall efficacy-evaluable population included 74 adults from the 3 trials, with 12 different NTRK-fp tumor types and >25 histopathologies. In these pts, ORR by BICR was 63.5% (95% CI 51.5-74.4), including five complete responses (CR) and 42 partial responses (PR). Median (95% CI) DoR, PFS and OS were 12.9 (9.3-not estimable [NE]), 11.2 (8.0-15.7) and 23.9 (16.0-NE) months, respectively. The efficacy-evaluable NTRK-fp breast cancer cohort included 6 pts with a median age of 63 (range 36-67) years; most had an Eastern Cooperative Oncology Group performance status of 0 (3/6; 50%) or 1 (1/6; 17%). Breast cancer tumors were classified as secretory (4/6; 67%; all NTRK3-fp) or non-secretory (2/6; 33%; all NTRK1-fp). Pts had received 0 (3/6; 50%), 1 (1/6; 17%) or ≥4 (2/6; 33%) lines of prior therapy for metastatic disease. At data cut off, the median survival follow-up was 17.4 (range 1.7-23.9) months. ORR was 100% (2 CR, 2 PR; 95% CI 39.8-100.0) in pts with secretory and 50% (1 PR, 1 missing/unevaluable; 95% CI 1.3-98.7) in pts with non-secretory histology. Median (95% CI) DoR, PFS, and OS were 12.9 (4.2-NE), 10.1 (5.1-NE), and 23.9 (5.1-23.9) months, respectively. At baseline, 2 pts had CNS mets per investigator assessment; 1 of these pts had missing response data. CNS mets were confirmed by BICR in the other pt (non-secretory); this pt had received whole brain radiotherapy 2-6 months before starting entrectinib treatment, and had systemic PR and intracranial non-CR/non-progressive disease (non-measurable CNS lesion). The overall integrated safety-evaluable population comprised 504 pts with any gene fusion who received ≥1 dose of entrectinib. Most treatment-related adverse events (TRAEs) were Grade ≤3 (96.1%); the most frequently reported TRAEs were dysgeusia (39.7%) and fatigue (31.5%). Seven breast cancer pts were evaluated for safety, of whom six (85.7%) reported TRAEs; all were Grade ≤3. The most frequently reported TRAEs (each occurring in 3/7 pts; 42.9%) were nausea, anemia, and increased alanine or aspartate aminotransferase. Dose reductions and interruptions due to TRAEs were each reported in 3/7 pts (42.9%); no discontinuations or deaths due to TRAEs were recorded.

In this updated integrated analysis, entrectinib induced objective responses in all pts with NTRK-fp breast cancer who had data available, and was generally well tolerated with no discontinuations due to TRAEs.

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Three-dimensional H-scan ultrasound imaging for acute detection of breast cancer response to neoadjuvant treatment - Initial results using a preclinical animal model

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**Introduction:** The use of noninvasive ultrasound (US) for tumor tissue characterization is an exciting prospect for anticancer treatment response monitoring. To that end, our group has developed a new technology termed H-scan US imaging, which links differences in the raw backscattered US signals to various-sized tissue structures. The purpose of this research project was to develop a 3-dimensional (3D) H-scan US imaging system and method for tissue characterization in volume space and evaluate using a preclinical animal model of breast cancer.
**Methodology:** Preliminary studies were conducted using female nude athymic mice ($N$ = 20, Charles River Laboratories) implanted in the mammary fat pad with 1 million breast cancer cells (MDA-MB-231, ATCC). Once tumors reached about 1 cm in size, animals were sorted into four groups so that mean tumor size in each was comparable ($N$ = 5 per group). Animals were then US imaged at baseline and before receiving intraperitoneal injections, namely: (1) 0.3 mg sterile saline (control), (2) 0.2 mg of agnostic TRA-8 monoclonal antibody to human death receptor 5 (DR5) + 0.1 mg sterile saline, (3) 0.1 mg paclitaxel + 0.2 mg sterile saline, and (4) 0.1 mg TRA-8 + 0.2 mg paclitaxel. Image data was acquired using a programmable US scanner (Vantage 256, Verasonics Inc) equipped with a volumetric imaging transducer (4DL7, Vermon) at baseline and again every 24 hours for 3 days. To generate the H-scan US images, a set of Gaussian-weighted Hermite filters were convolved with the radiofrequency (RF) data to measure the relative strength of the received signals. The signal envelope for each of the filtered signal then was calculated using a Hilbert transformation. Finally, the lower frequency backscattered signals were assigned to a red (R) channel and the higher frequency components to a blue (B) channel. The unfiltered original RF signal was assigned to the green (G) channel to complete the RGB colormap and 3D H-scan US image display. After US imaging on day 3, animals were humanely euthanized and tumors excised for histological processing using the TUNEL HRP-DAB assay and immunofluorescent staining for activated caspase-3, PARP1, Ki-67, and DAPI.
**Results:** The *in vivo* results show that 3D H-scan US imaging is considerably more sensitive to tumor changes after neoadjuvant treatment as compared to traditional B-scan US. While there was no difference at baseline ($p$ = 0.52), repeat H-scan US results from treated tumors exhibited progressive increases in image intensity (164.9 ± 23.4%, 180.29 ± 11.6%, and 229.2 ± 14.6% for groups 2, 3, and 4 at day 3, respectively; $p < 0.05$) due to cancer cell nuclear condensation and apoptotic activity. Moreover, 3D H-scan US exhibited less variance than planar measurements due to increased sample size and statistical averaging. Histological findings also confirmed increased apoptosis and decreased proliferation that matched H-scan US data trends.
**Conclusions:** 3D H-scan US imaging is a promising technique that allows visualization of the heterogenous tissue microenvironment and improves the evaluation of treatment at an early stage of therapy as validated by histologic findings.

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# The gut microbial signatures of premenopausal breast cancer in Taiwan

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**Background** Unlike western countries, breast cancer tends to occur in older and postmenopausal female; in Taiwan, 40% of patients are younger than 50 years old and are mainly diagnosed in premenopausal women. Increasing evidence has demonstrated that microbiome-host interactions may contribute to breast cancer development and treatment in addition to genetic variations. Interestingly, current studies suggest the gut microbial community likely affects the risk for estrogen-related diseases in older adults. We aimed to explore the gut microbial profiles in regarding with menopausal status and elucidate whether the gut microbiomes and related function pathways were different in premenopausal and postmenopausal breast cancer patients in Taiwan. **Methods** A total of 70 healthy female controls (premenopausal/Pre-C, n=20; postmenopausal/Post-C, n=50) and 146 stage I/II breast cancer patients (premenopausal/Pre-BC, n=70; postmenopausal/Post-BC, n=76) were enrolled in our study. The microbial composition in fecal samples was analyzed using 16S rRNA amplicon sequencing (V3-V4 region) on the Illumina Miseq platform. The obtained data was analyzed using CLC Microbial Genomics Module (Qiagen, Germantown, MD, USA). Linear discriminant analysis effect size (LEfSe) and Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt) were analyzed with Galaxy/HutLab and Metagenomic Profiles (STAMP) software. **Results** Alpha diversity of the Shannon index was unexpectedly higher in Pre-BC when compared with that of Pre-C. Weighted beta-diversity with the principal coordinate analysis (PCoA) demonstrated that total microbial compositions were significantly different between Pre-C versus Pre-BC ($p$=0.001) and Post-C versus Post-BC ($p$=0.054). The Operational Taxonomic Units (OTUs) and Krona analysis showed that the abundance of *Proteobacteria* was significantly increased in both Pre-BC and Post-BC (p=0.011 and 0.017), whereas *Bifidobacterium* was significantly reduced in both Pre-BC and Post-BC1 (p<0.001 and 0.009) when compared with the matched controls, Pre-C and Post-BC. We further clarified the microbial markers based on the linear discriminant analysis effect size (LEfSe). As compared with Pre-C, Pre-BC had a much higher abundance of pathogens including *Shigella*, *Clostridium*, *Haemophilus* and others. The total microbial composition was also significantly different between Pre-BC and Post-BC ($p$=0.001). Intriguingly, the abundance of the microbiomes in alpha-Linolenic acid metabolism was reduced in Pre-BC when compared with Post-BC, whereas alpha-Linolenic acid metabolism were increased in both Pre-BC and Post-BC as compared with their matched controls. **Conclusion** Our results provide hints that, dysbiosis might be one of triggers or niches in contributing to Taiwan Pre-BC and might modulate multiple signaling pathways in relation to lipid metabolism and pathogen infections. The mechanisms underlying the link of specific gut microbiomes to Taiwan breast cancer require further investigations.

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Outreach to families with known BRCA mutation through the reach (research, education, and awareness of cancer family history) registry

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Background: Women with germline mutations in the BRCA1 or BRCA2 (BRCA1/2) genes have a significantly increased lifetime risk of developing breast and ovarian cancers. Since approximately 5-10% of breast and ovarian cancer is due to a hereditary predisposition, identification of a BRCA1/2 mutation has significant implications for early cancer detection, prevention, and cancer treatment options. Additionally, identifying women with a *BRCA1/2* mutation allows for targeted, family-based cancer screening and prevention in their at- risk relatives. Any first degree relative (parents, siblings, and children) of an individual identified to carry a *BRCA1/2* mutation has a 50% chance of carrying the same mutation. However, little is known if and how genetic test results are conveyed to family members and what they do with this information. UT MD Anderson Cancer Center initiated a project REACH (Research, Education and Awareness of Cancer Family History) that aims to maximize the identification of hereditary breast and ovarian cancer in at-risk family members of individuals identified to have a *BRCA1/2* mutation (pathogenic variant or variant of uncertain significance). Here we present the infrastructure and initial feasibility of this prospective initiative. Methods: This study is conducted through the University of Texas MD Anderson Cancer Center's Women Cancer Moonshot and Clinical Cancer Genetics program at MD Anderson. The probands consists of BRCA1/2 positive triple negative breast cancer (TNBC) patients that underwent universal BRCA testing between 2014-2019 on a preceding Universal BRCA Testing registry (published elsewhere) and BRCA1/2 positive patients that presented to the breast center clinic. Probands are consented for a prospective family outreach protocol (REACH registry) where they give us permission to contact their relatives. The REACH registry includes questionnaires (related to family communication, genetic testing, cancer risk reduction, and surgical choices), optional yearly follow ups, and active outreach to at-risk family members using an innovative information-technology platform and a variety of web-based patient education tools. Results: Since 2014 a total of 122 probands with TNBC and a BRCA germline mutation were enrolled into the REACH registry and of those 92 (75.4%) completed the baseline questionnaire. Of the 62 second year follow up questionnaires sent, 42 (67.8%) were completed. Before pausing study activities in 2017 (due to funding), of the 18 third year follow up questionnaires sent, 5 (27%) were completed. We were able to enroll 38 at-risk family members of TNBC probands into the registry. 31 (81%) of the family members completed the baseline questionnaire. Of the 26 second year follow up questionnaires sent to family members, 17 (65.4%) were completed. Before a pause in study, of the 10 year three questionnaires sent, 7 (70%) were completed. The study restarted in 2019, recruitment, questionnaires and web-based education are on-going. Conclusion: We have shown that it is feasible to develop a practical infrastructure that allows us to continue communication with our proband and to connect with their at-risk relatives to further communicate with them issues related to genetic testing, interpretation, implications and screening. The next phase will include to offer virtual genetic counseling and testing family members.

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# Rare variants in the germline genome holistically determine receptor-independent Her2 signaling pathway activation and immune suppression, shaping pathological type and risk of HER2-negative breast cancer

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**Background**: Pathogenic factors embedded in the germline genome are widely recognized as being crucial to breast cancer development. However, current knowledge is either concentrated on the pathogenic variants of a few individual genes or SNPs distributed sparsely across the genome in non-coding regions. **Methods**: We developed a multi-layered framework, DAGG, which converts somatic mutations or germline rare coding variants (gRCVs) into a functional spectrum of dozens of cellular functions and signaling pathways to identify potential pathogenic factors.**Findings:** We analyzed whole-exome sequencing (WES) data of 726 germline DNA samples and 169 breast tumor DNA samples from breast cancer patients with various pathological types and cancer-free female subjects, we found that germline pathogens of breast cancers were (1) mainly distributed in HER2-negative subtypes, and (2) involved Her2 signaling pathway activation and immune suppression. These computational discoveries were experimentally validated and can provide digital features to explain the germline differences between diseased and healthy genome (AUC = 0.76). Furthermore, an individual's risk for breast cancer can be estimated by calculating the combined effects of these identified germline pathogens. Carriers of BRCA1/2 pathogenic variants were found to have a significantly higher average risk (p = 0.02). Interpretation: The results demonstrated that the identified pathogenic mechanisms by DAGG were compatible with our current understanding of the causes of breast cancer. Moreover, DAGG provides improved performance over currently used polygenic risk score method of measuring complex disease risks. Our framework promises possible future applications for the prevention, diagnosis, and treatment of breast cancer.

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Solti-1502 aRIANNA: Targeting PAM50 HER2-enriched intrinsic subtype with enzalutamide in hormone receptor-positive/HER2-negative metastatic breast cancer

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**Background** Pre-clinical evidence and retrospective studies suggest that PAM50 HER2-Enriched (HER2-E), hormone receptor-positive (HR+)/HER2-negative tumors have estrogen receptor (ER)-independency and poor prognosis, but seem to have androgen receptor (AR)-addiction (1). Enzalutamide (EZM) is a potent inhibitor of androgen receptor signaling (3). AR expression has been shown to induce resistance to both tamoxifen and aromatase inhibitors in estrogen receptor HR-expressing cell lines (4,5) The hypothesis of the ARIANNA trial is that EZM induces a significant proliferative arrest in PAM50 HER2-E, HR+/HER2-negative advanced breast cancer (BC), leading to clinical benefit in this poor prognosis population. **Methods** ARIANNA is an exploratory, phase II clinical trial in two independent cohorts evaluating the effect of EZM on proliferation after 2 weeks (+7 days window) on treatment in pre- or post-menopausal female or male patients with endocrine-resistant, locally advanced or metastatic HR+/HER2-negative BC. Cohort A will include 22 patients with PAM50 HER2-E HR+/HER-negative tumors and Cohort B (control group) will include 22 patients with PAM50 Luminal A/B HR+/HER2-negative tumors. Fresh tumor biopsy will be obtained at screening and sent to central laboratory for PAM50 subtyping determination to confirm the molecular subtype status prior to study treatment initiation, and to determine PAM50 11-gene proliferation-related signature. Patients with PAM50 Basal-like or Normal-like tumors will be excluded. Patients will receive EZM 160 mg once a day (QD). After 2 weeks on treatment, a tumor biopsy from the same baseline lesion (or, if not feasible, a lesion in the same organ) will be obtained for the purpose of the primary endpoint analysis. After this on-treatment biopsy, exemestane 50mg QD can be added to EZM at physician's discretion. Tumor assessment will be performed at screening and every 8 weeks thereafter. Treatment will be continued until disease progression, unacceptable toxicity, investigator's decision or withdrawal of consent. An optional tumor biopsy will be collected at the end of treatment. The primary objective is to evaluate the anti-proliferative effect of EZM after 2 weeks of treatment in patients with HER2-E HR+/HER2-negative tumors, measured as relative changes in the PAM50 11-gene proliferation-related signature by the PAM50 nCounter-based assay between baseline and on-treatment tumor biopsies. Secondary objectives include: anti-proliferative effect of EZM after 2 weeks of treatment in patients included in Cohort B (control group), safety, overall response rate, progression-free survival, and further correlative molecular analyses both at the tumor tissue (IHC, RNA and DNA) and ctDNA level for both cohorts. The trial will enroll patients in 8 Spanish sites and recruitment period will be 18 months. Funding was granted by Breast Cancer Research Foundation and drug was supplied by Astellas Pharma Global Development, Inc./Pfizer, Inc. Trial identification: NCT04142060 1. Cochrane DR, Bernales S, Jacobsen BM, Cittelly DM, Howe EN, D'Amato NC, et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. Breast Cancer Res. 2014;16:R7. 3. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. Science. 2009;324:787-90. 4. Rechoum Y, Rovito D, Iacopetta D, Barone I, Andò S, Weigel NL, et al. AR collaborates with ERα in aromatase inhibitor-resistant breast cancer. Breast Cancer Res Treat. 2014;147:473-85. 5. De Amicis F, Thirugnansampanthan J, Cui Y, Selever J, Beyer A, Parra I, et al. Androgen receptor overexpression induces tamoxifen resistance in human breast cancer cells. Breast Cancer Res Treat. 2010;121:1-11

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# Racial disparities in breast cancer outcomes: A SEER population based study

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Introduction: Breast cancer (BC) is the second leading cause of female cancer-related mortality in the United States. Despite advances in therapies which have significantly lowered BC mortality rates over the years, the decline in mortality in African American/Black women continues to lag behind. Black women with BC continue to do poorly compared to non-Hispanic White women. The etiologies underlying this disparity are multifactorial and still remain unclear. Our study aims to investigate the differences in clinical and socioeconomic characteristics (cts) between Blacks and Whites and evaluate their prognostic value on long-term outcomes. Methods: We conducted a retrospective, population-based analysis utilizing the Surveillance, Epidemiology, and End Results (SEER) database, and studied BC pts from 1975-2017. Different demographic and clinical cts were analyzed by race. Univariate (UV) and multivariable (MV) analyses were performed to evaluate the associations of race with disease-specific survival (DSS), overall survival (OS) using Cox regression models. Results: A total of 816,763 pts were analyzed (n=720,144 White, n=966,19 Black). As compared to White BC patients (pts), Black pts were younger in age (median age 57 years vs. 62 years), with a higher tumor stage (III/IV; 25% vs. 16.3%) and a higher tumor grade (III/IV; 52.2% vs. 35.3%) at disease presentation (p<0.001). Furthermore, Black pts were more likely to present with triple-negative (23.9% vs. 11.1%) and Her-2+ BC (20.6% vs. 16.3%) than White pts (p<0.001). Black pts were also more likely to be uninsured (3.4% vs.1.1%), single (64.3% vs. 42.5%), and less likely to receive breast surgery (90.7% vs. 95.4%) as compared to White pts (p<0.001). A higher proportion of Black pts lived in urban areas (93.9% vs. 87.9%) and had a higher county-level availability of hospitals with oncology services per million population (median 126 vs. 120.6) than White pts (p<0.001). Black pts had a worse DSS (Hazard Ratio (HR) 1.68, 95% CI 1.66-1.71)) and OS (HR 1.30, 95% CI 1.29-1.31) compared to White pts (p<0.001). The racial differences in DSS and OS remained significant on both UV and MV analyses while controlling for each demographic and clinical variable. Conclusions: Our study confirms that Black pts with BC have a worse OS and DSS as compared to White pts. These disparities could be partially explained by observed differences in underlying aggressive tumor biology (stage, grade, hormone receptor status, age at diagnosis), lower access to health care (insurance status and % receiving breast surgery) and weaker social support systems (% single). However, the fact that the survival disparity persisted even after controlling for these factors suggests that there are potentially more variables driving these racial differences in breast cancer outcomes. We note that more Black pts resided in UA and had access to hospitals with oncology services reflecting that there could be disparities in health care utilization patterns. Further studies investigating these variables would be of paramount importance in order to identify underlying causes for poorer outcomes in Black pts and help eliminate this survival gap.

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# Determination of serum progranulin (GP88) levels complements CA15-3 to monitor disease progression & response to therapy in metastatic breast cancer patients

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Background: Progranulin (GP88) is a critical player in breast tumorigenesis. High PGRN/GP88 tumor expression measured by immunohistochemistry is associated with increased risk of recurrence and mortality in estrogen receptor positive breast cancer patients. PGRN/GP88 circulating levels are elevated in breast cancer patients, compared to healthy individuals. In the present study, we examined the possible correlation between serum PGRN/GP88 levels in metastatic breast cancer (MBC) patients with overall survival and disease status determined as response to therapy or progression of disease. Methods: An institutional review board (IRB) approved study prospectively enrolled 101 MBC patients at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center (UMGCCC). Blood samples were collected during follow-up visits. PGRN/GP88 serum levels were determined by PGRN/GP88 sandwich enzyme immunoassay developed in our laboratory and clinically validated. The serum levels were correlated with patients' disease status determined by RECIST 1.1 criteria and with survival outcomes by Kaplan Meier analysis and Logrank statistics. Results: Patients' survival was stratified by serum PGRN/GP88 level. Patients with serum PGRN/GP88 <56 ng/ml had a four-fold increased survival compared to patients with serum levels > 56 ng/ml. Examination of PGRN/GP88 serum levels in association with disease status showed a statistically significant association between serum GP88 levels disease progression or response to therapy. Cox proportional modeling showed that the association of serum GP88 level with survival was independent of age, race and tumor characteristics (ER/PR/Her-2 status, tumor size and lymph node status). We examined the association of serum PGRN/GP88 levels with response to therapy or progression of disease and compared the results with the ones obtained for CA15-3. While serum CA15-3 was strongly associated with progression of disease but not with response to therapy, serum PGRN/GP88 measurements were statistically associated not only with progression of disease but more importantly with response to therapy. Moreover, the information provided by GP88 on disease status (progression or response to therapy) was additive to the one provided by CA15-3 in this study population. Conclusions: The association of serum Progranulin/GP88 level with disease status and its additive value to CA15-3 measurements suggests the potential of using serum progranulin test for monitoring disease status in MBC patients during and post-treatment. Measurement of serum PGRN/GP88 levels in MBC patients will have clinical value as a cost-effective adjunctive to imaging MBC patient management and complementary to CA15-3 determinations. This test can fulfill needs for new and improved tumor biomarkers to monitor disease status and manage risk for patients with metastatic breast cancer. Support: This work was supported by grant 2R44CA210817 from the National Cancer Institute to Ginette Serrero.

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# Artificial intelligence-assisted interpretation of Ki-67 expression and repeatability in breast cancer

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**Objective:** Ki-67 Label Index (Ki-67LI) is a breast cancer(BC) predictive and prognostic factor. The lack of standardization and reproducibility of evaluation methods limits its use in routine work. In this study, Ki-67 standard comparison card (SRC) and artificial intelligence(AI) software were used to evaluate breast cancer Ki-67LI. We established training and validation sets and studied the repeatability between observers. **Methods:** A total of 300 invasive breast cancer specimens were randomly divided into training and verification sets, with each set including 150 cases. Breast cancer Ki-67 standard comparison cards ranging from 5% to 90% were created. The training set was interpreted by nine pathologists of different ages through microscopic visual assessment (VA), SRC, microscopic manual counting (MC), and AI. The validation set was interpreted by three randomly selected pathologists using SRC and AI. Friedman M was used to analyze the difference. The intra-group correlation coefficient (ICC) and Bland-Altman scatter plot were used for consistency analysis. **Results:** 1.Ki-67LI interpreted by the four methods in the training set did not obey a normal distribution ($P<0.05$). Friedman M test showed that the difference between pathologists using the same method was statistically significant ($P<0.05$). After Bonferroni correction, Ki-67LI interpreted using SRC and AI showed that the difference between each pathologist and the gold standard was statistically significant ($P<0.05$), and the difference between pathologists was not statistically significant ($P>0.05$); Ki-67LI interpreted using VA and MC showed that the difference between each pathologist and the gold standard and the difference between pathologists were statistically significant ($P<0.05$). 2. The intra-group correlation coefficient(ICC) obtained by nine pathologists in the training set that used SRC (ICC=0.918) and AI (ICC=0.972) to interpret Ki-67LI, was significantly higher than when VA (ICC=0.757) and MC (ICC=0.803) were used. 3. Through SRC, the initial and intermediate pathologists in the training set had an increased ICC. 4. In the homogeneous group of the training set, the agreement on observers of VA, MC, SRC, and AI among observes was very good, with all ICC values above 0.80. In the heterogeneous group, SRC and AI showed a good agreement among observers (ICC= 0.877 and 0.959 , respectively). In the homogeneous and heterogeneous groups of validation sets, the consistency among the pathologists that used SRC and AI was very good, with an ICC of>0.90. 5. In the verification set, using SRC and AI, three pathologists obtained results that were very consistent with the gold standard, having an ICC above 0.95, and the inter-observer agreement was also very good, with an ICC of>0.9. **Conclusion:** AI has satisfactory inter-observer repeatability, and the true value was closer to the gold standard, which is the preferred method for Ki-67LI reproducibility; While AI software has not been popularized, SRC may be interpreted as breast cancer Ki-67LI's standard candidate method.**Keywords:** Breast cancer, Ki-67, Artificial intelligence, Ki-67 standard comparison card, Repeatability

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Pixel-level tissue classification from ultrasound images of breast cancer and direct comparison to matched histological measurements

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**Introduction:** The use of noninvasive ultrasound (US) for quantitative tissue characterization has been an exciting research prospect for several decades now. Herein the challenge is to find hidden patterns in the US data to reveal more information about tissue function and pathology that cannot be seen in the more conventional US images. A new pixel-level analysis technique has been developed by our group for tissue classification. Termed H-scan US (H stands for hue or Hermite), this imaging approach links a special class of $n^{th}$-ordered Gaussian-weighted Hermite functions (GHn) to the physics of US scattering and reflection from different tissue structures. The sensitivity of *in vivo* H-scan US imaging to subtle changes in scatterer size is a question that has not been fully answered. To that end, the purpose of this study was to compare local H-scan US image intensity to direct (co-registered) histological measures made at the cellular level.

**Methodology** Female nude athymic mice were implanted into mammary fatty pad with breast cancer cells ($N$ = 8). Implanted tumors were allowed to grow for about four weeks before study enrollment. Image data was acquired using a programmable US scanner (Vantage 256, Verasonics Inc) equipped with a 256-element L22-8v CMUT linear array transducer (Kolo Medical). Plane wave imaging with 5 angles was performed at a center frequency of 15 MHz. To generate the H-scan US image, three parallel convolution filters (GH2, GH6, and GH10) were applied to the radiofrequency (RF) data sequences to measure the relative strength of the received signals. After envelope detection, the relative strength of the filter outputs is color coded whereby the lower frequency (GH2 = 9 MHz) backscattered US signal components are assigned to the R channel, moderate frequency (GH6 = 15 MHz) signals are assigned to the G channel, and the higher frequency (GH10 = 21 MHz) signals to the B channel. After performing H-scan US, the imaging cross-section was marked, and the tumors were excised and sliced along the same plane for histologic processing. After nuclear staining, tissue sections were scanned and digitized using confocal microscopy and fluorescent filters for DAPI. Automated segmentation of each cancer cell nucleus in the histologic sections was performed using an active contour technique. US images were interpolated to the same number of pixels as the histology image and spatial alignment between the two was performed. Lastly, nucleus size and density from histologic sections was compared to local H-scan US image features.

**Results:** Custom software was developed to compare local US image features at the pixel level to that of co-registered histologic images and measurements of nuclear size and density. In an attempt to properly match the histological and the H-scan US images, three different sized kernels of 0.16 × 0.16 mm, 0.32 × 0.32 mm or 0.5 × 0.5 mm were used to partition both the H-scan US and histology images into 1888, 448 or 62 distinct region-of-interests (ROIs), respectively. Mean nuclear size and density measurements from the histology ROIs was compared to the mean H-scan US image intensity from the many spatially matched ROI locations. A statistically significant linear relationship was found between local H-scan US image intensity and nuclear size ($R^2 > 0.4$, $< 0.001$) and density ($R^2 > 0.6$, $p < 0.001$).

**Conclusions:** Preliminary results from use of an animal model of breast cancer reveals that *in vivo* H-scan US images positively correlated with physical measures of nucleus size and density as quantified from co-registered histologic images.

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# Factors influencing fatigue in breast cancer patients undergoing breast irradiation

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**Background**: Fatigue is one of the most common acute complications of radiation therapy (RT). It can have a serious impact on a patient's quality of life and ability to engage in treatment, and has been associated with lower recurrence-free and overall survival in patients with breast cancer. The pathogenesis of radiation-induced fatigue remains elusive, and factors implicated include biological (low hemoglobin and elevated pro-inflammatory cytokines and chemokines) and psychological (pain, depression and anxiety). Although it is a common clinical issue, optimal treatment strategies are lacking, and a better understanding of the mechanisms involved is needed to devise effective interventions. The purpose of this exploratory, non-randomized, prospective study was to examine a number of possible biological and psychological factors influencing fatigue in patients undergoing breast irradiation for early stage breast cancer.

**Methods**: All subjects were assessed at five time points: immediately before RT, mid-point of RT, end of RT, and 6 months and 1 year after completion of RT. Clinical evaluation of skin toxicity and cosmetic outcome and laboratory measures evaluating anemia and hepatic toxicity were performed. Laboratory markers of systemic inflammatory/stress response included salivary cortisol, CRP and cytokines. Caspase-1 and caspase-3, novel markers of apoptosis, were also collected. Fatigue, distress, depression, anxiety, sleep, energy level and pain were assessed at each time point using validated measures. A two-sample student t-test or a non-parametric Wilcoxon rank sum test was used to identify significant associations between fatigued and non-fatigued subjects at each time point.

**Results**: Fifty-three subjects completed the study. Subjects were predominantly white and non-Hispanic, middle to upper-middle class, with a mean age of 59. Fatigued subjects were more likely than non-fatigued subjects to have a history of anxiety and/or depression. Across all subjects, fatigue increased during treatment and returned to or near baseline by 6 months after treatment. Fatigue was significantly associated with overall distress, energy level, and some measures of physical and functional well-being during treatment; these associations were not present at baseline and resolved by 6 months. Fatigued subjects were more likely to have increases in depression scores by the end of treatment, although mean depression scores did not reach clinical significance. Fatigue was significantly associated with breast-specific pain by the end of treatment, and this resolved by 6 months. Fatigue was significantly associated with some measures of sleep at baseline, and this persisted during treatment and resolved by 6 months to 1 year. Fatigue was not associated with measures of skin toxicity and cosmetic outcome and laboratory measures of anemia, hepatic toxicity, salivary cortisol, caspase-1, caspase-3, and IL-10; most other cytokines were undetectable.

**Conclusions**: This was a comprehensive, longitudinal study evaluating the association of biological and psychological factors with the development of fatigue in patients undergoing breast irradiation. As expected, in patients experiencing heightened fatigue during breast irradiation, fatigue was greatest at the end of treatment and returned to or near baseline by 6 months after treatment. Important associations with the development of fatigue included physical and functional parameters, and of particular significance were patients with a prior history of mental health diagnoses. In contrast to previous studies, we did not find an increase in pro-inflammatory or in novel biomarkers including caspase-1 and caspase-3. Identification of and interventions directed at those patients at risk could impact positively on the experience associated with fatigue and radiation.

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# Comparison of healthcare resource utilization and costs in women with HR+/HER2- metastatic breast cancer treated with ribociclib vs palbociclib or abemaciclib

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**Background**: Ribociclib, palbociclib, and abemaciclib are cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors for the treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer (mBC). The economic burden of women with HR+/HER2- mBC treated with different CDK4/6 inhibitors has not previously been compared. **Objective**: To describe and compare healthcare resource utilization (HRU) and healthcare costs in patients treated with CDK4/6 inhibitors in real-world clinical practice. **Methods**: Adult women with HR+/HER2- advanced or mBC who initiated treatment with ribociclib, palbociclib, or abemaciclib as the first CDK4/6 inhibitor (index therapy) were identified from IBM MarketScan Data (Q1 2000 - Q3 2018), a large US commercial claims database. HRU and healthcare costs were measured while patients were on treatment with their index CDK4/6 inhibitor. Total healthcare costs, measured from a payers' perspective, included medical (inpatient [IP], outpatient [OP], emergency room [ER]) and pharmacy costs, reported per-patient-per-month (PPPM). HRU and healthcare cost components were each separately compared between ribociclib and palbociclib cohorts, and between ribociclib and abemaciclib cohorts, using models adjusting for age, line of therapy, menopausal status, metastatic sites, and comorbidities. **Results**: A total of 4,320 women were included: 102 initiated ribociclib as first CDK4/6 inhibitor; 4,118 palbociclib; and 100 abemaciclib. The majority in each cohort were postmenopausal (ribociclib: 79%; palbociclib: 92%; abemaciclib: 92%), and received the index CDK4/6 inhibitor as either first-line (ribociclib: 40%; palbociclib: 31%; abemaciclib: 30%) or second-line therapy (ribociclib: 23%; palbociclib: 24%; abemaciclib: 22%). HRU was not statistically different between the ribociclib and palbociclib cohorts, whereas the ribociclib cohort had fewer IP days compared to the abemaciclib cohort (adjusted incidence rate ratio [IRR]: 0.25, 95% CI: 0.09; 0.67). Total healthcare costs were not statistically different between the ribociclib and palbociclib cohorts, although the ribociclib cohort had lower OP costs PPPM compared to the palbociclib cohort (-$1,339, 95% CI: -2,344; -209). Total healthcare costs were statistically lower for the ribociclib cohort compared to the abemaciclib cohort (-$6,519; 95% CI: -9,959; -2,984). IP costs, OP costs, and pharmacy costs (driven by CDK4/6 inhibitor costs) were all significantly lower for the ribociclib cohort vs the abemaciclib cohort (IP: -$3,398, 95% CI: -22,801; -768; OP: -$3,778, 95% CI: -6,502; -1,659; pharmacy costs: -$1,744, 95% CI: -2,881; -564).
**Conclusions**: HRU while on treatment was similar between ribociclib and palbociclib, while ribociclib had fewer IP days compared to abemaciclib, after adjusting for baseline covariates. Total healthcare costs while on treatment were higher in the abemaciclib cohort compared to the ribociclib cohort, while ribociclib and palbociclib cohorts tended to have similar total healthcare costs.

| | **Ribociclib vs. Palbociclib** | | | **Ribociclib vs. Abemaciclib** | | |
|---|---|---|---|---|---|---|
| **HRU** | **Adjusted IRR** | **Confidence interval** | **P-val** | **Adjusted IRR** | **Confidence interval** | **P-val** |
| IP admissions | 1.09 | (0.62; 1.91) | 0.76 | 0.67 | (0.29; 1.53) | 0.34 |
| IP days | 0.67 | (0.35; 1.28) | 0.22 | 0.25 | (0.09; 0.67) | 0.01* |
| Days with ER services | 1.44 | (0.80; 2.57) | 0.22 | 0.76 | (0.37; 1.59) | 0.47 |
| Days with OP services | 1.01 | (0.91; 1.14) | 0.80 | 0.88 | (0.73; 1.04) | 0.14 |
| **PPPM Healthcare costs** | **Adjusted cost difference** | **Confidence interval** | **P-val** | **Adjusted cost difference** | **Confidence interval** | **P-val** |
| **Total healthcare costs** | -1,013.82 | (-3,436; 1,924) | 0.48 | -6,519.18 | (-9,959; -2,984) | <0.01* |
| **Medical costs** | -1,222.84 | (-3,275; 1,231) | 0.32 | -6,142.36 | (-9,907; -2,844) | <0.01* |
| IP costs | -279.61 | (-1,516; 1,749) | 0.76 | -3,397.88 | (-22,801; -768) | 0.01* |
| ER costs | 481.32 | (-87; 1,503) | 0.19 | 577.82 | (-105; 2,449) | 0.16 |
| OP costs | -1,338.92 | (-2,344; -209) | 0.03* | -3,778.20 | (-6,502; -1,659) | <0.01* |
| **Total pharmacy costs** | -28.95 | (-798; 917) | 0.91 | -1,743.98 | (-2,881; -564) | <0.01* |
| CDK4/6 costs | 120.08 | (-592; 1,053) | 0.83 | -1,631.39 | (-2,755; -464) | 0.01* |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS17-29

Surgically induced weight loss corrects obesity associated tumor progression and improves responsiveness to immunotherapy

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Background: Obesity leads to a higher risk of cancer invasion, metastases, recurrence, mortality, and impaired therapeutic response through various mechanisms. One of these mechanisms is microenvironment dysfunction, where changes in immune cells, microbes, metabolites, and growth factors contribute to tumor aggressiveness. We study obesity-induced changes to the tumor microenvironment in Triple Negative Breast Cancer (TNBC), an aggressive subtype associated with obesity. The goal to compare tumor progression in lean vs. obese vs. weight loss manipulations to identify causal and targetable pathways associated with reprogramming the tumor microenvironment. Clinically, bariatric surgery induced weight loss reduced the risk of BC, with the greatest benefit detected in pre-menopausal patients with ER- tumors, like TNBC. We hypothesize surgically-induced weight loss will diminish obesity-associated tumor progression. Methods: To study weight gain and loss that best mimics human adiposity, we utilized obesogenic C57BL/6 females with a syngeneic orthotopic transplant of TNBC cells. Female mice placed on a high fat diet (HFD) at weaning became obese compared to mice on a low fat diet (LFD). After 16 weeks on an HFD diet, mice underwent the bariatric surgery Vertical Sleeve Gastrectomy (VSG). The VSG resulted in reduced body weight, adiposity, and correction of metabolic profiles compared to obese mice. Two weeks post-surgery, TNBC cells were OT into the mammary fat. Results: As expected, tumor growth was increased in obese mice compared to lean. Importantly, surgical weight loss rescued obese tumor progression. We identified key changes in tumor infiltrating of immune cells that could be responsible for the beneficial effects of bariatric surgery on tumor progression. We then exploited these changes with immunotherapy, which was uniquely effective in mice that underwent bariatric surgery. Conclusions: In conclusion obesity promotes a pro-tumor microenvironment, that can be corrected through surgically induced weight loss.

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# A prospective phase II trial to evaluate the feasibility of omit sentinel lymph node biopsy after integrate18F-FDG dedicated axillary PET in early breast cancer: SOAPET trial

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**Purpose:** Sentinel Lymph Node Biopsy (SLNB) is currently the standard of care in clinical node negative (cN0) early breast cancer. The aim of this study is to evaluate the negative predictive value of 18F-FDG dedicated axillary PET (DA-PET) and to verify whether SLNB can be omitted in patients with negative preoperative axillary assessment.
**Patients and Methods:** SOAPET is a prospective phase II trial consisted of 2 stages (NCT04072653). In the first stage, cN0 patients detected by clinical examination, received routinely axillary imaging evaluation (ultrasound and CT etc) and DA-PET, then received SLNB. In the second stage, SLNB will be omitted in the patients with negative preoperative axillary assessment after integrate DA-PET. Now we report the results of the first stage, the primary outcome is negative predictive value (NPV) of DA-PET to detect non-macrometastases of lymph nodes.
**Results:** From Sep 9, 2019 to May 30, 2020, 224 patients were screened, and 189 patients with invasive breast cancer (180 invasive ductal carcinoma, 9 invasive lobular carcinoma) received DA-PET followed by surgical operations with definitive pathological reports. Media tumour size was 2.2cm, 120 HR+HER2-, 23 HR+HER2+, 27 HR-HER2+, 19 HR-HER2-. 40 patients had at least 1 macrometastases lymph nodes (8 patients had over 3 nodes involved), and 16 patients had only micrometastasis nodes. Among 131 patients with DA-PET negative (maxSUV<0.27), 16 patients had macrometastases lymph nodes and 11 patients had micrometastasis diseases. For 58 patients with DA-PET positive (maxSUV>=0.27), 24 patients had macrometastases and 5 patients had micrometastasis nodes. The NPV of DA-PET was 87.8%. The NPV of ultrasound was 86.3%. When combine axillary imaging evaluation with ultrasound and DA-PET, 100 patients were screened out with both DA-PET and ultrasound negative, among which 9 patients had macrometastases and 9 patients had micrometastasis nodes, the NPV was 91%. **Conclusions:** DA-PET can be used to identify cN0 patients, reducing the false negative rate < 10%. The second stage of SOAPET trial is ongoing to validate the safety of omitting SLNB according to preoperational axillary evaluation when integrating DA-PET. **Key words:** Breast cancer, Sentinel lymph node biopsy; Dedicated PET;18F-FDG;

**Table 1:** Axillary lymph node detection efficiency of ultrasound and DA-PET

| Axillary imaging assessment | Patients n | macrometastases | micrometastasis only |
|---|---|---|---|
| ultrasound* | | 40 | 16 |
| US-neg | 124 | 17 | 12 |
| US-det | 46 | 14 | 4 |
| US-met | 19 | 9 | 0 |
| DA-PET** | | | |
| negative | 131 | 16 | 11 |
| positive | 58 | 24 | 5 |

*:US-neg: no lymph nodes detected by ultrasound;US-det: lymph nodes detected by ultrasound;US-met: suspected metastatic lymph nodes detected by ultrasound**:Maximum single-voxel Standard Uptake Value (maxSUV) cutoff value of DA-PET was set at 0.27 (<0.27 is negative)

Table 2: Intergrate axillary imaging assessment with ultrasound and DA-PET

| | | macrometastases | | |
|---|---|---|---|---|
| | | + | - | |
| axillary imaging assessment | + | 31 | 58 | 89 |
| | -* | 9 | 91 | 100 |
| | | 40 | 149 | 189 |

*:no lymph nodes detected by ultrasound and maxSUV in DA-PET < 0.27

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Insights into the molecular underpinnings of the mevalonate pathway-YAP/TAZ-driven anti-HER2 therapy resistance in HER2+ breast cancer (BC)

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**Background.** We recently reported that the biosynthetic mevalonate (MVA) pathway that produces cholesterol and isoprenoid intermediates, regulates the YAP/TAZ (Y/T) transcriptional co-activators to promote resistance to treatment regimens that effectively inhibit HER2 signaling in HER2+ BC. We further showed that the mTORC1 complex and survivin protein, which contribute to HER2-elicited oncogenic signaling in HER2-driven BC cells, are alternatively activated by the MVA pathway-Y/T axis in anti-HER2 therapy resistant cell models. Of note, other recent reports also showed that increased Y/T activity enables resistant cells to proliferate when other oncogenic pathways (*e.g.,* RAS, EGFR, and FGFR) were effectively inhibited. Here, we sought to further determine the molecular underpinnings of MVA-Y/T axis-driven anti-HER2 therapy resistance to discover novel therapeutic targets and predictive biomarkers for HER2+ BC.**Methods.** SKBR3 HER2+ BC parental (P) cells and their lapatinib plus trastuzumab (LT) resistant (LTR) derivatives with sustained HER2 inhibition were treated with the MVA pathway inhibitor simvastatin (Sim), with or without the MVA metabolite to rescue Sim's inhibitory effects. P and LTR cells were also transfected with control or combined Y/T siRNAs. The transcriptomes of all treatment groups were assessed by RNA-seq. Integrative bioinformatics analyses were used to identify differentially expressed (DE) genes and gene sets with functional annotations in LTR vs. P cells upon different interventions.**Results.** We found that cell cycle and cell proliferation processes were among the top common DE molecular signatures preferentially downregulated (DN) in LTR vs. P cells by both Sim and Y/T knockdown (KD). The top common genes preferentially DN in LTR vs. P cells include the cell cycle regulatory genes *CDCA3* and *ERCC6L*, and the nucleotide metabolism genes *TYMS* and *RRM2*. Interestingly, 20% of the genes preferentially DN in LTR vs. P cells by Sim or Y/T KD were predicted to be direct Y/T transcriptional targets based on previously reported ChIP-seq data (PMID: 26258633). Of the Y/T-dependent genes, a significant enrichment of Sim-repressed genes was observed in both P and LTR cells ($P$ = 1.2e-115 and $P$ = 5.5e-138, respectively). The proportion of these enriched genes was higher in LTR vs. P cells (61% vs. 29%). Of note, we found that the global inhibited genes in LTR cells upon Sim or Y/T KD were significantly enriched for the genes DN by short-term LT treatment in P cells ($P$ < 2.2e-16). Likewise, of the genes nominated as putative molecular players in the MVA pathway-Y/T-mediated resistance, *BIRC5* (survivin), *CDC6*, *KIF2C*, *RRM2,* and *TYMS* were recently also reported to be DN in HER2+ tumors treated with neo-adjuvant LT in the PAMELA trial (NCT01973660), a finding that is in line with what we observed in our P cells treated with short-term LT. **Conclusions.** Upon acquisition of resistance to sustained HER2 inhibition, the MVA pathway-Y/T axis takes over the regulation of pro-proliferative transcriptional programs that are generally downstream of HER2 signaling in treatment-naïve HER2+ BC. The MVA pathway-Y/T axis leads to Y/T-driven transcriptional reprogramming, an emerging mechanism of therapy resistance to anti-HER2 and other targeted therapies that warrants further investigation. The identification of multiple cell cycle related processes as putative targets of the MVA pathway-Y/T axis presents additional targetable vulnerabilities and implies that inhibitors of Y/T and cell cycle checkpoints may help circumvent anti-HER2 resistance in the clinical setting.

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# Pten regulates site specific hydroxylation of collagen proline in normal breast and breast cancer tissue

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**INTRODUCTION** We present the first report of translational and post-translational collagen regulation co-localized with PTEN signaling in breast cancer and breast tissues at-risk for breast cancer. Decreases in tumor suppressor phosphatase and tensin homolog (PTEN) have been associated with activated stroma surrounding tumors across many cancer types. In breast cancer, PTEN downregulation occurs concomitant with realignment of collagen fibers in stroma to promote oncogenic signaling and later recurrence. Collagen fiber organization and subsequent cell-fiber signaling is controlled mainly by hydroxylation at variable proline sites, however collagen regulation associated with PTEN signaling remains undefined. Here, data is presented showing that site-specific regulation of collagen proline hydroxylation with co-localizes with PTEN signaling in normal breast tissue and in triple negative breast cancer.

**METHODS** Formalin-fixed paraffin embedded tissues from a breast tumor microarray (TMA), normal breast TMA, biopsies and lumpectomies were tested with IRB approval. PTEN scoring was done based on previously published work (Sizemore et al, Nature Communications, 2018, 9, 2783). Tissues were analyzed by recently published collagen targeting approaches using imaging and chromatographic proteomics, done on the identical tissue section used for PTEN measurement. Imaging MALDI FT-ICR (7 Tesla Solarix, Bruker Scientific) measured collagen peptides co-localized to PTEN. Peptides were analyzed by reverse-phase chromatography coupled to an orbitrap mass spectrometer (Orbitrap Elite, ThermoScientific). Mascot, Sequest and Andromeda searches included a non-specific enzyme parameter against the human database and a subset of extracellular matrix proteins. Subset databases from confident protein identifications were used to search for PTMs. MaxQuant was used to score site localization of hydroxylated proline from collagen peptides.

**PRELIMINARY DATA** In breast cancer, stroma density increases due to aberrant myoepithelial-luminal regulation of stroma collagens and later abnormal regulation of fibrillary collagen by infiltrating macrophages. PTEN controls collagen alignment throughout breast health and is decreased in aggressive triple negative breast cancers and metastasis. However, the translational and post-translational mechanisms of collagen re-alignment by PTEN are unknown. PTEN expression was compared to collagen regulation in breast tissue of women who underwent reductive mammoplasty (RM) and in triple negative breast cancer (TNBC). High scoring PTEN linked to increased hydroxylation of proline (HYP) and 27 collagen peptides with HYP modifications were altered in RM between high PTEN and low PTEN (>3fold t-test p-value <0.01). However, it was very specific sites of collagen proline hydroxylation that co-localized with high PTEN in RM. For example, data suggests that COL1A2 peptide GPVGRTGEVGAVGPP from the triple helical region amino acids 825-840 is hydroxylated at the terminal proline (site localization scoring GPVGRTGEVGAVGP(probability=0.069)P(probability=0.931). In TNBC tissue with normal adjacent tissue, COL3A1 peptide VAVGGLAGYP(probability=1) co-localized to high PTEN staining. Interestingly, the same peptide was co-localized and co-regulated with high PTEN in RM (2.4 fold increase; Mann-Whitney p-value 0.01). Overall the data suggests that in the tissue microenvironment, PTEN activity is associated with collagen hydroxylation of specific proline sites, which may result in greater collagen structure stability and prevent malignant re-alignment. Current efforts measure cell-specific levels of collagen sequence variants in tissue and demonstrate that identified HYP sequences alter oncogenic signaling in cell culture.

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# A new pathological assessment method to assess residual lesions after neoadjuvant chemotherapy for breast cancer: Residual disease in breast and nodes combined with Ki-67 (RDBN-K)

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**Purpose** The accurate assessment of residual tumor tissue after neoadjuvant chemotherapy (NAC) for breast cancer is closely related to the subsequent treatment and prognosis of patients. Currently commonly used assessment methods, including Miller and Payne system (MPS), Residual Cancer Burden (RCB), and Residual Disease in Breast and Nodes (RDBN) assessment system, etc., have certain limitations in terms of accurate evaluation and determining prognosis. The limitation of MPS lies in the need to review the original tumor biopsy specimen and compare the cell contents of the biopsy specimen and the surgical specimen. The limitation of RCB is that it requires a broader sampling, as well as more time and energy in microscopic examination. Furthermore, determining the number of cells is subjective and differences exist among observers. The limitation of RDBN is its poor correlation with prognosis. Ki-67, as a marker to reflect cell proliferation, is widely used in prognostic judgment of invasive breast cancer and is also an important reference in treatment decision-making. This study aimed to combine the Ki-67 expression status after NAC with RDBN to design a new pathological assessment method, which we called residual disease in breast and nodes combined with Ki-67 (RDBN-K), and to study its significance for the prognosis of patients.**Methods** RDBN-K = 0.2 (residual breast tumor size in centimeters) + index of involved nodes + tumor histological grade+ index of Ki-67. The residual tumor size, index of involved nodes, and histological grade are the same as RDBN. The index of Ki-67 is scored as 0 for less than 14% and 1 for greater than or equal to 14%. The residual diseases of 723 patients with TNM staging of stage II to stage III who had undergone NAC and surgical treatment were evaluated by RDBN-K. RDBN-K includes 4 risk levels (levels 1-4) according to residual disease magnitude after neoadjuvant chemotherapy. The RDBN-K levels were defined as follows: RDBN-K-1 (equivalent to pCR) is an index of 0, RDBN-K-2 is an index between 0.1 and 3, RDBN-K-3 is an index between 3.1 and 5.3, and RDBN-4 is an index 5.4 or more. At the same time, RDBN was used to evaluate the residual disease of all patients after NAC. This study followed up the survival status of 723 patients. After combining the prognoses, the accuracy and clinical significance of the RDBN and RDBN-K were compared.**Results** During the follow-up, in the entire cohort, 147 (20.3%) recurrences or metastases were observed; local recurrence was 58 (8.0%), distant metastasis was 103 (14.2%), and 69 (9.5%) patients died. Among the RDBN-2 cases, 40 (5.5%) of 122 cases were reclassified to RDBN-K-3. Among the RDBN-3 cases, 17 (2.4%) of 295 cases were reclassified: 2 cases were reclassified to RDBN-K-4, and 15 cases were reclassified to RDBN-K-2. Among the 220 cases in the RDBN-4 category, 40 (5.5%) were reclassified to the RDBN-K-3 category using the RDBN-K calculation. Over the follow-up period, 13.6% of patients in the RDBN-4 category died, and 15.9% of patients in the RDBN-K-4 category died. RDBN and RDBN-K showed statistically significant differences in the disease-free survival (DFS) and overall survival (OS) of all patients ($P$ values are all less than 0.05). Pairwise stratified analysis showed that the differences in DFS and OS between RDBN-K-3 and RDBN-K-4 (DFS: $P = 0.019$, OS: $P = 0.035$) were greater than that between RDBN-3 and RDBN-4 (DFS: $P = 0.052$, OS: $P = 0.214$), and the differences in OS between RDBN-K-2 and RDBN-K-3 ($P = 0.023$) were greater than that between RDBN-2 and RDBN-3 ($P = 0.157$).**Conclusion** Compared with RDBN, RDBN-K is more accurate in assessing the residual tumor burden after breast cancer NAC and predicting the prognosis for breast cancer patients, and provides more basis for follow-up intensive treatment of patients.

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# Clinicopathological features of *PALB2* and *BRCA2* mutation carriers with breast cancer

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Background: The *PALB2* gene is recognized as one of the most clinically relevant moderate to high penetrance breast cancer (BC) predisposition genes. Its product, PALB2, plays a crucial role in the homologous recombination pathway as a partner and localizer of BRCA2. Previous studies have reported significant frequencies of germline *PALB2* and *BRCA2* pathogenic variants (PVs) in Hispanic populations. However, no study has yet compared the baseline clinicopathological features of Mexican BC patients who carry PVs in these closely related genes.
Methods: Medical records of BC patients from two centers located in Monterrey, Mexico who underwent a next-generation sequencing panel for BC predisposition genes (*APC, ATM, BRCA1, BRCA2, BRIP1, CHEK2, CDH1, CDKN2A, MLH1, MSH2, MSH6, MUTYH, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, TP53*) based on NCCN recommendations were reviewed. Patients with germline PVs in *PALB2* or *BRCA2* were considered eligible. Fisher's exact and Mann Whitney U tests were employed to evaluate differences between groups based on mutation status.
Results: Between 2014 and 2019, a total of 8 *PALB2* (1.8%) and 24 *BRCA2* (5.5%) pathogenic mutation carriers were identified from 437 BC cases. Baseline clinicopathological features are shown in Table 1. Overall, no statistically significant differences were observed between groups. The most common germline PVs were c.2167_2168delAT, p.Met723fs, frameshift mutation for *PALB2* (57% of cases) and c.274C>T, p.Gln92Ter, nonsense mutation for *BRCA2* (30% of cases). Of note, one male BC case occurred in a *PALB2* mutation carrier, representing 13% (1/8) of BC cases in this carrier group and the only male BC case (out of three) associated with a germline PV.
Conclusion: This is the first report detailing the clinicopathological features of Mexican BC patients with germline *PALB2* PVs. According to our findings, BC tumors in *PALB2* mutation carriers share similar baseline characteristics with those diagnosed in *BRCA2* mutation carriers. Long-term follow-up is required in order to determine if prognosis is similar between groups and to further solidify the clinical relevance of germline *PALB2* PVs in the Mexican population.

Baseline clinicopathological features of PALB2 and BRCA2 mutation carriers with BC

| | ***PALB2* mutation carriers** | ***BRCA2* mutation carriers** |
|---|---|---|
| **Median age at diagnosis (years)** | 39 | 38 |
| **Median body mass index (kg/m$^2$)** | 23 | 26 |
| **Family history of BC**<br>Yes<br>No | 5 (63%)<br>3 (38%) | 19 (79%)<br>5 (21%) |
| **Clinical stage**<br>I<br>II<br>III<br>IV | 2 (25%)<br>5 (63%)<br>0<br>1 (13%) | 2 (8%)<br>11 (46%)<br>8 (33%)<br>3 (13%) |
| **Histological type**<br>IDC<br>Non-IDC | 6 (75%)<br>2 (25%) | 22 (92%)<br>2 (8%) |
| **Histological grade**<br>G1<br>G2<br>G3<br>Missing | 1 (13%)<br>4 (50%)<br>3 (38%)<br>0 | 5 (21%)<br>10 (42%)<br>6 (25%)<br>3 (13%) |
| **Molecular subtype**<br>HR+/HER2-<br>HR+/HER2+<br>HR-/HER2+<br>HR-/HER2- | 6 (75%)<br>0<br>0<br>2 (25%) | 11 (46%)<br>4 (17%)<br>0<br>9 (38%) |
| **Laterality**<br>Unilateral<br>Bilateral | 8 (100%)<br>0 | 21 (88%)<br>3 (13%) |

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# Four cycles of docetaxel-cyclophosphamide versus anthracycline-taxane adjuvant chemotherapy in node negative, HER2-negative breast cancer: A real-world comparison

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**Background:** It is unknown whether four cycles of docetaxel-cyclophosphamide (DC) is an appropriate adjuvant chemotherapy option in patients with lymph node negative (LNN) and human epidermal growth factor receptor-2 (HER2) negative breast cancer in place of widely adopted anthracycline-taxane (AT) regimens. In the Canadian province of Alberta, four cycles of DC has been used preferably in the last decade as a standard adjuvant chemotherapy regimen in LNN, HER2-negative disease. We aimed to retrospectively compare the survival outcomes of patients diagnosed with LNN, HER2-negative breast cancer in Alberta who were treated with four cycles of DC as compared to those treated with an AT regimens. **Methods:** We identified all patients who were diagnosed with LNN, HER2-negative breast cancer treated with adjuvant chemotherapy following surgical resection in Alberta from 2008 through 2012. We used propensity score methods to match each patient treated with an AT regimen to up to 4 patients treated with four cycles of DC on all known/potential clinicopathologic and treatment variables (Table).We compared the 10-year invasive disease free survival (iDFS), breast cancer specific-survival (BCSS) and overall survival (OS) between the two patient groups and assessed effect of type of adjuvant chemotherapy on iDFS, BCSS and OS using Cox regression analyses.**Results:** Of the 726 eligible patients, 657 (90.5%) were treated with four cycles of DC and 69 (9.5%) were treated with an AT regimen. Prior to matching, women who received four cycles of DC compared to those treated with an AT regimen, were more likely to be older, have higher Charlson co-morbidity score and mastectomy for definitive surgery, and in terms of disease: earlier stage, lower grade, and HR-positive status. Matching created a group of 202 women treated with four cycles of DC and eliminated differences in clinicopathologic and treatment features between the two patient groups (Table). Four cycles of DC compared to an AT regimen was not associated with reduced iDFS (HR = 0.91, 95% CI = 0.52 to 1.6, P = 0.75), BCSS (HR = 1.10, 95% CI = 0.51 to 2.37, P = 0.8), or OS (HR = 1.01, 95% CI = 0.48 to 2.17, P = 0.96).**Conclusion:** In this real-life comparison, four cycles of DC as compared with an AT regimen, yielded similar survival outcomes amongst patients with LNN, HER2-negative breast cancer. **Table** Baseline patient and tumour characteristics of 726 patients diagnosed with LNN, HER2-negative breast cancer by type of adjuvant chemotherapy.

| Characteristic | AT (n=69) | DC (n=657) | p value* | Matched DC (n=202)† | p value‡ |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| Median | 46 | 53 | | 47 | |
| Mean (SD; range) | 45.8 (9.7; 25 - 69) | 52.6 (9.8; 23 - 78) | <0.0001 | 46 (9.4; 23 - 69) | 0.8 |
| **BMI** | | | | | |
| Median | 25.3 | 27.5 | | 26 | |
| Mean (SD; range) | 27.1 (6.7;17.5 - 62) | 28.5 (6.6;15.6 - 64) | 0.1 | 27.1 (5.8;17.3- 49.4) | 0.9 |
| **Year of diagnosis [n (%)]** | | | | | |
| 2007 - 2008 | 11 (15.9%) | 78 (11.9%) | 0.24 | 26 (13%) | 0.8 |
| 2009 - 2010 | 22 (31.9%) | 275 (41.9%) | | 68 (33.5%) | |
| 2011 - 2012 | 36 (52.2%) | 304 (46.3%) | | 108 (53%) | |
| **Charlson co-morbidity score [n (%)]** | | | | | |
| Mean (SD, range) | 0.04 (0.26; 0 - 2) | 0.33 (0.67; 0 - 4) | <0.0001 | 0.04 (0.27; 0-2) | 0.9 |
| Score > 0 - no. of patients (%) | 2 (2.9%) | 151(23%) | 0.0005 | 7 (3.4%) | 0.8 |
| 0 | 67 (97.1%) | 506 (77%) | | 195 (96.6%) | |
| 1 | 1 (1.45%) | 97 (14.8%) | | 4 (2%) | |
| 2 | 1 (1.45%) | 44 (6.7%) | | 3 (1.4%) | |
| 3 | 0 | 9 (1.4%) | | | |
| 4 | 0 | 1 (0.15%) | | | |
| **Histology [n (%)]** | | | | | |
| Ductal | 58 (84%) | 479 (72.9%) | 0.12 | 165 (82%) | 0.8 |
| Mixed Ductal-Lobular | 5 (7.25%) | 96 (14.6%) | | 20 (9.9%) | |
| Others | 6 (8.7%) | 82 (12.5%) | | 17 (8.4%) | |
| **T-stage [n (%)]** | | | | | |
| Stage I | 12 (17.4%) | 253 (38.5%) | 0.0005 | 37 (18.3%) | 0.9 |
| Stage II | 57 (82.6%) | 404 (61.5%) | | 165 (81.6%) | |
| **Grade differentiation [n (%)]** | | | | | |
| Well differentiated | 0 | 26 (4%) | <0.007 | 0 | 0.9 |
| Moderately differentiated | 6 (8.7%) | 139 (21.2%) | | 20 (9.9%) | |
| Poorly differentiated | 63 (91.3%) | 492 (74.9%) | | 182 (90.1%) | |
| **Hormone receptor status [n (%)]** | | | | | |
| Positive | 33 (47.8%) | 468 (71.2%) | <0.0001 | 95 (47%) | 0.9 |
| Negative | 36 (52.2%) | 189 (28.8%) | | 107 (52.9%) | |
| **Definitive breast surgery [n (%)]** | | | | | |
| Breast-conserving surgery | 30 (43.5%) | 390 (59.4%) | <0.01 | 90 (44.5%) | 0.9 |
| Mastectomy | 39 (56.5%) | 267 (40.6%) | | 112 (55.5%) | |
| **Radiotherapy [n (%)]** | 36 (52.2%) | 397 (60.4%) | 0.18 | 103 (51%) | 0.9 |
| **Time interval to first cycle of chemotherapy (months)** | | | | | |
| Median | 2.73 | 2.8 | | 2.71 | |
| Mean (SD; range) | 2.86 (0.77; 1.2- 4.8) | 3.25 (1.38; 0 - 15) | 0.5 | 2.82 (0.8; 0– 5.9) | 0.7 |
| No. of patients (%) | | | | | |
| 0 months ≥ – < 3 months | 39 (56%) | 404 (61.5%) | 0.42 | 122 (60%) | 0.6 |
| 3 months ≥ – < 6 months | 30 (43.4%) | 245 (37.2%) | | 80 (40%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | ≥ 6 months | 0 | 8 (1.2%) | | 0 | |
| **Type of adjuvant chemotherapy [n (%)]** | | | | | | | |
| | | DC×4 | | 657 (100%) | | 202 (100%) | |
| | | FEC×3→D×3 | 63 (91.3%) | | | | |
| | | AC×4→T×4 | 3 (4.35%) | | | | |
| | | TAC×6 | 3 (4.35%) | | | | |

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# A phase 2 study evaluating orteronel, an inhibitor of androgen biosynthesis, in patients with androgen receptor (AR)-expressing metastatic triple-negative breast cancer (TNBC)

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Background: Treatment options for TNBC are limited by the lack of estrogen and progesterone receptors as well as the absence of HER2 overexpression. AR is present in all breast cancer subtypes and up to 40% of TNBC have AR overexpression (AR+). Thus AR positivity in TNBC represents a potential targetable signaling pathway. Preclinical studies demonstrated that AR modulation inhibits cell proliferation, and clinical activity with anti-androgen monotherapy has been reported in breast cancer. Orteronel is a novel, oral, selective, nonsteroidal inhibitor of 17, 20-lyase, a key enzyme in androgen biosynthesis under evaluation as a potential therapeutic strategy in hormone-sensitive cancers. In this phase 2 study, we evaluated androgen blockade with single agent orteronel in AR+ metastatic breast cancer (MBC). Methods: Male or female pts with AR+ MBC (≥10% staining by central immunohistochemistry) were eligible. Pts were grouped into 2 cohorts for analysis: Cohort 1-TNBC (AR+/ER-/PR-/HER2-) and Cohort 2-ER+ (AR+/ER+/HER2 +/-). Results in Cohort 2 (ER+) have been previously reported; here we report results in the AR+ TNBC cohort. TNBC pts must have been previously treated with standard therapy (1-3 chemotherapy regimens for MBC). All pts received 300 mg orteronel PO BID over a 4 week cycle and underwent response assessment every 2 cycles. Treatment continued until disease progression or unacceptable toxicity. The hypothesized response rate for pts with previously treated metastatic AR+ TNBC was 11%. Results: From 7/2014 to 2/2019 a total of 26 AR+ TNBC pts were enrolled on cohort 1. The trial closed early due to slow accrual. Median age was 57 years (range, 33-92); 96% ECOG 0-1; all pts had ≥ 1 prior chemotherapy; 42% prior targeted therapy; 8% prior immunotherapy. All tumors were ER and PR negative per institutional standards. PI3K was mutated in 16% (3/19) tumors tested and 65% (13/20) were PTEN-negative. Median duration of treatment was 8 weeks (range 0.7-35.7) with 15% of pts on treatment ≥ 6 months (mo). All pts have discontinued treatment, 85% due to disease progression, and 15% due to AEs. Nausea and fatigue [8 pts each (31%)] were the most common AEs noted. G 3/4 AEs included hypertension, increased amylase and lipase [2 pts each (8%)] with 4 patients reporting SAEs (G2 pneumonitis, G2 chest pain and G2 peripheral edema, G4 prolonged QT and G4 hypokalemia). The ORR was 4% and DCR was 15%. Median PFS was 2.0 mo and median OS was 10.2 mo. Conclusions: Orteronel monotherapy was well tolerated but demonstrated limited clinical activity in this heavily pre-treated metastatic AR+ TNBC patient population. As novel AR targeting agents are being developed, future studies are needed to identify AR+ breast cancer patients most likely to benefit from AR inhibition.

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# Nomogram for predicting axillary lymph node pathological response in node-positive breast cancer patients after neoadjuvant chemotherapy

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**Background**: Pathological complete response (pCR) of axillary lymph nodes (ALNs) is frequently achieved in patients with clinically node-positive breast cancer after neoadjuvant chemotherapy (NAC). ALN status is an important prognostic factor for choosing the type of axillary lymph node surgery. Many patients with axillary pCR could replace axillary lymph node dissection (ALND) with sentinel lymph node biopsy (SLNB). Our goal is to develop a new predictive clinical model to detect axillary pCR after NAC and provide clinical clues for avoiding ALND. **Methods**: A retrospective series of 547 patients who had biopsy-proven positive ALNs at diagnosis from 2007 to 2014 in National Cancer Center/Cancer Hospital of Chinese Academy of Medical Sciences were involved. We analyzed the clinicopathologic features and developed a nomogram to predict the probability of ALN pCR. Univariate assessment was performed using chi-square test. A multivariate logistic regression stepwise model was used to generate a nomogram to predict ALN pCR in node positive patients. The receiver operating characteristic (ROC) curve was established and the area under the curve (AUC) was calculated to evaluate the accuracy of the model. Internal validation was estimated using 50-50 hold out validation method. Nomogram was validated externally with the prospective cohorts of 167 patients from 2016 to 2018 of Cancer Hospital of Chinese Academy of Medical Sciences and 75 patients from 2018 to 2019 of Beijing Tiantan hospital.**Results**: In the retrospective study, 172 (31.4%) patients achieved axillary pCR after NAC. Multivariate analysis indicated that clinical nodal (N) stage, hormone receptor (HR) status and clinical response of primary tumor after NAC were significant independent predictors for axillary pCR ($P<0.05$). The AUCs of the internal validation for the training and test sets were 0.719 and 0.753, respectively. The nomogram was validated in external cohorts with AUCs of 0.862 and 0.766, respectively.**Conclusion**: We developed a nomogram to predict axillary pCR in node positive breast cancer patients after NAC. The predictive model performed well in prospective external validation. This practical tool could provide information to surgeons about whether to avoid ALND after NAC.

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# Evaluation of factors related to efficacy and safety of neo/adjuvant chemotherapy for breast cancer as a brief estimate of the impact of COVID-19 pandemic

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**Background**
COVID-19 pandemic presented as a challenge to breast cancer (BC) treatment, especially considering safety concerns and resource scarcity. Treatment choices have been taken mainly based on safety according to guidelines which aim hierarchically categorize the clinical benefits of any clinical decision. Considering the magnitude of benefit, neo/adjuvant breast cancer treatment is positioned at medium/high levels. Despite these recommendations, patients might be refusing chemotherapy (CT) or avoiding emergency care utilization due to concerns about COVID-19 infection. There have been described factors related to the reduction of effectiveness of neo/adjuvant CT for breast cancer, like relative intensity dose (RDI) <85%, which could be used to a brief analysis of latter impact of modifications in clinical protocols. We aimed to analyze the impact of COVID-19 pandemic, to the date, in the neo/adjuvant breast cancer chemotherapy in a university hospital to support strategies to minimize unfavorable outcomes.

**Methods**
Medical records from 307 breast cancer patients who started neo/adjuvant chemotherapy from January 2018 to June 2020 at the Hospital das Clínicas de Ribeirão Preto, University of Sao Paulo (HCRP-USP) were retrospectively analyzed, with a total of 2,074 cycles. It was considered the period from June 2018 to June 2020 to analyze the total cycles prescribed/month. Clinical data, treatment information and outcomes were collected. Considering COVID-19 restraining policies in our region were initiated on March 23th 2020, we considered the pandemic period from April 2020 to June 2020, and compared to the period before pandemic (Jan/2018-Mar/2020). A RDI <85% was considered a factor related to worse efficacy of chemotherapy. For safety assessment, it was considered the demand for medical care at emergency unit. The study was approved by the local ethics committee (HCFMRPUSP-33148920.5.0000.5440).

**Results**
During the period before pandemic, an average of 10% (±4%) of the patients who received CT, monthly, sought the emergency unit, while only 3% (±4%) sought during the pandemic (p=0.17). In our institution, the average number of neo/adjuvant CT initiated monthly during pandemic tended to be lower than before the pandemic (7.0 ± 2.0 vs. 10.6 ± 3.5; p=0.06), while the average cycles prescribed monthly showed a 14% reduction compared to the period before pandemic (68 ± 5 vs. 79 ± 13; p=0.02). The frequency of treatments with RDI <85% during the pandemic was lower than before pandemic (6% vs. 23%; n=275; p=0.03).

**Conclusions**
COVID-19 pandemic presented as a challenge for the treatment of BC patients, including lower acceptance of neo/adjuvant treatment and reduced search for emergency unit due to chemotherapy adverse effects, which could compromise the of the treatment goals. In our institution, we found 23% of patients treated with neo/adjuvant chemotherapy had not reached the expected RDI ≥85% before the pandemic, similar to the literature. Despite the lower rate of RDI <85% during pandemic (6%), this may be related to treatments that are still in progress, greater refusal of chemotherapy by patients with morbidities or advanced age, or even related to treatment modification aiming to minimize toxicities and avoid interruptions (ie. prescription of colony-stimulating factors). Further analysis may help to identify the factors related to these findings. Despite this, every effort must be made to achieve the maximum effectiveness of CT and to ensure safety during treatment. The impact of treatment modifications should be monitored to minimize unfavorable outcomes.

**Publication Number:** PS16-30

Pms1 gene: A new risk-mutation description?

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**INTRODUCTION:** *PMS*1 is part of the cluster of genes related to Mismatch repair genes (MMR) and has been used for investigation in oncogenetic panels. The MMR genes play an important role in tumor control and progression, however, the role of PMS1 in this process still poorly understood and information about its role in increasing the risk of developing a hereditary cancer predisposition syndrome (SHPC) is not completely understood.**AIM:** To characterize clinically and genetically cancer patients with NCCN criteria for SHPC and carriers of variants in the *PMS*1 gene.**METHODOLOGY:** A total of 368 patients suspected of having SHPC, according to the *National Comprehensive Cancer Network* (NCCN) criteria, were investigated using a Next-Generation Sequencing (NGS) in a panel containing 31 genes. Those that showed variation in the *PMS*1 gene were grouped, and the tumors were characterized in clinical and molecular aspects.**RESULTS:** From the 368 patients analyzed, 6.8% (25/368) patients presented Variants of Uncertain Significance (VUS) in *PMS*1. There was a case of Breast Cancer (BC) with a variant in *PMS*1, not described in ClinVar, presented in heterozygosis, probably pathogenic [Chr2:190.738,325 NM_000534: c.2578delA: p.(Arg860.Glufs*14)]. Besides, this case was associated with a family history (FH) of cancer breast cancer and melanoma. It is worth mentioning that only one patient was a man, with colorectal cancer (CRC), and his FH also was CRC in addition to stomach cancer. The only change founded was the presence of VUS NM_000534:c.1615A>G:p.(Met539Val) which was identified in 32% (8/25). This VUS was the only genetic alteration observed in 20% (5/25) patients with tumors in the breast (3), thyroid (1), CRC (1), and ovary (1). One of these patients had bilateral breast cancer and thyroid tumor. The patients had their age at diagnosis ranged from 25 to 65 years, with an average of 41 years. The carriers of variants exclusively in *PMS*1 [40% (10/25)] had different tumors: breast (6); CRC (3); ovary (2); lymphoma (1); thyroid (1); others 32% (n = 8/25) that presented additional VUS in different genes: [*ATM* (2); *BARD* (1); *CDH*1 (1); *CHECK*2 (1); *NBN* (1); *APC* (1); *POLE* (1)]. Different pathogenic variants (PV) [28% (n = 7/25)] also were identified, besides the previous *PMS*1 VUS described. The PV was founded in *ATM* (1); *BRCA*1 (3); *NF*1 (1); *TP*53 (1); *MUTYH*-heterozygosis (1), and *PMS*1 (1) gene. A double pathogenic variation was identified in a patient (*MUTYH* in heterozygosis and *BRCA*1). The findings in *PMS*1, even currently classified as VUS, should highlight observation for the clinical and familiar history. Genetic panels should be increasingly used in the investigation of SPHC.**CONCLUSION:** The roles of *PMS*1 in cancer progression need further investigations. A few numbers of reports have been identified on germline *PMS*1 mutations, considering defined disease phenotypes. Therefore, the performance of genetic panels, including the *PMS*1 gene, in SHPC further investigations will expand our knowledge and permit precise genetic counseling.

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# Combined use of MammaPrint and BluePrint assays to evaluate patients for response to neo-adjuvant chemotherapy for locally advanced breast cancer

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**Background:** The main goal of the Multi-Institutional Neo-Adjuvant Therapy MammaPrint (MINT) project was to determine the predictive power of the combination of the molecular assays MammaPrint and BluePrint (Agendia Inc., Irvine, CA) for chemosensitivity as measured by complete pathological response (pCR) in patients with locally advanced breast cancer (LABC). MammaPrint is a 70-gene microarray-based assay that classifies each breast cancer patient as low or high risk to develop metastases within 10 years after diagnosis. The BluePrint test is an 80-gene molecular subtyping profile that discriminates between luminal, basal and HER-2 subtypes.
**Methods:** After appropriate IRB approval, 270 female patients with histologically-proven invasive breast cancer and no distant metastases were enrolled in this study. Patients had a clinical tumor classification of T2-T4 with 0-3 positive lymph nodes. DCIS or LCIS was allowed in addition to invasive cancer at the T2 or T3 levels. At least one lesion had to be accurately measured in two dimensions utilizing mammogram, ultrasound, or MRI images to define specific size and validate pCR. Patients were required to have adequate bone marrow reserves, renal function and hepatic function, as determined by standard blood and serum measurements. Patients under 18 years of age or those with confirmed metastatic disease, inflammatory breast cancer, any serious uncontrolled intercurrent infections, or other serious uncontrolled concomitant disease were excluded. Patients with any prior chemotherapy, radiotherapy, or endocrine therapy for the treatment of breast cancer were also excluded. Tumor samples were collected via incisional or core needle biopsy and shipped to Agendia for processing of the MammaPrint and BluePrint gene panels, as well as whole human genome expression microarrays. Comparison of response rates between MammaPrint and BluePrint molecular subtypes was conducted using Pearson Chi-square test with chemo-responsiveness measured as a binary response: pCR or residual disease.
**Results:** Of 270 patients enrolled, 56 did not have TNM or RCB staging information reported in the case report form and/or were not submitted for central pathology review. Of 214 patients evaluated by central pathology review, 68 (32%) exhibited a pCR. Patients with a high risk MammaPrint result had a higher pCR rate (37%) compared to patients with a low risk MammaPrint (0%). And patients with a HER-2 or basal molecular subtype by BluePrint had significantly higher rates of pCR (62%, 37%, respectively).
**Conclusion:** Upfront evaluation of LABC tumors using the combination of MammaPrint and BluePrint can help in the clinico-pathologic evaluation to determine which patients are more likely to benefit from neo-adjuvant chemotherapy, ranging from expected minimal response in Luminal A to substantial responses for HER2-type and Basal-type tumors. Additional studies to evaluate the prognostic and/or predictive values of additional gene panels from the whole human genome microarrays are underway.

**Rate of pCR in MammaPrint and MammaPrint/BluePrint groups**

| Groups | Residual Disease | pCR | P value |
|---|---|---|---|
| **MP Risk Group** | | | |
| Low Risk | 27 (100%) | 0 (0%) | ***0.0004*** |
| High Risk | 114 (63%) | 67 (37%) | |
| **BP subtype** | | | |
| Basal | 42 (63%) | 25 (37%) | $2 \times 10^{-9}$ |
| HER2 | 20 (38%) | 33 (62%) | |
| Luminal A | 26 (100%) | 0 (0%) | |
| Luminal B | 53 (85%) | 9 (15%) | |

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**Publication Number:** PS3-30

Peri-operative diagnostic accuracy of magnetic resonance imaging and ultrasonography in breast cancer: A meta-analysis

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Background: Accurate determination of the extent of tumor is essential when a breast-conserving therapy (BCT) is considered. Due to its high sensitivity, breast magnetic resonance imaging (MRI) is increasingly used for the accurate diagnosis and surgical planning of breast cancers. However, a recent meta-analysis showed that peri-operative evaluation with MRI leads to higher mastectomy rates in patients that could have potentially underwent BCT.
Objective: The aim of this study is to compare the pre-operative diagnostic accuracy of MRI to ultrasonography (US) in breast cancer.
Methods: We identified eligible studies that examined peri-operative tumor size using MRI and US and compared it to its pathological counterpart. Databases of PubMed, Embase and Google Scholar were reviewed. To keep the study homogenous, only studies evaluating invasive ductal carcinoma were included and studies evaluating ductal carcinoma in-situ and lobular ductal carcinoma were excluded. An accurate tumor estimation by MRI or US was defined as within 10 mm from the pathological tumor size. An overestimation was defined as imaging tumor size more than 10 mm larger than its pathological counterpart. Odds ratios (ORs) were calculated using a random-effects model with 2-sided p-value of 0.05 set as the significance level.
Results: Twenty-five studies with 3,562 patients were included in the final analysis. MRI was 1.6-fold more accurate than US in preoperative diagnostic evaluation of breast cancer (OR 1.65; 95% confidence interval (CI) 1.24-2.18, p-value <0.00001). However, MRI was 20 folds more likely to overestimate the tumor size compared to US (OR 20.25; 95% CI 9.46-43.33; p-value <0.0001).
Conclusion: MRI remains the most accurate modality for the diagnosis of breast cancer. However, it is highly likely to overestimate tumor size and can result in unnecessary mastectomies. US is a reasonable diagnostic option for most patients with breast cancer.

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Can metronomic maintenance therapy (MMT) after completion of standard therapy help prevent relapses in patients (Pts) with non-metastatic triple-negative breast cancer (TNBC)

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Background: In-spite of the standard neoadjuvant and adjuvant therapies, stage for stage many more patients with TNBC relapse. This may be because of lack of effective maintenance therapy for TNBC Pts. Recently MMT is being explored to improve outcomes in TNBC. We present a retrospective and prospective analysis of consecutive Pts with TNBC treated at BKLWalawalkarHospital, the rural outreach center of Tata Memorial Centre (India), wherein the outcome of TNBC Pts receiving MMT is being compared to historical control group who did not receive the same.
Methods: After standard anthracycline or anthracycline+taxane based therapy, TNBC Pts were either observed (Sept 2003 to March 2011) or received MMT (Nov 2008 to Dec 2018).MMT consisted of 2 phases: initial 12 weeks of daily oral celecoxib (200 mg BD) and cyclophosphamide (50 mg OD) along with 12 doses of weekly IV cisplatin (25 mg/m2). This was followed by 1 year of Phase II maintenance consisting of oral daily metformin (500 mg BD), cyclophosphamide (50 mg OD) along with weekly methotrexate (12 mg/m2).When CAF is the standard regimen 2 phases of maintenance was given , after anthracyclines and taxanes were proved as a standard regimen maintenance was restricted to Phase II considering overlapping toxicities like neuropathy.
Results: There were 118 evaluable TNBC Pts. 25 Pts did not receive any MMT.Of the 93 remaining Pts initial 25 received both Phase I & II MMT , 1 patient received only phase I and subsequent 61 Pts have received only Phase II MMT. 6 patients progressed while on initial standard therapy and were not evaluable to assess the effect of MMT .Hence 112 patients are analysed further for outcome.STAGE STRATIFICATION : 8 Pts(6.7%) had AJCC Stage I; 48 Pts(40.6%) had AJCC Stage II; & 62 patients(52.5) had AJCC Stage III disease.MMT and observation groups were comparable with respect to baseline characteristics such as age & stage . Out of 112 patients 87 received MMT and 9 events were noted ,25 did not received MMT and 12 events were noted.EFS by March 2020 is 89.7% in MMT group and 52% in non- MMT group . Median EFS in MMT group is 11.3 yrs ( 9.4 yrs-13.14 yrs 95% CI) , in Off MMT group median EFS 9.2 yrs( 6.4-12 yrs 95% CI).Overall comparison was done by Log rank analysis (Significance 0.006).Median overall survival in OMCT group is 11.8yrs ( 9.9yrs-13.8yrs 95% CI), in non MMT group OS is 9.8yrs( 7.1 yrs-12.6yrs) with significance 0.002.61 patients who received Phase II MMT OS is 13.4 yrs ( 12.5yrs-14.4 yrs 95% CI).By stage stratification in non MMT group 2 patients belong to Stage I , 9patients belongs to Stage II and 14 patients belongs to Stage III.
TOXICITIES : MTX 25% dose reduction was done in 7 patients due to Grd2 Mucositis, cyclophosphamide alone was stopped in 1 patient due to grade 3 fatigue, MTX and Cyclophosphamide was stopped in 2 patientsdue grade3 anemia and grade 4 neutropenia, blood transfusion was done in them.Toxicities are much less when compared to CREATEX trial and the follow up duration is very long.
Conclusion: Most of the TNBC patients relapse in the early period of follow up and there is an unmet need in the improvement of management. If low dose chemotherapy is given for 1 yr there is a significant improvement in EFS and OS without muchdecrease in QOL.l. This strategy is worthy of being evaluated in definitive randomized trials in TNBC women with large numbers. ..

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The expression of PD-L1 (Ventana SP142) in HER2-positive breast cancer and its relationship with clinicopathological characteristics

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**Objective:** This article aims to investigate the correlation between the expression of PD-L1 and tumor-infiltrating lymphocytes, clinicopathological features and prognosis in HER2-positive breast cancer.**Methods:** This study included 156 cases of HER2-positive breast cancer. Three 2mm tumor cores were selected for each case, and the expression of PD-L1 on ICs was detected by Immunohistochemistry. Statistical software SPSS 24.00 was used for analysis, $\chi 2$ test and Fisher exact test were used for correlation and consistency analysis; Logistic regression analysis was used for multivariate analysis; Kaplan-Meier analysis was used for univariate survival; Cox regression analysis was used for multivariate survival; TILs and PD-L1 correlation was analyzed by Spearman rank; $P<0.05$ was considered statistically significant.**Results:** In HER2-positive breast cancer the expression rate of PD-L1 on ICs was 31.4%. In HER2-positive breast cancer the expression of PD-L1 on ICs was significantly correlated with the tumor size, the presence or absence of lymphovascular invasion, the expression of TILs, CD4 and CD8 ($P<0.05$); obtained using Logistic multivariate regression analysis The tumor size, the presence or absence of vascular tumor plugs, the expression of TILs and CD8 were independent factors affecting PD-L1 expression ($P$ <0.05). Spearman rank correlation analysis showed that TILs infiltration level was positively correlated with interstitial immune cell PD-L1 expression in HER2-positive breast cancer patients ($r$ = 0.486,$P$ <0.05). Univariate survival analysis of disease-free survival (DFS) for HER2-positive breast cancer the patient's tumor size, lymphovascular invasion, lymph node metastasis, TILs, tumor immune microenvironment classification-CD4 (TIME-CD4) and tumor immune microenvironment classification-CD8 (TIME-CD8) has a significant effect on patients' DFS (P<0.05); multivariate survival analysis revealed that patients had lymphovascular invasion, TILs, TIME-CD4 and TIME-CD8 as HER2-positive breast cancer independent factors of DFS ($P<0.05$).**Conclusions:** The expression of PD-L1 on ICs in HER2-positive breast cancer is related to tumor size, presence or absence of lymphovascular invasion, TILs,CD4 expression and CD8 expression.The independent influencing factors of disease-free survival in patients with HER2-positive breast cancer are the presence or absence of lymphovascular invasion, TILs, TIME-CD4 and TIME-CD8. Among them, patients with no lymphovascular invasion and higher levels of tumor infiltrating lymphocytes had better prognosis; CD4-/PD-L1- group had better prognosis in the TIME-CD4 and CD8+/PD-L1- group had better prognosis in the TIME-CD8. There is a positive correlation between TILs infiltration level and PD-L1 expression, suggesting that HER2-positive breast cancer patients can be accurately treated according to different TILs infiltration levels and PD-L1 expression.**Key words**: breast cancer; HER2-positive;PD-L1;TILs

**Publication Number:** PS5-30

# Effect of level of hormone-receptor expression on treatment outcomes of “triple-positive” early-stage breast cancer

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**Introduction**: 20-25% of breast cancers overexpress the human epidermal growth factor receptor-2 (HER2) and have an aggressive clinical behavior; 50-70% of them also express both estrogen (ER) and progesterone (PR) receptors. Multiple regulatory and signaling pathways regulate and affect breast cancer response to various therapies. Breast cancer that overexpress HER2 and both ER and PR receptors, which represents nearly 10-15% of all breast cancers, are recently recognized as a subtype (triple-positive: TPBC) with distinctive behavior and response to treatment. However, the idea of separating this type of breast cancer according to the level of ER and PR expression is still debated. In this study, we retrospectively investigate the clinical features and treatment outcomes of early-stage TPBC patients treated at a tertiary care center, and how survival patterns are affected by levels of HR expression. **Methods**: Adult patients with pathologically confirmed diagnosis of early-stage (stage I-III) TPBC were included. ER or PR were considered positive if staining of tumor cell nuclei was ≥ 1%. Due to drug approval and availability, 50 (16.0%) patients (Cohort A) had not received trastuzumab throughout their treatment and were treated with chemotherapy alone (anthracycline and taxane-based regimens). The rest of the patients received standard adjuvant chemotherapy and trastuzumab and were divided based on level of HR expression into two cohorts; patients whose immunohistochemical staining displayed ≥ 50% in both ER and PR scores were classified as Cohort B and constituted 41.7% of the study population (n=130) while patients who displayed < 50% ER and/or PR staining scores were designated to Cohort C and comprised 42.3% of the population (n=132).The primary endpoint was DFS, defined as the time from the date of diagnosis to the date of the first occurrence of local recurrence in the breast or axilla, the development of ipsilateral or contralateral breast cancer, distant metastasis, or death by any cause without evidence of disease. Moreover, overall survival (OS) of all the patients was defined as the time from the date of diagnosis until the death from any cause. **Results:** Between 2006 and 2016, a total of 312 patients were included. Median age (range) was 47 (20-83) years and majority were premenopausal (n=190, 61.3%). Moreover, 170 (54.7%) patients had grade-III tumors at diagnosis while 223 (71.5%) presented with positive axillary lymph nodes; significantly higher in Cohort C (79.5%) compared to 66.9% in Cohort B and 62.0% in Cohort A, p=0.02. The median follow-up time was 47 months. Among the whole group, distant metastasis, with or without local recurrence, was documented in 47 patients (15.1%) while 12 (3.8%) others had local recurrence only and 5 (1.6%) died while disease-free. The 5-year OS and DFS of the population was estimated to be 86.3%, and 75.4%, respectively. Patients in Cohort A had the highest percentage of events (28.0%, n=14), followed by Cohorts B (23.1%, n=30) then C (15.2%, n=20). The estimated 5-year DFS rate of all the patients was also calculated to be worst (56.2%) for patients of Cohort A, who did not receive anti-HER2 therapy. On the other hand, 5-year DFS for the two cohorts who received trastuzumab were 75.4% and 80.8% for cohort B and cohort C, respectively. The DFS curves continued to separate after 5-years with an estimated DFS rate at 7-years of 67.1% for patients in Cohort B, who had higher ER and PR scores, and 78.0% for patients in cohort C with lower ER/PR scores. The log-rank test showed a significant difference in the DFS rates between the three cohorts (p < 0.001). **Conclusions**: HER2+ tumors are not homogeneous; stronger ER/PR co-expression may weaken the beneficial effect of anti-HER2 therapy. Such findings may have potential implication on modifying anti-HER2 treatment based on strength of HR expression.

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**Publication Number:** PS8-30

Longitudinal clinical outcomes of a multi-center universal genetic testing registry

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**Background:** Growing evidence indicates that restrictive criteria for determining eligibility of breast cancer patients for germline genetic testing (e.g. NCCN, etc.) can missa significant number who may benefit from testing. However, the clinical utility and outcomes of patients with germline pathogenic variants (“positive patients”) who fall outside of current criteria has not been studied,and there is limited data on the clinical impact of nonBRCA pathogenic variantsin patients who fall inside testing criteria. We present longitudinal data from a previous cohort of patients, who are being followed in a new genetics registry that correlates germlinetest results with impact on clinical decision making, disease status, treatmentcourse, clinical trial enrollment and overall survival. **Methods:** A large multi-center IRB approved prospective Registry initiated in 2017 collected andanalyzed data on 959 breast cancer patients, newly or previously diagnosed, atthe time of genetic test result return (Beitsch et al. JCO 2018)[1].This abstract presents clinical data over the intervening 18-24 months on patients with positive variants (83) both in-criteria (IC) and out-of-criteria (OOC),collected via medical record review as part of the iGAP Registry(igapregistry.org), sponsored by Medneon (Cupertino, Ca). **Results:** Of the 44 positive patients for whom longitudinalclinical outcomes data have been analyzed to date, 24 met guidelines fortesting and 20 did not. 6 had a history of additional primary cancers at thetime of testing. 40/44 patients are disease free; of these 20 were IC,20 were OOC. 1/44 has stable disease and was OCC. 3/44 have progressive orrecurrent breast cancer and 2 were OCC and 1 was IC. 13/44received chemotherapy; 6 IC and 7 OOC. 5 patients (with mutations in BRCA1,BRCA2, PALB2, MUTYH) received carboplatin consistent with the sensitivity toplatinum agents conferred by deficiencies in homologous recombination (HR) andbase-excision repair (BER). Longitudinal outcomes stratified by gene result arein Table 1. **Conclusions:**This studyprovides initial evidence for the impact of germline genetic test results onlongitudinal patient outcomes, stratified by gene. It also begins to correlategermline results and chemotherapy, as 3/5 OOC patients receiving carboplatinhad mutations in HR or BER genes. This raises the possibility that certain treatment advantages and other beneficial changes in management could bewithheld from OOC patients if restrictive criteria persist, as well as limiting the opportunities for possible preventive interventions for their at-risk family members 1. BeitschPD, Whitworth PW, Hughes K, et al. Underdiagnosis of Hereditary Breast Cancer:Are Genetic Testing Guidelines a Tool or an Obstacle?. *J Clin Oncol*.2019;37(6):453-460. doi:10.1200/JCO.18.01631 **Table 1**

| Positive Gene Variant | # reported mutations-by gene | Subject Health Status Disease Free | Subject Health Status Stable or Progressive Disease | NCCN # IC | NCCN # OOC |
|---|---|---|---|---|---|
| ATM | 2 | 2 | 0 | 0 | 2 |
| BLM | 1 | 1 | 0 | 0 | 1 |
| BRCA1 | 2 | 2 | 0 | 2 | 0 |
| BRCA2 | 5 | 5 | 0 | 4 | 1 |
| CHEK2 | 6 | 6 | 0 | 3 | 3 |
| DIS3L2 | 1 | 1 | 0 | 0 | 1 |
| FH | 1 | 1 | 0 | 1 | 0 |
| MITF | 1 | 1 | 0 | 1 | 0 |
| MSH6 | 1 | 1 | 0 | 0 | 1 |
| MUTYH | 9 | 8 | 1 | 2 | 7 |
| NBN | 2 | 2 | 0 | 1 | 1 |
| NF1 | 1 | 0 | 1 | 0 | 1 |
| NTLH1 | 1 | 1 | 0 | 0 | 1 |
| PALB2 | 3 | 2 | 1 | 2 | 1 |
| RAD50 | 1 | 1 | 0 | 1 | 0 |
| RAD51C | 2 | 2 | 0 | 1 | 1 |
| RAD51D | 3 | 2 | 1 | 1 | 2 |
| RECQL4 | 2 | 2 | 0 | 1 | 1 |
| VHL | 1 | 1 | 0 | 1 | 0 |

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# Neutrophil-to-lymphocyte ratio or platelet-to-lymphocyte ratio as prognostic biomarkers in patients with metastatic breast cancer treated with CDK4/6 inhibitors

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**Background**: Immune regulation plays an important role in tumor growth and sustainability. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been reported as peripheral blood surrogates of tumor inflammation and immune response, and have been studied as prognostic markers of treatment response in breast cancer. Cyclin-dependent kinase (CDK) 4/6 inhibitors have shown to enhance the immune response against tumor cells. We aimed to evaluate the impact of NLR and PLR as prognostic biomarkers in patients with estrogen-receptor positive (ER+), human-epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancer (MBC) treated with first line CDK4/6 inhibitors.
**Methods:** This retrospective single cohort study analyzed patients with ER(+)/HER2(-) MBC treated with first line CDK4/6 inhibitors at Albert Einstein Cancer Center. Demographic, clinicopathological, laboratory and treatment characteristics were collected from electronic medical records. Absolute neutrophil count, absolute lymphocyte count and platelet count, were obtained at baseline ($T_0$) and after three months ($T_3$) of treatment with CDK4/6 inhibitors. Optimal cutoff points to define NLR and PLR high vs. low were identified using time-dependent receiver operator curves. Progression free survival (PFS) was calculated from the time of CDK4/6 inhibitor initiation to disease progression, death, or last clinical encounter. PFS was compared among patients with high vs. low ratios at $T_0$ ($NLR_0^{HIGH}$ vs. $NLR_0^{LOW}$ and $PLR_0^{HIGH}$ vs. $PLR_0^{LOW}$) and at $T_3$ ($NLR_3^{HIGH}$ vs. $NLR_3^{LOW}$ and $PLR_3^{HIGH}$ vs. $PLR_3^{LOW}$) of CDK 4/6 inhibitor treatment, using Cox-proportional regression models. **Results:** A total of 89 patients were evaluated. The median age was 61 years [interquartile range (IQR): 61-69]. Of these, 60% were Non-Hispanic, 40% were Hispanic, 46% were Black, 19% were Caucasian and 6% were Asian. Premenopausal and postmenopausal status was identified in 21% and 75% of patients, respectively. The median Charlson Comorbidity Index (CCI) was 8 [IQR: 7-9]. Visceral metastases were seen in 67% of patients. Palbociclib, Abemaciclib and Ribociclib were used in 78%, 16% and 7% of patients, respectively; with an endocrine therapy backbone of Letrozole, Fulvestrant and Anastrozole in 64%, 24% and 10% of patients, respectively. The median $NLR_0$ and $NLR_3$ were 2.6 [IQR: 1.8-3.6] and 1.3 [IQR: 0.8-2.3], respectively. The median $PLR_0$ and $PLR_3$ were 158 [IQR: 115-250] and 142 [IQR: 94-290], respectively. The cutoff points for defining ratios as being high vs. low for $NLR_0$, $NLR_3$, $PLR_0$, and $PLR_3$ were 3.7, 2.2, 108, and 309, respectively. The median PFS was 10 vs. 19 months for $NLR_0^{HIGH}$ vs. $NLR_0^{LOW}$ [Hazard Ratio (HR):1.8, 95% Confidence Interval (CI):0.95-3.49, p=0.07] and 12 vs. 19 months for $NLR_3^{HIGH}$ vs. $NLR_3^{LOW}$ (HR:1.46, CI:0.71-3.00, p=0.3). In multivariable models adjusted for age, CCI, and visceral metastases, neither $NLR_0$(p=0.1) nor $NLR_3$ (p=0.2) was associated with PFS. The median PFS was 13 months vs. not-reached for $PLR_0^{HIGH}$ vs. $PLR_0^{LOW}$ (HR: 5.5, CI:1.3-23.0, p=0.018), and 32 vs. 16 months for $PLR_3^{HIGH}$ vs. $PLR_3^{LOW}$ (HR:0.62, CI:0.23-1.64, p=0.3). In multivariable models adjusted for age, CCI, and visceral metastases, an increased $PLR_0$ was associated with worse PFS (HR 4.67, 95%CI 1.1-20, p=0.04), while $PLR_3$ was not associated (p=0.37). **Conclusions**: Our study is the first in the United States to evaluate NLR and PLR as prognostic biomarkers in MBC patients receiving CDK4/6 inhibitors. $PLR_0$ is a potential biomarker for prognostic stratification in this setting. $NLR_0$, $NLR_3$, and $PLR_3$ were not independent factors for PFS in this setting when other clinicopathological factors were considered. Further studies with a larger sample size are required to validate our results.

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# Differential efficacy, safety and tolerability of low-dose versus standard dose tamoxifen as breast cancer prophylaxis: A network meta-analysis

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BACKGROUND: Despite reduction in the risk of breast cancer occurrence, the use of prophylactic tamoxifen does not improve longer term outcomes such as survival and comes at the cost of toxicity. As such, chemoprophylaxis is utilized poorly in routine practice. Lower dose tamoxifen has been proposed as a more acceptable alternative for breast cancer prevention. Here, we explore efficacy and treatment-related adverse events (TRAEs) comparing the two tamoxifen dosing regimens in a network meta-analysis.
METHOD: We searched PubMed to identify randomized trials (RCTs) of tamoxifen for breast cancer prophylaxis in high-risk patients (as defined in individual trials). Low-dose tamoxifen was defined as less than 20mg per day. We extracted the hazard ratio (HR) for breast cancer events relative to placebo. We also collected data on common and serious TRAE, and calculated odd ratios (OR) for each TRAE relative to placebo. Data were then included in a network meta-analysis comparing low-dose (experimental group) to standard dose tamoxifen (control group). Associations between TRAEs and patient characterics tics were explored using meta-regression which comprised a weighted linear regression using mixed effects modelling.
RESULTS: Ten RCTs comprising 35,505 patients were included in the analysis (4 low-dose trials (n=3712 patients) and 6 standard dose trials (n=31,793 patients). There were no significant differences between low-dose and standard dose trials in age (53.3 vs 50.8, p=0.25), post-menopausal status (77.5% vs 49%, p=0.63) or BMI (24.1kg/$m^2$ vs 26.95 kg/$m^2$, p=0.40). Efficacy was similar between the two dosage regimens (HR for breast cancer recurrences: 1.04, 95% CI 0.77-1.41, p=0.78 and for invasive breast cancer: 1.04, 95% CI 0.69-1.56, p=0.85). Differences in TRAEs are shown in the Table. There was a statistically significant reduction in headache with low-dose tamoxifen, and a non-significant reduction in endometrial cancers, other cancers, cardiovascular diseases and all-cause deaths. Hot flashes, vaginal bleeding and endometrial polyps were non-significantly higher with low-dose tamoxifen. In meta-regression analysis, age was associated with lower risk of endometrial carcinoma (p=0.049) and hot flashes (p=0.03).
CONCLUSION: The use of prophylactic low-dose tamoxifen provides similar efficacy to standard dosing, but may reduce the risk of certain common and serious TRAEs.

| TRAE | OR | 95% CI | p-value |
|---|---|---|---|
| Deaths | 0.63 | 0.14-2.86 | 0.55 |
| Endometrial cancer | 0.32 | 0.08-1.24 | 0.10 |
| Endometrial polyps | 1.66 | 0.84-3.28 | 0.15 |
| Other cancer | 0.71 | 0.40-1.26 | 0.24 |
| DVT or PE | 0.90 | 0.12-7.58 | 0.93 |
| Coronary heart disease | 0.72 | 0.24-2.15 | 0.56 |
| Cerebrovascular disease | 1.60 | 0.29-8.97 | 0.59 |
| Hot flashes | 1.34 | 0.63-2.86 | 0.45 |
| Vaginal dryness | 0.84 | 0.34-2.03 | 0.69 |
| Vaginal bleeding | 1.26 | 0.52-3.06 | 0.61 |
| Vaginal discharge | 1.08 | 0.58-1.99 | 0.81 |
| Headache | 0.11 | 0.05-0.86 | 0.04 |

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# Trps1 disrupts angiogenesis in triple negative breast cancer by down regulating genes involved in angiogenesis pathways

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Breast cancer is the second leading cause of cancer-related deaths in the United States. The Cancer Genome Atlas (TCGA) network has classified breast cancer into four main subtypes: luminal A, luminal B, HER2+, and Triple- negative breast cancer (TNBC). TNBC constitutes 10-20% of all breast cancer and has a higher rate of distal recurrence and a poorer prognosis than other breast cancer subtypes. Less than 30% of women with metastatic TNBC survive 5 years and almost all die from their disease despite adjuvant chemotherapy. Although all of the cancer genome-sequencing efforts, there is still an incomplete understanding of the genes and genetic networks driving TNBC. To better understand the genetic forces involved in TNBC, we performed a transposon mutagenesis screen in Pten mutant mice that identified several candidate trunk drivers and a much larger number of progression genes. A major finding of our screen was the discovery and functional validation of TRPS1 as a metastasis tumor suppressor in human TNBC. Consistent with these results, in SB-Pten tumors, Trsp1 was insertionally mutated only in TNBC. Remarkably, tumor cells from ER+ breast cancer patients after antihormone therapy have decreased TRPS1 expression and increased expression of mesenchymal markers, suggesting that breast tumors with low TRPS1 expression might be more resistant to chemotherapy and have a higher probability to metastasize. TRPS1 is a GATA-like transcription factor, which functions as a transcriptional repressor or activator, depending on cell type, stage of development, or pathological conditions. Based on this assumption, we explored additional roles of TRPS1 in tumor progression. ChIP-seq array studies indicated that TRPS1 modulates the expression of genes involved in the angiogenesis pathway. To validate the functional role of TRPS1 in angiogenesis, we perform tube formation and sprouting assays using MDA-MB-231 cells overexpressing TRPS1-ORF and inactivation of TRPS1 expression in HCC70 cells by different shRNAs. Interestingly, inactivation of TRPS1 expression accelerates tube formation structures compared to the vector control as well as cell branching in the sprouting assay. Overexpression of TRPS1 prevents tubing and branching formation in vitro assays. Moreover, immunohistochemistry staining of CD31 detected a reduced number of blood vessels in MDA-MB-231 tumor xenografts overexpressing TRPS1, and an increase of angiogenic vasculature in HCC70 TRPS1-shRNA tumor xenografts. In vitro and in vivo assays demonstrate the role of TRPS1 in tumor angiogenesis and ChIP-seq data suggest a direct interaction in the modulation of genes involved in pathological neovaculature mechanisms.

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# AMEERA-3, a phase 2 trial of SAR439859 vs endocrine monotherapy in pre- and post-menopausal, estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (her2−), locally advanced or metastatic breast cancer (BC) with prior exposure to hormonal therapies

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**Background** Endocrine therapy (ET) targeting ER signaling is the mainstay of care for ER+ metastatic BC. There remains an unmet need in patients whose tumors become resistant to currently available ET. Selective ER degraders (SERDs) were developed to overcome resistance to existing ER-directed therapies by both competitively antagonizing and degrading ERs, while exploiting continued dependence of the tumor on ER signaling. SAR439859 is a potent SERD with robust preclinical ER degrading activity. In AMEERA-1, a Phase 1 dose escalation trial, SAR439859, had a favorable safety profile with no dose-limiting toxicities across all doses (20-600 mg once per day; QD). ER occupancy generally exceeded > 87% with plasma concentrations > 100 ng/mL. Overall response rate was 6.3% and the recommended Phase 2 monotherapy dose was 400 mg QD. **Methods** AMEERA-3 is an international, prospective, open-label, randomized Phase 2 study (NCT04059484; ACT16105) designed to assess safety and efficacy of SAR439859 in pts with ER+ (>1%)/HER2− metastatic or locally advanced BC progressing on ≥ 6 months of continuous ET (0-2 lines in the metastatic setting). Prior cyclin-dependent kinase (CDK) inhibitors are allowed. Exclusion criteria include: Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2, life expectancy < 3 months, > 1 chemotherapy or targeted therapy in the metastatic setting, concomitant illness and factors potentially affecting SAR439859 absorption. Patients are randomized 1:1 to SAR439859 400 mg QD orally or physician's choice of endocrine monotherapy (fulvestrant, tamoxifen, aromatase inhibitor). Patients receive 28-day cycles until unacceptable toxicity, progression, death, investigator decision, or patient request. Stratification factors include visceral metastases, prior CDK4/6 inhibitors, and ECOG PS. The primary endpoint is progression-free survival (Response Evaluation Criteria in Solid Tumors v1.1). Secondary endpoints include overall survival, response rate, duration of response, clinical benefit, pharmacokinetics, quality of life and safety. Target enrollment: n = 282; current enrollment: n = 9. Funding: Sanofi. © 2020 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2020 ASCO Annual Meeting. All rights reserved.

**Publication Number:** PS9-30

# The efficacy of a comprehensive bone health program in maintaining bone mineral density in postmenopausal women with early-stage breast cancer treated with endocrine therapy

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**Introduction**: Given the recent advances in early detection, improving access to care and the introduction of more effective anti-cancer medications including endocrine therapy, targeted and immunotherapy, more women with breast cancer survive their disease. Majority of patients with breast cancer express hormone receptors (estrogen and or progesterone receptors) on cancer cells. Aromatase inhibitors (AI) are the gold standard treatment of hormone-sensitive postmenopausal women with breast cancer. Several studies had documented the accelerated bone loss associated with AI. The use of bone modifying agents like bisphosphonates and denosumab had resulted in significant improvement in bone mineral density among females treated with AI. In this paper, we study the efficacy of implementing a comprehensive program on bone health for such patients. **Patients and Methods**: Postmenopausal women with hormone-sensitive early-stage breast cancer treated with endocrine therapy (ET) were included. A comprehensive bone health program was implemented. The program includes extensive counselling by medical oncologist, calcium and vitamin-D supplements, increase milk intake and exercise. Patients with baseline lumbar spine or total hip T-scores ≥ -2 were given short intravenous bisphosphonate infusion every 6 months. Patients with osteoporosis are referred to and followed in a specially designed “osteoporosis clinic”. **Results**: Between 2013 and 2019, a total of 210 patients fulfilled the eligibility criteria and were enrolled. All were female, median (range) age 67 (43-86) years. All patients had a pathologically confirmed diagnosis of breast cancer, treated and followed up at our institution. High risk patients (n=103, 49.0%) were treated with 6-8 cycles of chemotherapy, including anthracyclines and taxanes. Following the completion of chemotherapy, all patients were treated with endocrine therapy. Patients with low-risk disease (n=107, 51.0%) were treated with upfront endocrine therapy-alone. Aromatase inhibitors, letrozole or anastrozole, were the endocrine therapy of choice in all patients. At baseline, and prior to start of AI, the median T-scores at the hip and lumber spines were -1.0 (range: -3.6, 1.9) and -1.4 (range: -3.9, 2.6), respectively. Osteoporosis was documented in 38 (18.1%) patients while 101 (48.1%) others had osteopenia; none were on any treatment or even aware of their BMD. 46 (25.3%) patients had vitamin-D deficiency while 74 (40.7%) others had vitamin-D insufficiency and none were on prior active replacement therapy or even aware of this problem. Following at least 12-months of endocrine therapy, 32 (84.2%) of patients with osteoporosis and 69 (68.3%) of those with osteopenia had a stable or higher BMD. Thus, the number of patients with osteoporosis declined to 27, 12.9% of the total cohort. On the other hand, 41 (57.7%) of those with normal baseline BMD had a drop in their follow up BMD. Vertebral fractures, presented with back pain and documented by imaging studies, were reported in 3 (11.1%) patients with osteoporosis compared to none in patients with normal BMD, p=0.021. Rib fracture and hip fracture were reported in one patient each and both had normal BMD before and after AI therapy. **Conclusions**: Postmenopausal women with breast cancer are at risk of osteopenia and osteoporosis. Such risk increases significantly with the use of AI. However, early interventions with modifiable risk factors, Vitamin-D supplements and use of bone-modifying agents can lower this risk.

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An open label, pilot study of veliparib and lapatinib in patients with metastatic, triple negative breast cancer

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**Purpose:** Poly (ADP-ribose)-polymerase inhibitors (PARPi) have been approved for cancer patients with germline *BRCA1/2*(g*BRCA1/2*) mutations, and efforts to expand the utility of PARPi beyond *BRCA1/2* are ongoing. In preclinical models of triple negative breast cancer (TNBC) with intact DNA repair, we previously showed an induced synthetic lethality with combined EGFR inhibition and PARPi. We report the safety and clinical activity of lapatinib and veliparib in patients with metastatic TNBC. **Experimental Design:** A first-in-human, pilot study of lapatinib and veliparib was conducted in metastatic TNBC (NCT02158507). The primary endpoint was safety and tolerability. Secondary endpoints were objective response rates and pharmacokinetic evaluation. Gene expression analysis of pre-treatment tumor biopsies was performed. Key eligibility included TNBC patients with measurable disease and prior anthracycline and taxane therapy. Patients with g*BRCA1/2* mutations were excluded. **Results:** Twenty patients were enrolled of which 17 were evaluable for response. Median number of prior therapies in the metastatic setting was 1 (range 0-2). Fifty percent of patients were Caucasian, 45% African-American, and 5% Hispanic. Of evaluable patients, 4 demonstrated a partial response and 2 had stable disease. There were no dose-limiting toxicities. Most AEs were limited to grade 1 or 2 and no drug-drug interactions noted. Gene expression analysis suggest baseline DNA repair pathway score was lower and baseline immunogenicity was higher in the responders compared to non-responders. **Conclusions**: Lapatinib plus veliparib therapy has a manageable safety profile and promising antitumor activity in advanced TNBC. Further investigation of dual therapy with EGFR inhibition and PARP inhibition is needed.

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# Loss of NF1 leads to rho GTPase activation and sensitivity to multiple agents in breast cancer

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**Background:** The Ras signaling pathway is a key oncogenic growth signaling pathway. The neurofibromatosis gene (NF1) is a tumor suppressor gene and negative regulator of Ras. Approximately 20% of breast cancers experience loss of active NF1 protein, leading to unabated Ras activity. Germline inactivation of NF1 leads to neurofibromatosis, which can be treated with MEK inhibitors. The functional consequences of NF1 loss have not been thoroughly explored in breast cancer. Therefore, we created a cellular model for the loss of NF1 in breast cells in order to identify novel therapies that would target NF1 null breast cells.

**Methods:** We used CRISPR CAS9 to knock out (KO) NF1 through targeted disruption of both NF1 alleles in the human non-tumorigenic breast cell line MCF-10A. Immunoblotting confirmed loss of the protein and this cell line was used to identify changes in cellular signaling that resulted from the loss of NF1. We then used a rational approach to select drugs that may target the cellular changes in NF1 null cells. Finally, the candidate drugs were tested in a tumor xenograft model in mice.

**Results:** Loss of NF1 endowed cells with a more transformed phenotype, including EGF growth independence and anchorage-independent growth. We observed increased activation of MAPK and activated Rho GTPase. The MEK inhibitors trametinib and PD0325901 (IC50=0.25 nM and 0.16 nM, respectively) inhibited growth of NF1-null, but not parent cells. We explored inhibitors of other proteins in the MAPK signaling pathway, including the Raf inhibitors sorafenib and vemurafenib and the dual MAP3K1/MAP2K4 inhibitor LY2228820. However, these compounds did not selectively inhibit growth of NF1-null cells, suggesting that Raf and MAP3K1/MAP2K4 are not vulnerable targets in NF1-null cells.

Vincristine and zoledronic acid can indirectly affect Rho GTPase function. NF1-null cells were more sensitive to both as single agents (IC50=1.1 nM and 6.9 μM, respectively) than parental cells. We also tested multiple combinations of these drugs and observed benefits from several combinations that exceeded single agent use. Similar sensitivity was not observed to docetaxel or ixabepilone.

We then tested the drugs as single agents and in combination against mouse tumor xenograft models with the human breast cancer cell lines Hs578T (NF1 null) or MCF-7 (wild type NF1). Treatment with single agent vincristine or zoledronic acid for 19 days resulted in statistically-significant decreases of 37.3% and 38.9%, respectively ($p<0.05$) in Hs578T tumor xenografts. The combination treatment resulted in an enhanced reduction in tumor size of 48.8% with a higher level of significance ($p<0.01$). Treatment of mice with MCF-7 bearing tumors with single agent vincristine resulted in a statistically significant decrease of 35.2% ($p<0.05$); however, this effect was not observed using the combination treatment, as the change in growth compared to saline treatment was not statistically significant.

**Conclusions:** Our results suggest that loss of NF1 results in a transformed phenotype. Our results provide the first evidence that vincristine in combination with zoledronic acid may be efficacious in treating breast cancers. Additionally, we provide evidence that other drugs and drug combinations may be more effective at treating breast cancers with NF1 loss than MEK inhibitors, warranting further exploration.

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Molecular markers of response to s-equol, a novel oral estrogen receptor (ER) beta agonist for triple negative breast cancer

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Introduction: Patients with TNBC breast cancer have inferior treatment outcomes compared to other breast cancer subtypes and targeted therapies are lacking. S-equol is a novel oral Estrogen Receptor (ER) Beta agonist with preclinical data showing suppression of TNBC cellular proliferation, and recently presented data showed a decrease in Ki-67 in patients treated with S-equol. This abstract will present the molecular markers that correlate with Ki-67 change in patients with TNBC treated with neoadjuvant S-equol. Methods: We conducted a neoadjuvant window trial that enrolled 39 patients with confirmed TNBC on diagnostic core needle biopsy. Cohort A (20 patients) received a daily dose of 50 mg PO twice daily and Cohort B (19 patients) received a higher dose of 150 mg twice daily. Paired biopsies were evaluable for 36 patients. Both cohorts were treated for a duration of 10-21 days. Primary outcome was change from pre- to post-treatment Ki-67 evaluated by paired t-test and that data was previously published. Secondary endpoints include: Tumor infiltrating lymphocytes in intratumoral and peritumoral (stromal) locations using CD3 (pan T cell) and CD8 (cytotoxic T cell) immunohistochemistry, density of lymphocytes per high power field (40x) for both locations in pre-treatment and post-treatment specimens, Cyclin-D1 protein expression in pre-treatment and post-treatment biopsies as percentage of total tumor cells in pre-treatment and post-treatment specimens, and total estrogen receptor-beta protein expression using immunohistochemistry qualitatively and quantitatively using All-red score in pre-treatment and post-treatment specimens.Results: The primary outcome of Ki-67 decrease of at least 20% from baseline was observed in 28% of the patients. This is a placeholder abstract and an updated abstract with the correlative molecular markers as outlined above will be provided. Conclusion: S-equol is a novel well tolerated oral ER-Beta agonist with inhibition of proliferation in patients with TNBC as measured by a decrease in Ki-67. RNA-seq data, also previously presented, supports potential immune activation during this short period of drug exposure. Future studies aim to evaluate S-equol as an immune activating agent for combination with immunotherapies such as checkpoint inhibitors in TNBC. The pending molecular predictors of response will inform future therapeutic clinical trials for this novel therapy.

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*SKT11* loss drives rapid cancer progression and fatal pulmonary tumor thrombotic microangiopathy (PTTM) in a breast cancer patient: A case report

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**Introduction:** Pulmonary tumor thrombotic microangiopathy (PTTM) is a rare cancer-associated respiratory complication characterized by widespread tumor cell emboli in small arteries and arterioles of the lung. Breast cancer is the second most common cancer causing PTTM. The pathogenesis and molecular background of PTTM have not been clarified. Here we present a case of breast cancer that experienced early onset of liver metastasis after surgical resection of the primary tumor and rapid progression leading to death due to severe respiratory distress. Autopsy was performed and it revealed that the main cause of her death was PTTM. Comprehensive next generation sequencing (NGS) analysis of the tissue obtained serially during the clinical course was performed. **Case Presentation:** A 48-year-old woman was diagnosed with invasive ductal carcinoma of the left breast, which was ER positive, PgR negative, and HER2 negative. FEC followed by docetaxel was administered as preoperative chemotherapy. Her tumor dramatically shrunk with chemotherapy and left partial mastectomy with left axillary lymph node dissection was performed. Histopathological analysis of the resected breast tissue revealed that there were a lot of residual cancer cells, which were ER negative, PgR negative, HER2 negative, and the result indicated that response to preoperative chemotherapy was insufficient. Additional two courses of FEC therapy were performed. Postoperative radiation therapy including the left supraclavicular lymph node area was given and adjuvant endocrine therapy with anastrozole started at the same time. At 3 months of anastrozole administration, she presented hepatic dysfunction and abnormal CT findings in the liver. Liver biopsy revealed multiple liver metastasis of breast cancer. Unresponsive to weekly paclitaxel and bevacizumab, she developed rapid respiratory failure leading to her death in two weeks. Postmortem microscopic analysis revealed an intimal fibrocellular proliferation in the pulmonary arterioles regardless of microscopic tumor emboli and extensive sinusoidal metastasis of the whole liver. **NGS Analysis:** We analyzed four specimens, breast cancer biopsy specimen at diagnosis, surgical resection specimen, liver needle biopsy specimen, and liver specimen obtained at autopsy, with the Ion AmpliSeq Comprehensive Cancer Panel (Thermo Fisher). The results were compared with NGS analysis of her normal lung tissue to exclude single nucleotide polymorphisms. Deep sequencing revealed that only *TP53* R213* was detected as an oncogenic mutation in all four specimens. There were no mutations associated with the development of liver metastasis and her death. Comparison of the samples obtained between before and after liver metastasis revealed that *STK11* loss and *IKBKE* amplification were harbored only in the specimens after liver metastasis. RNA sequencing analysis with the samples of initial biopsy and liver biopsy showed that the RNA expression associated with apoptosis and adhesion molecules was strongly suppressed in the liver sample. **Conclusion:** *STK11* encodes a serine/threonine kinase, which organizes cell polarity and inhibits tumor growth. In the present patient, *STK11* loss had occurred during the treatment and could induce rapid progression of her disease and PTTM.

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# Investigating the estrogen receptor Y537S mutation in transgenic models of luminal B breast cancer

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Breast cancer is the most prevalent cancer in women and over two-thirds of cases express the estrogen receptor (ER). Significantly, metastatic ER positive breast cancer is the leading cause of breast cancer mortality. Despite the success of endocrine therapy to treat ER-positive breast cancers, resistance to treatment is a major problem and relapse commonly occurs though patients initially respond well to treatment. The ER Y537S mutant represents one of the most common gain-of-function mutations detected in the metastatic biopsies of patients with ER-positive breast cancer. Previous *in-vitro* analyses have shown that the ER Y537S mutant exhibits enhanced ER transcriptional activity by adopting a ligand-independent agonist confirmation. In our study, we seek to provide a deeper understanding of the role of this mutant by modeling the human ER Y537S mutant (ER Y541S in mice). Our lab has generated a Cre-inducible knock-in mouse model expressing the activating point mutation driven by the endogenous ER promoter, and it has been shown that when expressed ubiquitously the mutated ER leads to dramatic developmental effects. In order to further our observations in the context of endocrine resistant metastatic breast cancer, we characterize mamary tumour growth of the ER Y541S mutant in combination with luminal B models of mammary tumourigenesis. Consistent with the notion that these ER mutations occur seldom in primary tumours, preliminary data shows that tumour onset and tumour outgrowth is unaffected by the activating point mutation. When analysing tumours from both ER mutant and wildtype ER control animals, it was found that tumours with mutant ER display more basal-like cytokeratins at the RNA level via RNA sequencing and at the protein level via immunohistochemistry. This expression pattern is often associated with poorer prognosis in the clinic. Through ongoing analyses, we also seek to better understand our model through tumour regression studies (doxycycline withdrawal), treatment with tamoxifen and blocking the main source of estrogens via ovariotomies. By studying the ER Y537S mutation in models of luminal B breast cancer, we hope to investigate the factors leading to tumour recurrence and provide a deeper understanding of potential escape pathways to therapy.

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# Circulating miR-99a-5p expression in plasma: A potential biomarker for early diagnosis of breast cancer

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BACKGROUND: MicroRNAs have emerged as new diagnostic and therapeutic biomarkers for breast cancer. Herein, we analyzed miR-99a-5p expression levels in primary tumours and plasma of breast cancer patients to evaluate its usefulness as a minimally invasive diagnostic biomarker.
METHODS: MiR-99a-5p expression levels were determined by quantitative real-time PCR in three indepent cohorts of patients: I) Discovery cohort: breast cancer tissues (n=103) and healthy breast tissues (n=26). II) Testing cohort: plasma samples from 105 patients and 98 healthy donors. III) Validation cohort: plasma samples from 89 patients and 85 healthy donors. Receiver operating characteristic (ROC) curve analyses were applied to evaluate the diagnostic potential of miR-99a-5p expression levels in tissue and plasma samples.
RESULTS: MiR-99a-5p was significantly downregulated in breast cancer tissues compared to healthy breast tissues ($p < 0.0001$), being able to discriminate BC from healthy breast tissues with an AUC of 0.85, 87.38% sensitivity, 76.92% specificity, and 85.27% accuracy. Conversely, miR-99a-5p levels were significantly higher in breast cancer patients than in healthy controls in plasma samples from both testing and validation cohorts ($p < 0.0001$). ROC curve analysis revealed that miR-99a-5p has good diagnostic potential, with an AUC of 0.76, 63.81% sensitivity, 79.59% specificity, and 71.43% accuracy. The value of circulating miR-99a-5p levels as a breast cancer biomarker was further validated in an independent cohort, where it was able to identify breast cancer with 57.30% sensitivity, 67.06% specificity, and 62.07% accuracy. Besides, we also confirmed that circulating miR-99a-5p levels were able to discriminate early breast cancer from healthy controls with a 66.67% accuracy, 68.80% sensitivity, 65.28% specificity, and an AUC of 0.69 ($p < 0.0001$).
CONCLUSION: MiR-99a-5p's deregulated expression distinguished healthy individuals from breast cancer patients in two different types of samples (tissues and plasma). Interestingly, plasma expression levels were significantly lower in healthy controls than in early-stage breast cancer patients. Our findings suggest that circulating miR-99a-5p as a novel promising non-invasive biomarker for breast cancer detection.

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Breast cancer risk assessment combined with a polygenic risk score in the general population for personalized screening

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**Background:** Polygenic risk scores (PRS) composed of single nucleotide polymorphisms (SNPs) known to increase breast cancer risk could improve the performance of existing breast cancer risk prediction tools. However, data is still limited on the feasibility of risk assessment including PRS in the general population of women undergoing routine screening mammography.**Patients and Methods:** Women, aged 40 or older and not previously identified as high risk, underwent a complete breast cancer assessment, including a questionnaire on personal and family history, mammogram with evaluation of breast density using DenSeeMammo®, and saliva-based testing of 76 SNPs. The PRS was calculated using published per-allele odds ratio corresponding to the SNP associations with breast cancer. We analyzed whether the addition of PRS in eligible women modified risk classification. PRS was not used for risk assessment in non-Caucasian women, but was calculated for comparison between ethnicities.**Results:** A total of 140 Caucasian women underwent a breast cancer assessment and 130 were eligible for MammoRisk® assessment, with a median age of 51 (38-71). With MammoRisk without PRS: 26 (20%) were found to have moderate risk (5-year risk <1%), 71 (55%) intermediate risk (between 1 and 1.67%), and 33 (25%) high risk (≥1.67%). When PRS was performed and integrated into MammoRisk score, 34 (26%) were found to have moderate risk, 45 (35%) intermediate risk, and 51 (39%) high risk. The use of PRS changed the risk classification in 57 women (44%), 32 (25%) to a higher category and 25 (19%) to a lower category. When PRS was assessed for women of sub-Saharan African origin (n=36) using allele frequencies and odd-ratio observed in Caucasian populations, mean PRS was much higher (mean=1.89, [0.65-5.33], median = 1.65 ; n=36) than in the group of Caucasian women (mean=0.97 [0.33-3.05], median = 1.02 ; n=130), which would overestimate the PRS and the risk of developing breast cancer in women of African origin. **Conclusions:** The use of PRS changed the risk classification in a large subset of women. Results of ongoing large-scale studies will inform on the benefits of personalized risk-based screening compared to annual screening (Wisdom [NCT02620852], MyPEBS [NCT03672331]). As current PRSs have been developed and validated in women of European ancestry, population-specific PRSs need to be developed with data from ongoing large-scale genome-wide association studies for improved risk assessment in women of other ethnicities (Confluence Project, Nigerian Breast Cancer Study).

Number of women by risk category

| | W/O PRS | With PRS |
|---|---|---|
| Moderate | 26 | 34 |
| Intermediate | 71 | 45 |
| High | 33 | 51 |

Number of women with change in risk category when using PRS

| | |
|---|---|
| Intermediate to Moderate | 16 |
| Moderate to Intermediate | 5 |
| High to Intremediate | 9 |
| Moderate to High | 3 |
| Intermediate to high | 24 |

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Characteristics of HER2/*neu* positive breast cancer among patients with and without germline *BRCA*mutations

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**Introduction:** Breast cancer in *BRCA 1/2* carriers is a well-characterized disease process, and its association with triple negative breast cancer has been extensively studied. In contrast, there is limited data on *BRCA* carriers and HER2/*neu* positive breast cancer, which identifies this topic as an area for further investigation. The *BRCA* protein plays an important role in DNA replication, whereas HER2/*neu* is a proto-oncogene that, when overexpressed, correlates with aggressive cancers. The relationship between these two mutations is poorly understood. There have been major strides with anti-HER2/*neu* therapies for HER2/*neu* positive disease and PARP inhibitors for *BRCA* germline positive patients, however there is a clinical knowledge gap in *BRCA* carriers who also have HER2/*neu* positive breast cancer. Further research into the characteristics of this population, treatment strategies, and outcomes is needed. More specifically, determining the utility of anti-HER2/*neu* therapies, PARP inhibitors, or the combination in this population could prove to have clinical utility. We aim to characterize the clinical characteristics, treatment strategies, and outcomes within this population.

**Methods:** Using a prospective research patient database at the UT MD Anderson Cancer Center 1038 patients were identified to have HER2/*neu* associated breast cancer who had undergone genetic counseling and testing for hereditary breast cancer syndromes between 1996 and 2019. This population was descriptively characterized to evaluate the prevalence of *BRCA* 1/2 positivity. Clinical and pathological characteristics as well as treatment, and recurrence were collected. Chi-square was used for statistical analysis. The Kaplan-Meier method was used to compare overall survival based on *BRCA* status.

**Results:** Amongst 1038 patients, germline *BRCA* mutation was detected in 49 (4.7%) of the patients. The median age at diagnosis for patients with *BRCA* mutations was significantly younger, 41.7 years (27-76), compared to 44.9 years (21-83) in the *BRCA* negative group (p= 0.0147). More patients were premenopausal in the BRCA positive group (p=0.027). Further characteristics are shown in Table 1. Overall survival was 71.6 months for the *BRCA1* population, 81.3 months for the *BRCA2* population, and 70.7 months for the *BRCA* negative population (*p* = 0.63). Recurrence free survival was 71 months for the *BRCA1,* 51.2 months for the *BRCA2*, and 59.6 months for the *BRCA* negative cohort (*p* = 0.4).

| | | **BRCA negative** | | **BRCA positive** | | ***p* value** |
|---|---|---|---|---|---|---|
| | | **n** | **%** | **n** | **%** | |
| **Race** | ASIAN | 66 | 6.7 | 2 | 4.1 | 0.0122 |
| | BLACK | 97 | 9.8 | 5 | 10.2 | |
| | HISPANIC | 167 | 16.9 | 3 | 6.1 | |
| | NATIVE AMERICAN | 5 | 0.5 | 0 | 0.0 | |
| | OTHER | 11 | 1.1 | 4 | 8.2 | |
| | WHITE | 643 | 65.0 | 35 | 71.4 | |
| **Menopause Status at Dx** | N/A | 4 | 0.4 | 0 | 0.0 | 0.0268 |
| | POST | 178 | 18.0 | 3 | 6.1 | |
| | PRE | 534 | 54.0 | 32 | 65.3 | |
| | Unknown | 273 | 27.6 | 14 | 28.6 | |
| **Age at Dx** | avg (range) | 44.9 (21-83) | | 41.7 (27-76) | | 0.0147 |
| **Histology Type** | ductal | 936 | 94.6 | 45 | 91.8 | 0.3741 |
| | lobular | 18 | 1.8 | 1 | 2.0 | |
| | mixed | 26 | 2.6 | 3 | 6.1 | |
| | other | 9 | 0.9 | 0 | 0.0 | |
| **Stage** | I | 235 | 23.8 | 16 | 32.7 | 0.3293 |
| | II | 467 | 47.2 | 20 | 40.8 | |
| | III | 282 | 28.5 | 12 | 24.5 | |
| | Unknown | 5 | 0.5 | 1 | 2.0 | |
| **Hormone Receptor Status** | ER and/or PR positive | 626 | 63.3 | 30 | 61.2 | 0.7271 |
| | ER/PR negative | 357 | 36.1 | 19 | 38.8 | |
| | Unknown | 6 | 0.6 | 0 | 0.0 | |
| **Nuclear Grade** | I | 9 | 0.9 | 1 | 2.0 | 0.3474 |
| | II | 222 | 22.4 | 7 | 14.3 | |
| | III | 693 | 70.1 | 36 | 73.5 | |
| | Unknown | 65 | 6.6 | 5 | 10.2 | |
| **Ki67** | avg (range) | 40.5 (0-99) | | 46 (10-90) | | 0.1858 |
| **Chemotype** | adj | 327 | 33.1 | 16 | 32.7 | 0.2932 |
| | neoadj | 567 | 57.3 | 25 | 51.0 | |
| | no chemo | 95 | 9.6 | 8 | 16.3 | |
| **Herceptin Trx** | adj | 270 | 27.3 | 14 | 28.6 | 0.4093 |
| | neoadj | 506 | 51.2 | 21 | 42.9 | |
| | none | 211 | 21.3 | 14 | 28.6 | |
| | unknown | 2 | 0.2 | 0 | 0.0 | |
| **Adj Hormone** | N | 442 | 44.7 | 24 | 49.0 | 0.5558 |
| | Y | 547 | 55.3 | 25 | 51.0 | |
| **XRT** | N | 380 | 38.4 | 22 | 44.9 | 0.3637 |
| | Y | 609 | 61.6 | 27 | 55.1 | |
| | | 989 | 100.0 | 49 | 100.0 | |

Table 1:

**Conclusion:** HER2/*neu* positive breast cancer patients with and without germline *BRCA* mutations have different clinical presentations. While we did not detect a survival difference due to small number of patients, this presents an opportunity to evaluate whether new treatment strategies, such as combining anti-HER2/*neu* therapies with PARP inhibitors can further improve outcomes for these patients.

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# Training multi-professional mammogram readers to interpret abbreviated breast MRI (FAST MRI): A UK multi-centre study

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**Background:** As a breast cancer screening test, FAST MRI has the potential to combine the sensitivity of dynamic contrast enhanced breast MRI (DCE-MRI) with costs nearer to those of mammography. In the UK the NHS Breast Screening Programme (NHSBSP) screens women aged 50-70 with a mammogram every 3 years and has a workforce of radiologists, breast clinicians and advanced practitioner radiographers who interpret over 2 million screening mammograms annually. For FAST MRI to be used as a UK population screening tool it will need to be interpreted by the existing multi-professional workforce of mammogram readers. Our research team developed a single study day of standardised training in FAST MRI interpretation. In our single centre pilot study, a group of readers with no previous experience of DCE-MRI interpretation achieved an accuracy just 5% less than expert DCE-MRI readers (Br J Radiol 2019:**92** DOI:10.1259/bjr.20190663).
Our current study aimed to validate the feasibility of training the NHSBSP workforce in FAST MRI interpretation. We developed display software (MedXViewer) containing ground truth information for each FAST MRI case to train and assess mammogram readers, who represented multiple NHSBSP sites in the South West Region of England.
**Methods:** The study was funded by the National Institute for Health Research (Research for Patient Benefit funding stream; ISRCTN 16624917).
A per breast analysis of the frequency of results against the true outcome was obtained overall and for each reader. Differences in accuracy, sensitivity and specificity across reader groups (group 1 = mammogram readers experienced in DCE-MRI interpretation; group 2 = mammogram readers with no previous experience in DCE-MRI interpretation) were analysed using a multilevel generalised mixed model to account for multiple readers per case.
**Results:** 37 NHSBSP mammogram readers at 6 NHSBSP sites attended the training day and completed interpretation of the summative assessment dataset (17 in group 1 and 20 in group 2). All 37 readers completed the reading task of 125 cases (250 breasts), for a total of 9250 reads. Median interpretation time was 99.08 seconds (interquartile range 66.83-150.54).
The table below shows per breast analysis comparing the readers' classification with the true outcome (cancer or normal):

| | **Total** | **Group 1** | **Group 2** |
|---|---|---|---|
| **Measure** | | | |
| **Concordance (Accuracy)** | 7943/9250 (86%) | 3814/4250 (90%) | 4129/5000 (83%) |
| **True positive rate (Sensitivity)** | 1806/2109 (86%) | 858/969 (89%) | 948/1140 (83%) |
| **True negative rate (Specificity)** | 6137/7141 (86%) | 2956/3281 (90%) | 3181/3860 (82%) |
| **False positive rate** | 1004/7141 (14%) | 325/3281 (10%) | 679/3860 (18%) |
| **False negative rate** | 303/2109 (14%) | 111/969 (11%) | 192/1140 (17%) |

The concordance with the ground truth (accuracy) of 83% achieved by Group 2 (4129/5000 (95% CI 82-84%)) was significantly lower than that achieved by Group 1 (3814/4250 (90%; 89-91%); $p<0.0001$) but differed by only 7%. The concordance with the true outcome improved for the group 2 readers from the first 55 cases to the remaining 70 cases ($p=0.02$), whereas there was no significant improvement for the expert readers of group 1 ($p=0.81$).
**Conclusions:** This study validates the feasibility of training the workforce of mammogram readers to interpret FAST MRI with only one day of standardised training. Improvement in performance with experience by the group 2 readers indicates a learning curve and suggests the performance gap between the two groups might be narrowed by further training for group 2.

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Identification of cell surface proteins in triple negative breast cancer for the development of novel targeted therapies

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Triple negative breast cancer (TNBC) stands out due to its aggressive course and high metastatic rates. No consistent protein biomarker has been described for TNBC, resulting in a scarcity of adjuvant therapies for the afflicted patients. Hence, there is an urgent need to determine novel TNBC-associated proteins for the development of new therapeutics and the identification of novel molecular mechanisms driving this malignancy. Cell surface proteins represent attractive targets for novel therapies, due to their easily accessible localization and their involvement in essential signaling pathways.
Objectives: We aimed to uncover novel TNBC-associated cell surface proteins involved in carcinogenesis and metastasis for the development of novel targeted therapeutics.
Rationale: Taking advantage of the fact that cell surface proteins are often N-glycosylated, we employed hydrazide chemistry to isolate N-glycopeptides. The glycoproteome of six immortalized TNBC cell lines and five ‘healthy’ controls (HC) (the immortalized cell line MCF10A and four patient-derived human mammary epithelial cell lines) was analyzed using LC-MS/MS and label-free quantification. A data mining strategy was employed to select candidates of interest. We knocked-down (k.d.) the top five candidates of interest (using siRNA technology) and evaluated cell growth using growth-curve analysis. Plexin B3 (PLXNB3) was selected for subsequent functional validations. The effects of PLXNB3 k.d. (using siRNA and CRISPR technology) on cancer cell growth, apoptosis and adhesion were interrogated using western blotting and standard cell biology protocols.Results: The N-glycoproteomics approach led to the identification of 1044 glycoproteins, with over 70% described as plasma membrane/secreted proteins. Gene Ontology analysis revealed that the TNBC-associated glycoproteome was enriched in biological processes such as: mesenchyme development, MAPK signaling, positive regulation of proliferation and regulation of neuron projection development. Candidates of interest were selected from our list by focusing on those plasma membrane proteins that were enriched in TNBC cells compared to HC according to our label-free quantified proteomics data, and that showed limited expression in healthy tissues according to the Human Protein Atlas. We further restricted the list of candidates to those proteins whose k.d. impaired cancer cell growth, with little effect on the HC. PLXNB3, an understudied protein typically expressed in healthy neuronal tissues, was selected for in depth functional analysis. Elevated mRNA PLXNB3 levels in breast cancer patients is associated with poorer overall survival compared to low mRNA expression (Integrated TCGA Pan-Cancer Clinical Data Resource, 2018). PLXNB3 k.d. (using siRNA and CRISPR technologies) impaired TNBC cell growth (in both adherent and spheroid cultures) and was associated with elevated levels of cleaved-caspase 3 and cleaved-caspase 7 compared to scrambled controls. Furthermore, PLXNB3 k.d. negatively impacted TNBC cell adhesion to extracellular matrixes compared to scrambled controls. Subsequent tests will evaluate PLXNB3’s role in tumor growth and metastasis *in vivo*, using orthotopic tumor models in immunocompromised mice.

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# A phase I/II open-label, first-in-human, multicenter, dose escalation and dose expansion study of OP-1250 monotherapy in adult subjects with advanced and/or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer

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**Background**: Endocrine therapy has been the primary treatment modality for HR+, HER2- metastatic breast cancer (MBC). Endocrine agents are administered sequentially, either in combination with targeted therapy or as monotherapy. The majority of patients with HR+, HER2- MBC will develop endocrine resistant disease. More effective and less toxic therapies are needed for the treatment of endocrine resistant disease.
OP-1250 is a small molecule Complete Estrogen Receptor ANtagonist (CERAN) that completely inactivates Estrogen Receptor (ER), blocks ER-driven transcriptional activity, inhibits ER-driven breast cancer cell growth, and induces degradation of ER. OP-1250 demonstrates anti-cancer activity *in vitro* and *in vivo*, including activity against metastases in the brain and in tumors with activating mutations in *ESR1.* OP-1250 is orally bioavailable with a favorable pharmacokinetic profile supportive of once-daily dosing. OP-1250 is hypothesized to completely antagonize ER resulting in superior efficacy compared to agents that only have partial antagonism of ER. Its favorable pharmacologic profile makes it an attractive agent for chronic use in patients with MBC.
**Trial design:** This is a Phase I/II open-label, first-in-human study to determine the Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD) and/or Recommended Phase II Dose (RP2D), to characterize the safety and pharmacokinetic (PK) profile, and to determine the preliminary efficacy of OP-1250 in adult subjects with HR+, HER2- MBC. Treatment will consist of oral, once a day dosing and subject evaluation will be performed in 28-day cycles. This study comprises 2 parts. Part 1 (Dose Escalation) will evaluate the safety and pharmacology of a range of doses of OP-1250 administered orally to subjects and to determine the maximum tolerated dose (if any) and/or the RP2D. Cohorts of 3 to 6 subjects will be sequentially enrolled and monitored for DLTs during the first cycle of study treatment. Part 2 (Dose Expansion) will evaluate the preliminary activity of OP-1250. Patients with and without central nervous system (CNS) disease will be enrolled at the RP2D. This is designed using a Simon 2 Stage Design. Total accrual will be determined by the number of dose levels needed to identify the RP2D.
**Eligibility criteria:**

- Males and females, age 18 or older, with ER+, HER2- advanced or MBC
- Prior treatment with endocrine therapy
- ECOG performance status of 0 or 1
- For dose expansion the subject must have measurable disease according to Response Evaluation Criteria in Solid Tumors Criteria (RECIST) 1.1

**Objectives**Part 1 (Dose Escalation)

- To identify the DLT, MTD and/or RP2D of OP-1250
- To assess the safety and tolerability of OP-1250
- To assess the pharmacokinetics of OP-1250

Part 2 (Phase II: Monotherapy Expansion)

- Objective response rate (ORR) of OP-1250 in subjects with HR+, HER2- MBC who have progressed on endocrine therapy and have no evidence of central nervous system (CNS) metastases.
- To conduct a preliminary assessment of the antitumor activity (ORR) of OP-1250 in subjects with HR+, HER2- MBC who have progressed on endocrine therapy and have CNS disease. Assessment of response will be determined according to RECIST 1.1 and Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria

Correlative Science

- To determine biomarker expression, such as, ER, PR, Ki67 and others in the most recently obtained archival tumor tissue sample
- To evaluate whether *ESR1* in circulating tumor DNA (ctDNA) can be correlated with response and/or activity of OP-1250
- To examine ctDNA pre- and post-therapy for *mutESR1* and *PIK3CA* variants, and other relevant markers

For more information, please contact clinical@olemapharma.com

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# Correlations between tumor-infiltrating lymphocytes, CD3, CD8 cells, and Immunoscore®, with pathological CR and time to progression in triple-negative breast cancer patients undergoing neoadjuvant chemotherapy

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**Background** High levels of stromal tumor-infiltrating lymphocytes (TILs) have been associated with better prognosis in early triple-negative breast cancer (TNBC). The Immunoscore® (IS) is a prognostic tool, which categorizes the densities of spatially positioned CD3 and CD8 cells in both invasive margins (IM) and the center of the tumor (CT), yielding a five-tiered classification (0-4). High IS values have been reported to predict improved outcomes in colorectal cancer. **Methods** The cohort consisted of 53 TNBC patients (pts) who previously received neoadjuvant anthracycline- and taxane-based chemotherapy. Quantitative analysis of the immune cells was carried out using computer-assisted image analysis in different tumor locations for CD3 and CD8 T-cell markers. Additionally, we measured stromal TILs according to the International TILs Working Group. Pre-treatment tumor samples were immune-stained for CD3 and CD8 T-cell markers and stromal TILs. The relationship between various clinical-pathological factors, and immune factors, was analyzed by $Chi^2$ and Fischer exact test. The log-rank test and the Kaplan Meyer methods were used to estimate relapse-free survival. **Results** The median age of the pts was 50 years (27-84 years). Tumor sizes were categorized as T1 = 9 pts (17%), T2 = 41 pts (77%) and T3 = 3 pts (6%). Pts with positive glands = 19 (36%) pts and pts without gland involvement = 34 (64%). Stage grouping included stage 1 = 5 (9%), stage IIA = 33 (63%) pts, stage IIB = 9 (17%) pts, stage III = 6 (11%) pts. The median Ki-67 was 45% (range 5 - 90%). The median density of CD3 CT cells = 1190mm² (range 34 - 4614), CD3 IM = 1855mm² (range 57 - 6190), CD8 CT 508mm² (range 17 - 2486) and CD8 IM 805mm² (range 90 - 3156). The median percentage of stromal TILs was 5% (0 - 60%). Pts with an IS of 0 = 4 pts (8%), IS 1 = 3 (5%), IS 2 = 20 pts (38%), IS 3 = 24 pts (45%) and IS 4 = 2 pts (4%). The pathological complete response (pCR) rate of the entire cohort was 62%. A positive correlation was found between TILs and CD3 CT ($R = 0.641$, $p < 0.0000$), CD8 CT ($R = 0.5623$, $p < 0.0000$), CD3 IM ($R = 0.6099$, $p < 0.0000$), and CD8 IM. ($R = 0.5010$, $p < 0.0010$). TILs correlated with IS ($R = 0,3603$, $p < 0.0087$). There was no correlation between TILs and Ki-67 ($R = 0.1497$, $p < 0.2943$). On univariate analysis, factors associated with higher pCR included nodal status (positive = 42,11% vs. negative = 73,53% (p<0,02362) and Ki67 <40%= 33,33% vs. ≥40% = 76,47% (p<0,00235). A high density of CD3 (> than 1100mm$^2$) and CD8 (> than 400mm$^2$) positive T-cells in the CT was associated with higher pCR (CD3 CT: 30% vs. 70%, p=0.00489 and CD8 CT: 30% vs. 70%, p=0.03344). Analysis of CD3 (> than 1200mm$^2$) (CD3 IM: 12% vs 88%, p=0.0.02367) and CD8 in the IM (> than 550mm$^2$) was also significant for an association with pCR (CD8 IM: 23% vs. 77%, p=0.03). High IS (3+4= 73%) vs. intermediate (2=55%) vs. low (0+1=43%) showed a numerical difference that did not, however, reach a statistical significance with pCR (p=0.111). Analysis of TILs ≥ 20% showed a pCR of 76% compared to pts with TILs < 20% with a pCR of 54% ($p < 0.12295$). A Ki67 ≥40% was associated with a pCR of 76% compared to pts with Ki67 < 40% with a pCR 33% ($p < 0.00235$). The median time to progression (TTP) of the pts not attaining a pCR was 1600 days compared to those who did attain a pCR with a median PFS not reached yet, but exceeding 1800 days. The TTP of pts with Ki67 < 40% was 1700 days, while the pts with Ki67 ≥40% was not been reached ($p < 0.03$). At 1800 days, 95% of pts with CD3 > 1100mm$^2$ did not relapse, compared to 75% pts with CD3 ≤ 1100 ($p < 0.03$). **Conclusions** This exploratory study shows that analyzing CD3 and CD8 cells in the center of the tumor and invasive margin might be more useful than examining TILs in TNBC pts. Further prospective, well-designed, adequately powered studies are required to confirm these findings.

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Ribecca - a phase 3b, multi-center, open label study for women with estrogen receptor positive, locally advanced or metastatic breast cancer treated with ribociclib (lee011) in combination with letrozole: Final results

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**Introduction:** RIBECCA is a national, multi-center, open-label, single-arm phase IIIb trial assessing the efficacy and safety of ribociclib in combination with letrozole in a patient population similar to the populations of MONALEESA-2, -3 and -7, including premenopausal and postmenopausal patients without pretreatment as well as patients with up to 3 previous treatment lines for advanced disease. Here we present the final analysis for the primary endpoint. **Methods:**The study enrolled women or men with metastatic or locally advanced breast cancer irrespective of their menopausal status, who were not amenable to curative treatment by surgery or radiotherapy. Histological or cytological confirmation of HR+, HER2- breast cancer was required. 502 patients were enrolled in two Cohorts. Cohort A (n=319): postmenopausal women and men without pretreatment for advanced disease; Cohort B (n=183): premenopausal women without pretreatment for advanced disease and pre- or postmenopausal women and men with ≤ 1 line of chemotherapy and/or ≤ 2 lines of endocrine therapy in the advanced situation. The primary endpoint was to assess the clinical benefit rate (CBR, defined as CR, PR or SD, or NCRNPD) at 24 weeks for the overall study population. Secondary endpoints included: progression free survival (PFS), overall survival (OS), safety, and changes in quality of life as assessed by EORTC QLQ-C30 and -BR23 questionnaires. **Results:** The study ended 84 weeks after the enrollment of the last patient. The median observation time was 10.6 months (0.1-38 months). Baseline characteristics: of 502 pts, 5 were male, 497 were female(46 pre-or perimenopausal, 451 postmenopausal); median age: 64 yrs; ECOG 0-1: 96.8%; 71.1 % of pts had bone metastases (40.8% bone only), 30.6% liver, 27.5% lung and 30.1% other metastases. 97.3% had at least 1 metastatic site: 48.7% had 1, 35.1% had 2, 12.9% had 3 and 1.6% had 4 metastatic sites, respectively. 78.9% received at least one prior antineoplastic therapy: 4.9% received neoadjuvant, 56.8% adjuvant and 37.8% palliative treatment as last antineoplastic therapy before study start. The most common treatment emergent AEs (all grades) were neutropenia and/or neutrophil count decreased (60.6%), nausea (42%), fatigue (39.2%), alopecia (35.1%), leukopenia or WBC decreased (30.7%), nasopharyngitis (28.5%), diarrhea (25.3%), ALT increased (22.9%) and AST increased (20.7%). The CBR at week 24 for the overall study population was 69.2%. Median PFS was 16.5 [95%CI 13.7; 19.3] months in the overall study population, 21.8 [15.4; 25.3] months and 9.3 [8.1; 16.3] months in Cohort A and B, respectively. At 72 weeks, the Kaplan-Meier estimate for OS was 86.8% [83.3; 89.6]. Because of the low number of events during the study period, median OS could not be determined. **Conclusion:** The results of the final analysis confirmed clinical benefit of ribociclib and letrozole in this patient population. No new safety signals emerged.

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Developing an outreach model to healthcare providers treating newly diagnosed metastatic breast cancer patients

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**Background**: Metastatic breast cancer (MBC) patients report a lack of information tailored to their stage IV diagnosis (MBCA Landscape Analysis, 2013; LBBC's Silent Voices 2006). Recent research by Living Beyond Breast Cancer (LBBC) showed that patients seek information in the weeks following a metastatic diagnosis as part of their sense-making. At the time of diagnosis, when patients report high uncertainty and vulnerability, Healthcare Providers (HCPs) are highly trusted as information sources. HCPs, particularly in smaller, community-based hospitals and cancer centers, cite lack of time and informational resources as their greatest barriers to addressing the psychosocial and educational needs expressed by their newly diagnosed metastatic patients (LBBC 2018). In 2019, LBBC focused on developing a model outreach program to HCPs to distribute evidence-based educational resources and support programs to their patients newly diagnosed with metastatic breast cancer (MBC).
**Methods:** LBBC conducted research with MBC patients and HCPs to determine needs, topics of interest, resource formats and optimal resource distribution channels through HCPs. LBBC held two MBC patient focus groups and two HCP focus groups of nurses and social workers. The findings from the patient focus groups and the first HCP focus group informed the development of a survey for HCPs, which was fielded in November 2019. The survey data was analyzed, and key findings from the HCP survey and MBC focus groups determined the topics of the final HCP focus group in January 2020.
**Results:** Surveys were sent to LBBC's HCP provider database and the memberships of select professional associations. A total of 352 surveys were completed; 50 percent of respondents were social workers, 46 percent were nurse navigators or nurse practitioners, and 4 percent were physicians or other. The data from the survey and focus groups showed that patients and HCPs had difficulty finding MBC-specific materials and programs despite a distinct need within the community. Both groups wanted information to help patients better understand their diagnosis, treatment plan, and overall prognosis. Resources on mental health, talking to family about diagnosis, and financial toxicity were also of primary importance.
HCPs reported needing materials for patients that are evidence-based, credible and conveyed in plain language. Patients reported wanting a reliable online hub of MBC information and resources. Both patients and HCPs preferred printed or digital downloadable materials, or both. Additional findings showed MBC patients who are African-American or under age 45 are underrepresented in the existing content. Other gaps include content for spouses/partners, family, and caregivers.
**Conclusions:** People newly diagnosed and living with MBC, and the HCPs who serve them, want evidence-based information, tailored to the MBC patient, to help them understand their diagnosis and its psychosocial and financial impact, developed by credible organizations and delivered in easy-to-read, printable, or digital formats, or both. Using the data from this research, LBBC is developing a model outreach program to assist HCPs meet the needs of their newly diagnosed metastatic breast cancer patients.

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# A multicentre prospective feasibility study of carbon dye tattooing of biopsied axillary node and surgical localisation in breast cancer patients

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**Background:** The primary aim of this prospective, multicentre feasibility study was to determine whether the biopsied axillary node in patients with breast cancer can be marked using black carbon dye and successfully identified at the time of surgery. **Methods:** We included patients undergoing needle biopsy of the axillary lymph gland. The biopsied node was tattooed at the time of needle biopsy (fine needle aspiration or core biopsy) or at a separate visit with black carbon dye (Spot™ or Black Eye™). Participants underwent primary surgery or neoadjuvant chemotherapy and axillary surgery (SNB or ALND) as per routine care. **Results:** 110 patients were included. Median age of the women was 59 (range 31 to 88) years. 48 of 110 (44%) underwent SNB and 62 (56%) ALND. The median volume of dye injected was 2.0 ml (range 0.2-4.2).Tattooed node was identified in 90 of 110 (82%) patients. The identification rate was higher (86%) in the primary surgery group compared with NACT (64%). Of those undergoing NACT, the identification rate was better in the patients undergoing SNB (3 of 4, 75%) compared with ALND (11 of 18, 61%). The tattooed node was the sentinel node in 78% (28 of 36) patients in the primary surgery group and 100% (3 of 3) in the NACT group. For surgeons who had performed ≥5 operations, there was no learning curve. The identification rate did not vary with body mass index or volume of dye injected. There was no correlation between volume of dye and number of tattooed nodes removed. **Conclusion:** It is feasible to mark the axillary node with carbon dye and identify it intraoperatively. Modifications of the technique, such as injecting the dye in the cortex alone, restricting the volume to 0.2 to 0.4 ml and combining with clip, will improve the technical ability to identify the marked node.

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Patterns, predictors and prevalence of germline *BRCA1* and *BRCA2* mutations among young patients with breast cancer in Jordan

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**Introduction**: Hereditary causes, mostly related to *BRCA1* and *BRCA2* mutations, are not uncommon causes for breast cancer. Western studies had shown that such mutations are more prevalent among younger patients. In this study, we evaluate the prevalence of germline mutations in *BRCA1* and *BRCA2* among breast cancer patients diagnosed at age 40 or younger. **Methods**: Data on Jordanian breast cancer patients diagnosed at age 40 years or younger was reviewed. Blood samples were obtained for DNA extraction and *BRCA* sequencing was performed at reference labs. *BRCA1* and *BRCA2* mutations were classified as pathogenic/likely pathogenic and variant of uncertain significance (VUS). **Results**: A total of 616 patients aged 40 years or younger were enrolled. Genetic testing and genetic counseling have been completed for all. Majority (n=499, 81.0%) had a family history of breast cancer and 12.6% had triple-negative disease. Among the whole group, 75 (12.2%) were tested positive for pathogenic or likely pathogenic mutations, mostly (66.7%) in *BRCA2* and an additional 57 (9.3%) had VUS. In multivariate analysis, triple-negative disease (Odd Ratio [OR]: 5.37; 95% CI: 2.88-10.02, p<0.0001), breast cancer in two or more family members (OR: 4.44; 95% CI: 2.52-7.84, p<0.0001), and a personal history of two or more primary breast cancers (OR: 3.43; 95% CI: 1.62-7.24, p=0.001) were associated with higher *BRCA* mutation rates (Table).

| **Variables** | **Total** | **Positive Mutations** | | | | |
|---|---|---|---|---|---|---|
| *BRCA1* | *BRCA2* | *BRCA1& BRCA2* | P-Value | | | |
| **Age at diagnosis (years)** | ≤ 35 | 341 | 16 | 34 | 50 (14.7%) | 0.017 |
| > 35 | 275 | 9 | 16 | 25 (9.1%) | | |
| **One or more close relative with breast cancer at any age** | Yes | 305 | 9 | 37 | 46 (15.1%) | 0.029 |
| No | 311 | 15 | 14 | 29 (9.3%) | | |
| **One or more close relatives with breast cancer diagnosed at age 50 years or younger** | Yes | 153 | 3 | 24 | 27 (17.6%) | 0.017 |
| No | 463 | 22 | 26 | 48 (10.4%) | | |
| **Diagnosed at ≤ 60 years with triple negative disease** | Yes | 69 | 16 | 7 | 23 (33.3%) | <0.001 |
| No | 547 | 9 | 43 | 52 (9.5%) | | |
| **Any age with at least 2 breast cancer primaries** | Yes | 48 | 6 | 8 | 14 (29.2%) | <0.001 |
| No | 568 | 19 | 42 | 61 (10.7%) | | |
| **Two or more close relatives with breast cancer** | Yes | 97 | 5 | 24 | 29 (30.0%) | <0.001 |
| No | 519 | 20 | 26 | 46 (8.9%) | | |
| **All Patients** | **616** | **25** | **50** | **75 (12.2%)** | | |

In multivariate analysis, triple-negative disease (Odds Ratio [OR]: 5.37; 95% CI: 2.88-10.02, p<0.0001), breast cancer in two or more family members (OR: 4.44; 95% CI: 2.52-7.84, p<0.0001), and a personal history of two or more primary breast cancer (OR: 3.43; 95% CI: 1.62-7.24, p=0.001), were associated with higher *BRCA* mutation rates. A spectrum of 39 different mutations, 22 in *BRCA2* and 17 in *BRCA1* were detected. To our knowledge, three mutations in *BRCA2* (c.4222_4223del and c.6193C>T in exon 11 and c.1013del in exon 10) have not been reported previously in any database. **Conclusions:** Among young Jordanian patients with breast cancer, mutation rates are significantly higher in patients with triple-negative disease, personal history of breast cancer and those with two or more close relatives with breast cancer.

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# Prospective observational study to explore the effectiveness of eribulin as first- or second- line chemotherapy in patients with HER2-negative hormone-resistant advanced or metastatic breast cancer (KBCRN A001: E-SPEC study)

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**Background**Eribulin (E) is a chemotherapeutic drug that prolongs overall survival (OS) of patients with HER2-negative advanced or metastatic breast cancer (AMBC), mainly in multi-line chemotherapy (ChT) or later. However, the effectiveness and optimal scheduling of E remain unclear. We prospectively investigated the impact of E use in 1st- and 2nd-line ChT (early E) for patients with endocrine-resistant AMBC.
**Methods** In this multi-institutional prospective cohort study, we registered patients with hormone receptor-positive AMBC who relapsed during or within 6 months after ending adjuvant endocrine therapy, were refractory to at least one previous endocrine therapy, or patients with triple negative AMBC. The endpoints were 1st-line OS (OS1), 2nd-line OS (OS2), and 3rd-line OS (OS3), defined as the time from the start of treatment to death. In addition, the time from the start of 1st-line ChT to death was also analyzed for 2nd-line and 3rd-line ChT groups. In addition to E therapy, oral FU-based therapies (FU) and anthracycline or taxane-based therapies (A/T) were also analyzed (ClinicalTrial.gov number, NCT02551263).
**Results** Between June 2015 and July 2017, a total of 201 patients were enrolled, and full analysis was conducted for 180 patients. The median OS1, OS2, and OS3 of all patients was 2.69, 1.74, and 1.13 years, respectively. Major patient characteristics are described in the Table. Concurrent or maintenance endocrine therapy was used by 14.9%, 31.6%, and 12.9% of patients receiving E, FU and A/T in 1st-line ChT, respectively. The median OS of patients using E was OS1: 2.25 years (N=47), OS2: 1.75 years (N=70) and OS3: 0.94 years (N=16). The median OS of patients using A/T was OS1: 2.60 years (N=70), OS2: 1.69 years (N=44) and OS3: 0.96 years (N=49). The median OS of patients using FU was OS1: 3.49 years (N=57), OS2: 2.33 years (N=27), and OS3: 1.45 years (N=24). The time from the start of 1st-line ChT to death was 2.58 and 3.18 years among patients who received E in 2nd- and 3rd-line ChT, respectively. Multivariate analysis of patients who used 1st-line and 2nd-line E demonstrated that higher LDH (≥300) (HR 3.50, 95% CI 1.78-6.73; p<0.001), brain metastasis (HR 2.64, 95% CI 1.02-6.83; p=0.045) and smoker (HR 2.33, 95% CI 1.20-4.53; p=0.013) were associated with shorter OS. Overall, OS data for E were comparable to those for A/T. While OS tended to be better for FU, patient characteristics for 1st-line ChT showed that FU was often used for patients with less aggressive AMBC. We also present data on second progression-free survival and new metastasis-free survival, prognostic factor analysis and prognostic factor-adjusted comparison, and predictive factor analysis for early E.
**Conclusions** This prospective observational study of AMBC patients showed that E and A/T had similar survival outcomes in each treatment line. While FU led to relatively longer survival, it was often used for patients with less aggressive AMBC. Analysis data on survival outcomes will also be presented.

Patient characteristics according to 1st-line therapy

| | E (n=47) | | Oral FU based (n=57) | | A/T based (n=70) | |
|---|---|---|---|---|---|---|
| **Median age (IQR)** | 61 | (54-71) | 64 | (51-68) | 59 | (48-66) |
| Triple negative, n (%) | 15 | (31.9) | 11 | (19.3) | 23 | (32.9) |
| Disease-free interval, n (%) | | | | | | |
| <2 years | 15 | (31.9) | 9 | (15.8) | 12 | (17.1) |
| 2-5 years | 12 | (25.5) | 18 | (31.6) | 15 | (21.4) |
| 5-8 years | 4 | (8.5) | 9 | (15.8) | 9 | (12.9) |
| >8years | 3 | (6.4) | 10 | (17.5) | 8 | (11.4) |
| Stage4 | 9 | (19.1) | 9 | (15.8) | 23 | (32.9) |
| (neo) Adjuvant chemotherapy, n (%) | 30 | (63.8) | 36 | (63.2) | 32 | (45.7) |
| Metastatic sites at 1st-line ChT, n (%) | | | | | | |
| Liver | 16 | (34.0) | 12 | (21.1) | 22 | (31.4) |
| Lung | 15 | (31.9) | 17 | (29.8) | 25 | (35.7) |
| Bone | 24 | (51.1) | 27 | (47.3) | 36 | (51.4) |
| Brain | 6 | (12.8) | 1 | (1.8) | 2 | (2.9) |

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Survival among female breast cancer patients who have survived a previous cancer

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**Background**
A growing number of women newly diagnosed with breast cancer have survived a previous cancer. Although little is known about their prognosis, this population is frequently excluded from clinical trials. Additional evidence about the survival of this population is needed, so that trial sponsors and investigators can create evidence-based trial eligibility criteria. Among women newly diagnosed with breast cancer, we examined the impact of previous cancer on overall and cancer-specific survival. **Methods** This population-based cohort study included patients age ≥66 years and diagnosed with breast cancer between 2005-2015 in linked SEER-Medicare data. Separately by breast cancer stage, we estimated overall survival using Cox regression and cause-specific survival using competing risk regression for women with and without previous cancer, adjusting for numerous covariates and competing risk of death from previous cancer, other causes, or the incident breast cancer. **Results** Of 138,576 women diagnosed with incident breast cancer, 10,822 (8%) had a previous cancer of another organ site. Many of these (n=5,014, 46.3%) were diagnosed ≤5 years of breast cancer. For all breast cancer stages except IV in which there was no significant survival difference, women with vs. without previous cancer had worse overall survival. This survival disadvantage was driven by deaths due to the previous cancer and other causes. In contrast, women with previous cancer generally had favorable breast-cancer specific survival; however this varied somewhat by stage and over time. **Conclusions** Many women newly diagnosed with breast cancer are already cancer survivors. These women had generally worse overall survival, worse survival from other causes, but their disease-specific survival varied depending on their breast cancer stage and over time.

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# Hyperleptinemia in obese state renders luminal breast cancers refractory to tamoxifen coordinating a crosstalk between Med1, miR205 and Erb B kinases

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**Background and Aim:** Obese state is associated with increased breast cancer growth, metastasis, and poor overall survival. In this study, we seek to decipher the underlying molecular mechanisms by which obesity/hyperleptinemia reduces the efficacy of tamoxifen. **Methods**: The impact of obesity on tamoxifen was evaluated utilizing clonogenicity, high-fat-diet- induced obese mice and leptin-treated xenograft-models. Mechanistic studies involved immunoblotting, real-time PCR, immunocytochemistry, chromatin immunoprecipitation assay, phosphokinase array and *in silico* analysis. **Results**: Obese mice with hyperleptinemia exhibit increased tumor progression and respond poorly to tamoxifen compared to non-obese mice. Exogenous leptin abrogates tamoxifen-mediated growth inhibition and potentiates breast tumor growth even in the presence of tamoxifen. Mechanistically, leptin induces nuclear translocation of phosphorylated-ER and increases the expression of ER-responsive genes while reducing tamoxifen-mediated gene repression by abrogating tamoxifen-induced recruitment of corepressors NCoR, SMRT and Mi2. Further, we found that coactivator Med1 potentially associates with 48 (out of 75) obesity-signature genes. Interestingly, leptin upregulates Med1 expression by decreasing miR-205 and increases its functional activation via phosphorylation that is mediated by activation of Her2 and EGFR. It is important to note that Med1 silencing abrogates the negative effects of leptin on tamoxifen efficacy. Additionally, honokiol or adiponectin treatment effectively inhibits leptin-induced Med1 expression and improve tamoxifen efficacy in hyperleptinemic state.**Conclusion:** In conclusion, these studies show the molecular mechanisms by which obese/hyperleptinemic state may contribute to poor response to tamoxifen implicating leptin-miR205-Med1 and leptin-Her2-EGFR-Med1 axes and present bioactive compound honokiol and adipocytokine adiponectin as agents that can block leptin's negative effect on tamoxifen.

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Characterization of HOXB13-induced estrogen receptor reprogramming in breast cancer cells

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**Background**: The Breast Cancer Index (BCI) is a gene expression-based signature that consists of two functional biomarker panels, HOXB13/IL17BR (H/I) and Molecular Grade Index (MGI), that interrogate important proliferation and estrogen signaling pathways in breast cancer. The BCI prognostic score reports individualized risk of overall and late distant recurrence and is based on the algorithmic combination of the H/I ratio and MGI, while the predictive component, BCI (H/I), reports a categorical prediction of high versus low likelihood of benefit from extended endocrine therapy.The homeobox transcription factor HOXB13 has previously been shown to reprogram genome-wide binding of the androgen receptor (AR) during prostate cancer tumorigenesis, where it colocalizes with FOXA1 at reprogrammed AR binding sites. The aim of the current study was to characterize the potential role of HOXB13 in estrogen receptor (ER) reprogramming by analyzing changes in the global ER binding pattern induced by transient overexpression of HOXB13 in breast cancer cells. In addition, gene ontology (GO) analysis was performed to delineate the functional role of HOXB13 in modulating estrogen signaling and response to endocrine therapy.**Methods:** HOXB13 was overexpressed in MCF-7 cells by electroporating HOXB13 mRNA, or eGFP mRNA as control. Cells were harvested at different time points and analyzed by western blot and chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) using antibodies against ER, HOXB13, FOXA1 and H3K27ac. After aligning reads with Bowtie2, peak calling and data integration were performed using HOMER v4.10. Gene ontology (GO) analysis was performed using the Genomic Regions Enrichment of Annotations Tool (GREAT v4.0.4) (http://great.stanford.edu/) to identify annotations enriched among genes near ER genomic binding sites.**Results:** ChIP-seq analysis revealed substantial binding of HOXB13 to a large number of genomic binding sites compared to the eGFP control. HOXB13 overexpression in ER+ breast cancer cells significantly increased ER binding with a majority of ER binding sites being co-bound by FOXA1 and HOXB13. GO analysis of both proximal and distal genomic regions showed significant enrichment of genes associated with mammary gland development, such as “mammary gland epithelium development”, “mammary gland development”, and “mammary gland epithelial cell differentiation”.**Conclusion:** Findings from this analysis show that transient HOXB13 overexpression reprograms and expands the ER binding pattern in breast cancer cells. Genomic regions newly bound by ER are enriched for genes involved in mammary gland and epithelial differentiation suggesting that HOXB13 activates ER transcriptional programs that link oncogenic and developmental pathways. These results will be compared to ongoing experiments using an inducible HOXB13 expression system to assess the effects of HOXB13 expression on ER binding and function in response to estradiol and tamoxifen.

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Patient reported outcomes (PROs) with poly(ADP-ribose) polymerase inhibitors (PARPi) versus chemotherapy (CTX) in patients (pts) with germline *BRCA1/2* mutated (*gBRCA1/2*mut) HER2- advanced breast cancer (ABC): Results from a multi-country real-world (RW) study

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**Background:** In ABC, where treatment is palliative, an important goal is the maintenance or improvement of quality of life (QoL). In the past 3 years, PARPi have demonstrated improved progression-free survival and favorable PROs compared with CTX in randomized clinical trials (RCTs) in pts with ABC and a *gBRCA1/2*mut. These agents are now available in multiple countries for the treatment of *gBRCA1/2*mut HER2- locally advanced and/or metastatic breast cancer. Limited information is available on the PRO benefit of these agents in the RW setting. We assessed RW cancer-related and breast-cancer specific PROs among adult pts with *gBRCA1/2*mut HER2- ABC in Germany, France, Italy, Spain (EU4), US, and Israel.
**Methods:** Oncologists were recruited to abstract data from medical records (2019/2020) for pts with *gBRCA1/2mut* HER2- ABC. A subset of pts completed the European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and the breast cancer module QLQ-BR23. PROs were compared between CTX and PARPi monotherapy utilizing inverse probability weighted regression adjustment (IPWRA) controlling for age at therapy initiation, Charlson Comorbidity Index at time of data collection, baseline symptoms, hormone receptor (HR) status, ECOG score at therapy initiation, stage of therapy initiation (locally advanced breast cancer or metastatic breast cancer) and number of lines of ABC treatment.
**Results:** Overall 96 female pts participated; mean age was 51 years. Tumor characteristics were: 34.4% HR+/HER2-, 65.6% triple negative breast cancer. CTX (n=58) was received among 60.4% of pts [n=29 (50.0%) platinum based, n=29 (50.0%) non-platinum based], and PARPi monotherapy (n=38) was received among 39.6% of pts. Compared to pts receiving CTX, pts receiving PARPi reported significantly better scores in physical and social functioning **(Table 1)**. Pts receiving PARPi reported significantly better symptoms scores vs. CTX in constipation, breast symptoms, arm symptoms and systemic therapy side effects **(Table 1)**. Pts receiving PARPi reported significantly worse scores vs. CTX in nausea/vomiting **(Table 1)**. Global health status (GHS)/QoL scores were numerically better among pts receiving PARPi vs. CTX **(Table 1).**
**Conclusions:** PARPi have demonstrated superior efficacy and favorable PROs vs. CTX in RCTs in pts with *gBRCA1/2*mut HER2- ABC. In this RW study, the PRO benefits reported with PARPi were consistent with what has been observed in RCTs, further supporting the value of PARPi. Additional studies to validate these findings are planned.
**Funding:** Pfizer

Table 1. IPWRA Analysis for the EORTC QLQ-C30 and QLQ BR-23a scores

| | CTX (n=58) | PARPi Monotherapy (n=38) | P value |
|---|---|---|---|
| EORTC QLQ-C30 GHS/QoL and functional scales | | | |
| GHS/QoL | 56.56 | 65.24 | 0.10 |
| Physical | 71.90 | 79.98 | 0.045 |
| Role | 64.55 | 68.06 | 0.55 |
| Emotional | 61.24 | 64.58 | 0.61 |
| Cognitive | 78.20 | 78.84 | 0.89 |
| Social | 63.57 | 81.95 | 0.01 |
| EORTC QLQ-BR23 Functional scales | | | |
| Sexual | 12.37 | 17.23 | 0.31 |
| Future perspective | 46.68 | 44.53 | 0.81 |
| Body Image | 53.22 | 65.36 | 0.13 |
| EORTC QLQ-C30 Symptoms scales | | | |
| Fatigue | 40.67 | 39.62 | 0.87 |
| Nausea/vomiting | 18.28 | 34.51 | 0.005 |
| Pain | 34.26 | 38.88 | 0.42 |
| Dyspnea | 22.15 | 23.29 | 0.82 |
| Insomnia | 30.78 | 32.40 | 0.82 |
| Appetite loss | 24.85 | 31.99 | 0.29 |
| Constipation | 18.75 | 1.85 | <.001 |
| Diarrhea | 16.26 | 14.57 | 0.81 |
| Financial difficulties | 16.26 | 16.83 | 0.92 |
| EORTC QLQ-BR23 Symptoms Scales | | | |
| Breast symptoms | 13.28 | 0.35 | 0.008 |
| Arm symptoms | 11.39 | 2.60 | 0.001 |
| Systemic therapy side effects | 29.39 | 13.48 | <.001 |

[a]EORTC QLQ-BR23 categories sexual enjoyment and upset by hair loss were excluded from the analysis due to low sample size

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# Mario-3 phase II study safety run-in evaluating a novel triplet combination of eganelisib (formerly IPI-549), atezolizumab (atezo), and nab-paclitaxel (nab-pac) as first-line (1L) therapy for locally advanced or metastatic triple-negative breast cancer (TNBC)

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**Purpose:** The IMpassion130 randomized trial in advanced TNBC has demonstrated improved efficacy with the addition of atezo to 1L nab-pac in patients with PD-L1+ tumors. Eganelisib is a first-in-class, novel oral agent targeting tumor-associated myeloid cells through selective inhibition of PI3K-gamma, with the goal of improving the immune response to the approved doublet combination of atezo and nab-pac. We report first results from a completed TNBC safety run-in cohort of a multicenter phase II study.
**Methods:** Eligible patients had measurable unresectable locally advanced or metastatic TNBC, ECOG performance status 0/1, and no prior systemic therapy for advanced disease. A safety run-in was completed to assess the safety of the triplet of oral eganelisib 30 mg daily in combination with nab-pac 100 mg/m$^2$ given on days 1, 8, & 15, and IV atezo 840 mg given on days 1 & 15. After establishing tolerability in the safety run-in (n=6), the expansion phase of the phase II study was initiated to enroll a total of approximately 60 patients (30 PD-L1+ and 30 PD-L1-). Cycles are repeated every 28 days until loss of clinical benefit, unacceptable toxicity, or consent withdrawal. The primary efficacy endpoint is confirmed Complete Response (CR) rate per RECIST v1.1. Secondary endpoints include the overall response rate (ORR) and safety assessment. Tumors are assessed every 8 weeks by CT/MRI scan.
**Results:** We report preliminary efficacy data (as of 6/27/2020) and safety data (as of 6/09/2020) for the completed safety run-in cohort with 6 patients evaluable for safety and 4 evaluable for response defined as having had at least one post-baseline tumor assessment. 1 CR (1/4) and 3 PRs (3/4) were observed with an ORR of 100% (4/4). Responses were seen irrespective of PD-L1 status. The most common all-grade adverse events were decreased white cell count (66.7%), fatigue (50%), diarrhea (33.3%), hyperglycaemia (33.3%), transaminase elevation (16.7%), pyrexia (16.7%), and rash (16.7%). Most common grade ≥3 adverse events occurred in 3 patients (50%) including decreased lymphocytes or neutropenia (33.3%), transaminase elevation (16.7%), fatigue (16.7%), rash (16.7%), and febrile neutropenia (16.7%). Treatment was generally tolerable. Eganelisib 30 mg daily was chosen as the dose for combination with nab-pac and atezo for the expansion phase of the study.
**Conclusions:** The novel triplet regimen of eganelisib, atezo, and nab-pac shows promising antitumor activity (4 responses/4 evaluable patients), irrespective of biomarker status, and has manageable toxicity. The expansion phase of the phase II study is currently enrolling. Updated efficacy, safety and biomarker data will be presented for the safety run-in cohort as well as initial data from the expansion phase of the phase II study.

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# Incidental malignant findings on pre-admission chest computed tomography scan for coronavirus disease screening in patients with breast cancer or other cancers

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**Background:** Amidst the coronavirus disease (COVID-19) pandemic, pre-admission chest computed tomography (CT) screening has been performed for all patients (pts) scheduled for cancer surgery to prevent the nosocomial spread of COVID-19 at our cancer center in Tokyo. This strategy was employed owing to a shortage of polymerase chain reaction assay opportunities and the relatively abundant availability of CT scanning in Japan. Notably, a screening CT may reveal incidental findings that are different from the original purpose of the examination. Thus far, there are no reports of incidental malignant findings on CT scans for COVID-19 screening. **Methods:** This single-institutional retrospective study included pts scheduled for surgery and who underwent pre-admission CT scans for COVID-19 screening between April 26, 2020, and June 12, 2020. Clinical and radiological data of pts were extracted from medical records. Clinical data included age, sex, medical history, and treatment. All CT scans for COVID-19 screening were examined one or two days before surgery and interpreted by two trained radiologists. This study aimed to reveal the ratio of incidental findings related to malignancy. **Results:** Between April 26, 2020, and June 12, 2020, 863 pts underwent pre-admission CT scans for COVID-19 screening. Median patient age was 58 years (range, 11-91 years), and 511 (59%) of the pts were female. The most common disease was breast cancer (n = 165, 19%), followed by colorectal cancer (n = 108, 13%), gynecological cancer (n = 107, 12%), and other cancers (n = 483, 56%). CT scan revealed radiological findings of pneumonia in 23 pts (2.7%); therefore, surgery was postponed for these pts. Incidental findings were detected in 28 pts (3.2%), including one pneumothorax and 27 findings related to malignancies. The present study included 165 pts (19%) with breast cancer and who were scheduled for curative surgery. Among them, incidental findings related to malignancies were detected in nine pts (5.5%), including small ground-glass pulmonary nodules (GGN) (n=5), pancreatic duct dilatation (n=1), suspected vertebral metastasis (n=2) and suspected liver tumor (n=1). All pts did not undergo breast surgery but underwent additional examinations after surgery. Five pts (2.5%) with GGN needed follow-up. One patient's pancreatic duct dilatation was diagnosed as benign using ultrasound. One patient with suspected vertebral metastasis was diagnosed with degenerative changes. The other patient was diagnosed with multiple bone metastases by bone scintigraphy, and further treatment was planned. Pre-admission screening CT scan for pts with other cancers was performed in 698 pts (81%). Among them, findings related to malignancies were detected in 18 pts (2.6%), including breast nodules (n=3), lung nodules (n=5), liver metastasis (n=1), progression of metastasis (n=3), mediastinum tumor (n=1), and GGN (n=5). Two of the three pts with breast nodules were diagnosed with invasive breast cancer and planned for breast surgery after the current cancer treatment. Two pts developed new lung metastasis, and the surgical strategy was changed. The progression of known liver or lung metastasis was detected in three pts, which led to the addition of systemic chemotherapy without modification of surgical treatment. One patient had a mediastinum tumor, and an MRI evaluation after surgery revealed an athymic cyst. Five pts were determined to have GGN, and follow-up was required. **Conclusion:** The proportion of pts for whom pre-admission CT for COVID-19 revealed incidental findings was 3.2%. Incidental breast cancer was found in 0.4% of female pts. GGNs needed follow-up examination in 2.5% of operable breast cancer pts. Physicians and surgeons should be aware of incidental malignant findings in the COVID-19 screening CT scan.

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# Molecular subtype and clinical stage influenced axillary lymph node response in breast cancer patients with breast pathological complete remission after neoadjuvant therapy

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***Background:*** It is unknown whether molecular subtype is associated with axillary lymph node (ALN) status (ypN) after neoadjuvant therapy (NAT) in breast cancer patients who achieved breast pathological complete remission (pCR), especially for patients with different clinical stage. Our study aimed to investigate the association of clinical stage and molecular subtype with ALN status (ypN) after NAT in breast cancer patients.
***Patients and methods:*** Breast cancer patients receiving ≥ 4 cycles of NAT with complete clinicopathological data were retrospectively included between January 2009 to January 2020. Status of ypN according to breast pCR status was compared in cT1-2N0, cT1-2N1, and local advanced breast cancer (LABC) patients with different molecular subtype. Univariate and multivariate analyses were conducted to identify potential predictive factors for ypN status.
***Results:*** A total of 1999 patients were included. cT1-2N0, cT1-2N1, and LABC disease were found in 457 (22.86%), 884 (44.22%) and 658 (32.92%) patients, whose ypN+ rate was 24.5%, 60.3%, and 66.4%, respectively ($P < 0.001$). Compared with cT1-2N0 patients, ypN+ rate was significantly higher in cT1-2N1 (OR = 5.48, 95%CI = 3.77-7.97, $P < 0.001$) and LABC (OR = 10.90, 95%CI = 7.12-16.70, $P < 0.001$). Moreover, ypN+ rate varied across different molecular subtypes, which was 60.0% in Luminal A subtype, 61.4% in Luminal B (HER2-) subtype, 47.6% in Luminal B (HER2+) subtype, 42.2% in HER2-amplified subtype and 52.5% in TNBC ($P < 0.001$). Patients achieving breast pCR also had a significantly lower ypN+ rate than those without breast pCR (23.9% *vs* 62.5%, univariate $P < 0.001$; OR =0.14, 95%CI = 0.09-0.21, $P < 0.001$). Furthermore, in breast pCR patients, multivariate analyses showed that clinical stage and molecular subtype were substantially related to ypN+ rate: the ypN+ rate was significantly higher in cT1-2N1 (OR = 5.64, 95%CI = 2.31-13.76, $P < 0.001$) and LABC (OR = 9.80, 95%CI = 3.88-24.77, $P < 0.001$), compared with cT1-2N0 patients; while it was significantly lower in Luminal B HER2+ (OR =0.20, 95%CI = 0.05-0.82, $P = 0.025$) and HER2-amplified (OR = 0.19, 95%CI = 0.05-0.83, $P = 0.026$) subtype, compared with Luminal A subtype. In the cT1-2N0 subgroup, all patients with breast pCR with Luminal B HER2+ or HER2-amplified subtype achieved ALN pCR.
***Conclusion:*** Clinical stage and molecular subtype were significantly associated with ypN status in breast pCR patients after NAT. Patients with cT1-2N0 and HER2-positive patients who achieved breast pCR had low ypN+ rate, which possibly guides further clinical ALN management after NAT.
**Key words:** Breast pathological complete remission; Neoadjuvant therapy; Molecular subtype; Clinical stage; Nodal residual burden.

**Table. Pathological node status stratified by clinical stage between patients with breast pCR and non-pCR.**

| | **Response in breast** | | | |
|---|---|---|---|---|
| | **pCR** | | **non-pCR** | |
| | **ypN0 (N, %)** | **ypN+ (N, %)** | **ypN0 (N, %)** | **ypN+ (N, %)** |
| Whole population | 331(76.1) | 104(23.9) | 586(37.5) | 978(62.5) |
| cT1-2N0 | 88(93.6) | 6(6.4) | 257(70.8) | 106(29.2) |
| cT1-2N1 | 159(74.3) | 55(25.7) | 192(28.7) | 478(71.3) |
| LABC | 84(66.1) | 43(33.9) | 137(25.8) | 394(74.2) |
| Luminal A like | 9(69.2) | 4(30.8) | 37(36.3) | 65(63.7) |
| cT1-2N0 | 6(85.7) | 1(14.3) | 19(73.1) | 7(26.9) |
| cT1-2N1 | 3(50.0) | 3(50.0) | 12(27.9) | 31(72.1) |
| LABC | 0(0.0) | 0(0.0) | 6(18.2) | 27(81.8) |
| Luminal B like (HER2-) | 112(70.4) | 47(29.6) | 220(31.4) | 480(68.6) |
| cT1-2N0 | 33(89.2) | 4(10.8) | 85(59.0) | 59(41.0) |
| cT1-2N1 | 59(71.1) | 24(28.9) | 75(23.8) | 240(76.2) |
| LABC | 20(51.3) | 19(48.7) | 60(24.9) | 181(75.1) |
| Luminal B like (HER2+) | 89(83.2) | 18(16.8) | 140(42.4) | 190(57.6) |
| cT1-2N0 | 19(100.0) | 0(0.0) | 70(83.3) | 14(16.7) |
| cT1-2N1 | 46(83.6) | 9(16.4) | 43(30.5) | 98(69.5) |
| LABC | 24(72.7) | 9(27.3) | 27(25.7) | 78(74.3) |
| HER2 amplified | 66(82.5) | 14(17.5) | 97(48.0) | 105(52.0) |
| cT1-2N0 | 14(100.0) | 0(0.0) | 42(82.4) | 9(17.6) |
| cT1-2N1 | 25(78.1) | 7(21.9) | 32(42.1) | 44(57.9) |
| LABC | 27(79.4) | 7(20.6) | 23(30.7) | 52(69.3) |
| TNBC | 55(72.4) | 21(27.6) | 92(40.0) | 138(60.0) |
| cT1-2N0 | 16(94.1) | 1(5.9) | 41(70.7) | 17(29.3) |
| cT1-2N1 | 26(68.4) | 12(31.6) | 30(31.6) | 65(68.4) |
| LABC | 13(61.9) | 8(38.1) | 21(27.3) | 56(72.7) |

Abbreviations: LABC, locally advanced breast cancer; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; pCR, breast pathological complete response.

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# Impact of COVID-19 on breast cancer care at a Bay Area academic center

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Background: Oncology practice has been transformed in response to the COVID-19 pandemic. Oncologists are postponing chemotherapies, delaying curative surgeries, and switching intravenous to oral therapies. These decisions are based on competing risks, and treatments are proceeding if the malignancy is more lethal than the virus. There is currently limited information quantifying the impact of COVID-inspired policies on breast cancer care. Methods: This is a retrospective analysis of all patients with a new diagnosis of breast cancer between October 1, 2019 and May 27, 2020, and who had a stage documented in the Stanford electronic medical record (EMR). Cases who had a recurrence of previously diagnosed breast cancer or who had their breast cancer care primarily outside of Stanford and did not have their outside health records accessible were excluded. Changes in treatment plan due to COVID-19 were defined as including “COVID” or “coronavirus” in the clinical medical decision making documented in clinical notes supporting any treatment decision affecting timing or type of systemic therapy, surgery, or radiation. This includes treatment affected by new policies because of COVID-19 or concerns expressed by the provider or patient due to COVID-19. If treatment was changed and no rationale was given, this was categorized as “unknown.” If patients experienced a change in other breast cancer treatment-related services (for example, physical therapy for lymphedema) due to COVID, this was categorized as “other” and not included in the analysis. Treatment changes were noted if documented prior to June 26, 2020.Results: 291 cases were analyzed. Overall, the majority had early stage disease (Stage 0 or 1; n = 190, 65.3%) (Table 1). 46 (15.8%) patients had a change in therapy (systemic therapy, surgery, or radiation). The most common treatment change was a delay of surgery (n = 21, 45.7%), which were mostly early stage cancers (Tables 1 and 2). There was no significant difference in the ages of patients who had a COVID-related treatment change (all patients: mean 56.9 years old at diagnosis; patients with treatment change: mean 57.0 years old). Another 20 (6.9%) patients had a change in other breast cancer treatment-related services due to COVID-19 related causes.Conclusions: During the COVID-19 outbreak, a significant minority of patients with recently diagnosed breast cancer had their treatment plan changed in response to COVID-19. In particular, patients with early stage breast cancers who were candidates for neoadjuvant endocrine therapy had surgeries delayed. Further follow-up will be needed to fully understand the impact COVID-19 has had on cancer care, as more recently diagnosed patients have not yet completed treatment. However, this early analysis can begin to quantify the impact of COVID-19 on cancer care.

Table 1 – Stage at diagnosis of breast cancer patients

| | All patients, n=291(%) | Patients with a COVID-related treatment change, n=46 (%) | Patients with delay in surgery, n =21 (%) |
|---|---|---|---|
| Stage 0 | 33 (12%) | 11 (25%) | 7 (35%) |
| Stage I | 1 (0.4%) | | |
| Stage IA | 124 (45%) | 16 (36%) | 6 (30%) |
| Stage IB | 32 (12%) | 6 (14%) | 3 (15%) |
| Stage II | 2 (0.7%) | 5 (11%) | |
| Stage IIA | 25 (9.1%) | 1 (2.3%) | 2 (10%) |
| Stage IIB | 14 (5.1%) | | |
| Stage IIIA | 12 (4.4%) | 2 (4.5%) | 1 (5%) |
| Stage IIIB | 12 (4.4%) | 2 (4.5%) | 1 (5%) |
| Stage IIIC | 4 (1.5%) | | |
| Stage IV | 16 (5.8%) | 1 (2.3%) | |
| Unknown | 14 (4.8%) | 2 (4.5%) | 1 (5%) |

Table 1 – Types of COVID-related treatment changes (more than one possible per patient)

| | N = 46 (%) |
|---|---|
| Delay in chemotherapy administration | 5 (10.9%) |
| Change in chemotherapy regimen to a different regimen | 4 (8.7%) |
| Decided not to give chemotherapy | 3 (6.5%) |
| Neoadjuvant endocrine therapy given | 17 (37.0%) |
| Delay in endocrine therapy | 1 (2.2%) |
| Delay in surgery | 21 (45.7%) |
| Change in planned surgery type | 7 (15.2%) |
| Change sequence of chemotherapy and surgery | 2 (4.3%) |
| Delay in radiation | 8 (17.4%) |
| Change in planned radiation course | 1 (2.2%) |

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Effects of DNA-damaging and demethylating agents on alternate mRNA splicing in *BRCA2*

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**Introduction** DNA sequence variants of unknown clinical significance (VUSs) are routinely identified during genetic testing of *BRCA2* and other tumor suppressor genes associated with hereditary breast/ovarian cancer syndrome (HBOC). To determine which VUSs could be classified as pathogenic mutations, sequence variants near intron-exon boundaries are tested for effects on normal splicing patterns. However, these investigations can be complicated by potential genome-wide disruptions of normal splicing patterns caused by therapeutic agents. To test the potential contribution of systemic therapies to alternative splicing events in *BRCA2*, we have tested the effects of two DNA damaging agents and two demethylating agents on the relative levels of the naturally occurring alternative splicing variant *BRCA2*Δ3. While the protein product of this alternative splicing event has not been characterized, the *BRCA2*Δ3 mRNA maintains the full-length translational reading frame, and lacks sequence encoding EMSY and PALB binding domains as well as transactivation function. Previous work has shown that, while some VUSs associated with increased levels of *BRCA2*Δ3 in lymphoblastoid cell lines are not pathogenic, germline deletions that eliminate *BRCA2* exon 3 are associated with increased breast cancer risk. Thus, alternative splicing events that alter relative levels of the *BRCA2*Δ3 mRNA variant may serve both as an indicator of the effects of some systemic therapies on genome-wide splicing defects and also *BRCA2* gene function *per se.* **Methods 1)** To determine whether therapeutic DNA damaging agents can alter the levels of Δ3 alternate splicing isoforms, the breast cancer cell line MCF7 was treated with either doxorubicin or bleomycin, and isoform-specific RT-PCR was used to compare relative levels of splice junctions containing or skipping exon 3. **2)** To determine whether DNA demethylating agents known to promote expression of some tumor suppressors can alter the levels of Δ3, MCF7 and/or the non-cancer breast cell line MCF 10A was treated with 5-aza 2'-deoxycytidine (5-AzadC) or 5-Azacytidine (5-AzaC), and again isoform-specific RT-PCR was used to compare relative levels of splice junctions containing or skipping exon 3. **3)** To determine whether the *BRCA2* Δ3 isoform was equally accessible to translational machinery in all cell types, RNA was prepared from separated nuclear and cytoplasmic fractions of MCF7 and MCF 10A and isoform-specific RT-PCR was used to estimate levels of cytoplasmic Δ3 available to translational machinery. **Results and conclusions 1)** While bleomycin decreases the relative levels of Δ3 compared with untreated controls, doxorubicin increases relative levels of Δ3 in MCF7. This suggests that some DNA damaging agents may cause changes in splicing patterns that may affect therapeutic effectiveness. **2)** While both 5-AzaC and 5-AzadC reduce relative levels of Δ3 in MCF7, 5-azadC does not reduce relative levels of Δ3 in MCF 10A, suggesting there may be a cell type-specific splicing response to genomic demethylation therapies. **3)** MCF 10A limits the level of Δ3 that can accumulate in the cytoplasm, but this regulatory mechanism is absent from MCF7, indicating there is a cell type-specific mechanism that limits the amount of alternately spliced mRNA variants that are available to translational machinery.

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# Overall survival outcomes of combination anastrozole and fulvestrant in molecular subsets of hormone receptor-positive breast cancer

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**Background:** The combination of anastrozole and fulvestrant (A+F) is associated with improvement in overall survival (OS) as compared to anastrozole (A) in patients (pts) with hormone receptor-positive (HR+) breast cancer (BC), specifically in pts with endocrine naïve disease or in pts with long disease-free interval (Mehta et al. NEJM 2019). We performed an IRB-approved retrospective assessment of the time-to-treatment failure (TTF) and overall survival (OS) outcomes in pts treated at our institution with A+F, and assessed the impact of A+F in various molecularly defined subsets of pts. **Methods:** We reviewed charts of 118 pts with advanced HR+ BC who received A+F. Pts with brain metastases were not excluded. Performance status (PS) ranged from 0-3. We compared TTF and OS outcomes in pts with and without molecular aberrations including HER2 overexpression/amplification, or mutations in PIK3CA, ESR1 or BRCA1/2. HER2 status was tested through tumor. PIK3CA and ESR1 were tested on tumor or ctDNA by next generation sequencing. Germline/somatic BRCA1/2 status was assessed either through ctDNA or germline testing. Kaplan-Meir survival curves were constructed. Primary statistical analysis was log-rank test, followed by Cox regression to estimate the hazard ratio and 95% confidence intervals. All p values are 2-sided. **Results:** Overall 68 patients had endocrine-sensitive (ES) disease and 50 patients had acquired endocrine-resistant (ER) disease. Median TTF was 26 months in the ES group vs. 10 months in the ER group (HR: 0.47;95% Cl: 0.30 - 0.75, p= 0.001). Median OS was 57 months in the ES group vs. 38 months in the ER group (HR: 0.51; 95% Cl: 0.30 - 0.86, p= 0.01). Among the 31 pts tested for PIK3CA mutation, 21 pts were negative (control) and 10 pts were positive (PIK3CA mutant). Median TTF was 23 months for control vs.14 months for PIK3CA mutant (HR: 0.89; 95% CI: 0.40 -1.95, p = 0.76). Median OS was not reached for control vs. 44 months for PIK3CA mutant (HR: 0.50; 95% Cl: 0.16 - 1.56, p = 0.23). Among the 35 pts tested for ESR1 mutation, 27 pts were negative (control) and 8 patients were positive (ESR1 mutant). Median TTF was 26 months for control vs. 10 months for ESR1 mutant (HR: 0.59; 95% CI: 0.23 - 1.52, p = 0.20). Median OS was 66 months for control vs. 65 months for ESR1 mutant (HR: 1.63; 95% Cl: 0.44 - 5.95, p = 0.46). In the 17 pts tested for BRCA mutation (germline or somatic), 6 of them were positive (BRCA mutant) and 11 of them were negative (control). Median TTF was 36 months for control vs. 10 months for BRCA mutant (HR: 0.40; 95% CI: 0.12 - 1.40, p = 0.09). Median OS was 35 months for control but has not been reached in the BRCA mutant group (HR: 1.16; 95% Cl: 0.23 - 5.88, p = 0.93). Of 118 patients, 92 pts were HER2 negative (control) and 26 patients were HER2 positive. Median TTF was 23 months for control vs. 14 months for HER2+ group (HR: 0.80; 95% CI: 0.46 - 1.39, p = 0.42). Median OS was 52 months for control vs. 40 months for HER2+ group (HR: 0.87; 95% Cl: 0.47 - 1.64, p = 0.67). **Conclusions:** The time-to-treatment failure and overall survival in the endocrine-sensitive disease are 2-fold higher compared to the endocrine-resistant disease. Patients with PIK3CA, ESR1 or BRCA1/2 mutation or with HER2 overexpression/amplification historically have poor survival outcomes, but in hypothesis-generating analysis, we showed statistically similar overall survival outcomes in these patients treated with anastrozole plus fulvestrant, compared to controls without these poor prognostic features. We suggest that anastrozole plus fulvestrant should be the preferred partner with molecularly targeted agents.

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# AMEERA-4, a phase 2 window study of SAR439859 vs letrozole in post-menopausal women with newly diagnosed estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer

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**Background** Endocrine therapy targeting estrogen receptor (ER) signaling is the standard of care for women with ER+ breast cancer. Selective ER degraders (SERDs) block ER signaling through dual competitive antagonism and receptor degradation. SAR439859, a potent, oral SERD, is in clinical development for ER+/HER- breast cancer. AMEERA-4 (NCT04191382; ACT16106) is a 14-day preoperative, non-therapeutic 'window of opportunity' trial to assess the direct effects of SAR439859 on tumor cell proliferation by evaluating the pharmacodynamic activity of SAR439859 in ER+/HER2- breast cancer. **Methods** This international, open-label, Phase 2 randomized study evaluates SAR439859 at two dose levels vs the aromatase inhibitor letrozole by assigning 126 preoperative patients 1:1:1 to receive SAR439859 400 mg/day, SAR439859 200 mg/day or letrozole 2.5 mg/day. SAR439859 dosing is based on an ongoing AMEERA-1 Phase 1/2 study (NCT03284957; TED14856) in metastatic breast cancer. Postmenopausal women with ER+/HER2- breast cancer indicated for immediate surgery (Stage I, Stage II or operable Stage III), Eastern Cooperative Oncology Group performance status 0-1, and Ki67 levels of ≥ 15% are eligible. Exclusion criteria include disorders potentially affecting absorption of SAR439859 or letrozole, and any prior therapy for breast cancer. Patients receive study treatment for 14 days, with the last dose given on the day before surgery. Paired tumor biopsies for assessment of biomarkers are performed at baseline and during surgery. The primary study endpoint is change in Ki67, a predictor of treatment benefit and long-term survival outcomes, after 14 days of treatment compared with baseline. Secondary endpoints include proportion of patients with ≥ 50% decrease in Ki67, ER expression to assess degradation, and safety. Pharmacokinetics of SAR439859, additional tumor markers, genomic mutation profile, Preoperative Endocrine Prognostic Index and pathological complete response will also be assessed. The study is currently recruiting. Funding: Sanofi. © 2020 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2020 ASCO Annual Meeting. All rights reserved.

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Physical activity platform to improve bone health in cancer survivors

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Background:Cancer treatment-induced bone loss in female breast cancer survivors affects not onlyquality of life, but also imposes a significant financial burden on national health care.Aerobic physical activity and resistance exercises can prevent bone health decline, andcan ameliorate side effects including fatigue, anxiety, depression, and muscle loss.Unfortunately, fewer than 25% of breast cancer survivors engage in and adhere toappropriate exercise routines, owing to poor awareness of the benefits of exercise, lackof motivation, and lack of access to tailored exercise programs. Web- and mobile app-based programs that encourage physical activity and exercises can address this gapand can be scaled for broader dissemination.Thrivors+Bone Health (Thrivors+BH™), is a cloud-based digital health product offeringclinically validated bone health exercises that can be customized to a survivor's painand energy levels. The platform provides interactive feedback and supportive modulesfor social connectivity, mindfulness training, nutritional advice, survivorship resourcesand bone health-relevant educational material. The platform's back-end measuresexercise sessions completed, utilization of supportive modules and user-reportedhealth outcomes.Methods:We conducted a single-blind randomized controlled trial (NCT03651037) with Stage 0 -Stage III exercise-naïve breast cancer survivors, to evaluate adherence to a 20-weekprogram of strength training and impact exercises, delivered through Thrivors+BH™.Control arm participants accessed Thrivors Basic, a platform version lacking pain andenergy customization, interactive feedback or bone health resources. All participantswere required to engage in at least two sessions per week, comprising 14-16 differentexercises progressing from foundational to resistance and impact exercises over 20weeks. The primary endpoint, exercise adherence, was defined as the mean number ofcompleted exercise sessions per cohort. Secondary endpoints were user engagement,assessed by the Patient Activation Measure (PAM), Short Form 36v (SF-36v) and user-satisfaction surveys.Results:Demographics (n = 134) were similar between cohorts. The adherence populationanalysis (participants logging in and recording exercises for >1 week) showed that60.0% of Thrivors+BH™ participants (n = 42) completed the 20-week program,compared to 47.8% of Thrivors Basic participants (n = 48). Also, a larger percentageof Thrivors+BH™ arm participants completed between 41-60 exercise sessions,compared to Thrivors Basic participants (17.5% vs. 8.7%) Participants in both armsreported discomfort and low energy as an obstacle to exercising and emphasized theneed for more frequent updates on progress and reminders to exercise.Conclusions:The feasibility study demonstrates breast cancer survivors' willingness to utilize adigital platform to help engage in prescribed exercise routines. Feedback fromparticipants suggest that incorporation of more personalized and interactive featuresmay encourage a higher frequency of engagement in bone-health specific exerciseand/or physical activity. A follow-up study will examine the impact of the exerciseprogram on bone health and the role of coaching to impact sustainable behaviorchange.

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# Hormone- and HER2 receptor change in non-pCR breast cancer specimens after neoadjuvant treatment

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Introduction: This study aimed at identification of breast cancer patients with a switched hormone- or HER2 receptor status after neoadjuvant chemotherapy. Therefore, patients without pathological complete response (pCR) were evaluated. The hormone and HER2 receptor status determined prior to neoadjuvant chemotherapy was compared with the corresponding receptor status determined in the surgical specimen after neoadjuvant chemotherapy.
Methods: Clinicopathological data of 249 patients, who received neoadjuvant treatment between 2016 and 2019 at the LMU breast center, Munich were reviewed. Among those, 129 patients (52%) with non-pCR were identified. Of those, 11 patients had a residual positive lymph node only. pCR was defined as absence of invasive tumor in breast and lymph node (ypT0/is; ypN0). According to German clinical guidelines, specimens were labeled hormone receptor positive, if ≥1% of tumor nuclei were reported estrogen receptor positive or ≥10% of tumor nuclei were reported progesterone receptor positive. Tumors were labeled HER2-positive if immunohistochemistry showed strong complete circular membrane staining of >10% of invasive cells or if in-situ-hybridization showed HER2 positivity. Surgical specimens of patients with non-pCR were pathologically evaluated in order to 1) detect a receptor status switch compared to the analysis prior to neoadjuvant chemotherapy and 2) to see whether additional post neoadjuvant treatment options become available.
Results: The following results apply exclusively to non-pCR cases. Median age at diagnosis was 51 years, 27 patients were younger than 40. One male patient is included.A total of 36 cases (28%) switched either hormone- or HER2-status, including two cases of a simultaneous switch. In 19 cases, the hormone receptor status switched. 3 patients switched from hormone receptor negative to positive, while 16 switched from hormone receptor positive to negative. A total of 17 cases showed a switch in HER2 receptor status. 6 patients switched from HER2-negative to HER2-positive, while 11 switched from HER2-positive to HER2-negative. Due to technical limitations, HER2 status was not evaluable in two cases, and hormone receptor status in one case. See table below.
Conclusion: Our results illustrate, that a biomarker status switch after neoadjuvant treatment occurs in almost a third (28%) of cases. Reassessment of hormone- and HER2-receptor status subsequent to neoadjuvant treatment is still under discussion, with regard to post-neoadjuvant treatment. Nevertheless, it may have potential benefits for patients regarding individualization of treatment and potentially even patient outcome. At present, only gain of receptors should impact treatment concepts; in case of loss of receptors, treatment should not be changed as results in the residual tumor tissue may not reflect receptor status on disseminated tumor cells.

Biomarker status in patients with non-pCR

| Biomarrker status in patients with non-pCR | Status at initial diagnosis | Status in surgical non-pCR specimen | Cases with **switch in biomarker status after NAC** |
|---|---|---|---|
| **HR positive** | 99 (77%) | 85 (66%) | 3 |
| **HR negative** | 30 (23%) | 43 (34%) | 16 |
| HR total | 129 | 128 | **19 (15%)** |
| **HER2 positive** | 35 (27%) | 28 (22%) | 6 |
| **HER2 negative** | 94 (73%) | 99 (78%) | 11 |
| HER2 total | 129 | 127 | **17 (13%)** |
| **Cases with switch in biomarker status** | | | **36 (28%)** |

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Obg-like ATPase 1 enhances chemoresistance of breast cancer *via* activation of TGF-β/Smad axis cascades

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**Background:** Understanding the molecular mechanism of drug resistance helps identify aneffective target for therapy of breast cancer. We investigated in this study the regulatory role ofObg-like ATPase 1 playing in multiple drug resistance of breast cancer.**Methods:** Paclitaxel resistant cell line (MCF-7-PTR) was developed by a continuous increasingpaclitaxel concentration. MTT assay was used to validate either acquired resistant or OLA1modified cell lines. qRT-PCR, immunoblot, apoptosis and cell cycle assays were performed toassess expression of genes and proteins in cell lines. A series of *in vitro* assays was performed inthe cells with RNAi-mediated knockdown to elucidate the regulatory role of OLA1 in breast cancer.**Findings:** We demonstrated that OLA1 was highly correlated with either acquired or intrinsicresistance of breast cancer. Further study showed that escalated expression of OLA1 promotedEMT process in tumor cells through TGF-β/Smad signaling cascades, resulting in the enhancedexpression of anti-apoptosis-related proteins (cleaved caspase3, Bax, Bcl-2) and the strengthendepolymerization of microtubules in tumor cells. Our findings revealed that OLA1 enhanced theanti-apoptotic ability and elucidated a regulatory role of OLA1 in promoting drug resistance ofbreast cancer.**Interpretation:** OLA1 is highly correlated with drug resistance of breast cancer. Chemo-sensitivity of the disease can be thus enhanced significantly by knocked down OLA1,which ledto inactivation of the TGF-β/Smad signaling cascades, polymerized microtubules, and promotedcell apoptosis. Our data suggest that OLA1 may be developed as a potential target to improvechemotherapy of patients with breast cancer.**Keywords:** breast cancer; Obg-like ATPase 1; multidrug resistance; γ-tubulin; paclitaxel

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# Tim3 expression on tumor infiltrating lymphocytes is associated with poor response to neoadjuvan chemotherapy in patients with locally advanced triple negative breast cancer

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**Background:** Expression of immune checkpoint receptors (ICR) on tumor infiltrating lymphocytes (TILSs) is associated with better response to immunotherapies via immune checkpoint inhibitors. Therefore, we investigated various ICR expressions on TILs in patients with locally advanced triple negative breast cancer (TNBC) after neoadjuvant chemotherapy (NAC). **Methods:** Expressions of ICRs were examined immunohistochemically by staining surgical specimen (n=61) using specific monoclonal antibodies for PDL-1, PD-1, TIM-3, LAG-3, CTLA-4. Positivity was defined staining ≥1% on TILs. **Results**: Median age was 49 (24-76) years. The majority patients were clinically T3-4 (n=31, 50.8%), and clinically N1-3 (n=58, 95.1%) before NAC. Of those, 82% were found to have CTLA-4 positivity, whereas TILs associated positivites for PD1, PDL-1, LAG3 and TIM-3 were 62.3%, 50.9%, 26.2%, 68.9%. High expression of CTLA-4 was found to be associated with a better chemotherapy response (OR=7.94, 95%CI: 0.9-70.12, p=0.06), whereas TIM-3 positivity was contrarly associated with a worse chemotherapy response (OR=0.253, 95%CI: 0.066-0.974, p=0.047) as measured by MDACC Residual Cancer Burden Index. At a 47-month follow-up, patients with ypN0 disease (DFS; HR=0.31, 95% CI: 0.12-0.83, p=0.02 and DSS; HR=0.21, 95% CI:0.07-0.62, p=0.005) and CTLA-4 high expression on TILs (DFS; HR=0.38, 95% CI=0.17-0.85, p=0.019 and DSS; HR=0.34, 95% CI:0.15-0.78, p=0.01) were found to have improved survival. **Conclusions:** These findings demonstrate that CTLA-4, PD-1, PDL-1 and TIM-3 were highly expressed in TNBC after NAC. Our results more favor an immuncheckpoint inhibitor therapy via CTLA-4 alone or in combination with other immune check point inhibitors against PDL-1 and/or TIM-3 in addition to NAC in advanced TNBC.

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Age of first full term pregnancy and other reproductive factors affect mammographic breast density in postmenopausal women

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The objective of this study is to determine the role of age at first full term pregnancy (FFTP), and mammographic breast density (MBD) in postmenopausal women. For this purpose women, age 50-69y, participating in the Flemish (Belgium) population based breast cancer screening program were invited to participate in the study during their visit at the mammography department in the University Hospital Leuven (UZLeuven) or at the mobile unit of their hometown. A self-administered questionnaire providing detailed information on lifestyle and environmental exposure was completed by the participants. In this analysis 1,034 women were included (mean age of 59.1 years (range: 49.2 to 69.8). The three parameters of MBD were the percentage glandular tissue of the total breast volume (GLAND), the ratio of the glandular tissue volume compared to the whole breast volume or Volumetric Breast Density (VBD) and the BI-RADS density classification (VolparaDataManager®, USA). The first two parameters (GLAND and VBD) were transformed according to the natural logarithm to improve normality. These two parameters were linked with the FFTP via a piecewise linear regression (PLR) model using the NLIN procedure in SAS (version 9.4, SAS Institute, Cary, NC, USA). For the BI-RADS, we used ordinal logistic regression analysis. All models were corrected for *a priori* chosen variables: age at menarche, the ever use of oral contraceptive pill (OC), hormonal use at menopause, age at MBD measurement, and the body mass index at participation. Estimates are provided as a % change (95% confidence intervals [CI]).The average age at FFTP was 26.1 years ($5^{th}$-$95^{th}$ percentile: 20 to 34). The PLR model estimated the breakpoint in our analysis at a FFTP of **25.7 years** (95% CI: 22.3 to 29.1). For the woman with a FFTP younger than 25.7 years, the association between GLAND or VBD and FFTP is statistically not significant. For woman with a FFTP above 25.7 years, each year increase in FFTP was associated with 1.3% increase in GLAND (95% CI: 0.0% to 2.5%) and 1.5% increase in VBD (95% CI: 0.2% to 2.8%). Analysis of the BI-RADS showed similar results, the odds of belonging to a higher BI-RADS classification (e.g. from class 1 to class 2) increased with 5.4% (95% CI: 0.0% to 11.0%) for each year increase in FFTP age after the age of 25.7 years. Among other reproductive factors such as age at menarche, for every year delay there is 3.5% higher GLAND (95% CI: 1.4 % to 5.6%) and 2.5% higher VBD (95% CI: 0.5% to 4.6%) and the ever use of OC resulted in 10.0 % decrease in GLAND (95% CI: -18.8% to -0.2%) and 10.2% decrease in VBD (95%CI:-19.1% to -0.3%).In conclusion, this study is to our knowledge the first one to show that mammographic breast density is significantly increased when pregnancy takes place after 25.7 years of age. Later age at menarche is increasing and use of oral contraceptive is reducing mammographic breast density at postmenopause. (*This study was supported by a Grant of the Breast Cancer Organization Think Pink of Belgium, the Department of Breast Radiology and Mobile Unit of the University Hospital Leuven, the Centre of Environmental Sciences and the Centre of Biostatistics of the Hasselt University, and NIH Grant CA06927 to FCCC, PA, USA*).

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Androgen receptor gene expression and prediction of clinical outcomes of breast cancers exhibiting triple negative or triple positive breast carcinoma cells procured by LCM

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**Background:** Clinical utility of AR, assessed by IHC of protein or by RT-qPCR of gene expression of intact tissue biopsies, has been the focus of many studies without uniform agreement. Due to cellular heterogeneity of most breast cancer biopsies, it is often unclear if measurements of AR and certain clinically relevant biomarkers accurately reflect their content in isolated cells. Using Laser Capture Microdissection (LCM) to procure only populations of breast carcinoma cells from tissue biopsies provides the inimitable opportunity to examine relationships of AR to a variety of parameters. **Methods:** We performed retrospective studies using a unique, de-identified dataset of ER/ESR1, PR/PGR and HER2/ERBB2 results with AR gene expression determined from LCM-procured carcinoma cells of biopsies from 247 breast cancer patients with associated clinical follow-up. ER/PR protein levels, expressed as fmol/mg cytosol protein, were quantified from each carcinoma biopsy with FDA-approved kits using enzyme immunoassay (EIA, Abbott Labs) or radio-ligand binding assay (NEN/DuPont). HER2 protein content of biopsies was quantified by EIA (Oncogene Sciences). Microarray analyses of ~22,000 genes were performed on RNA isolated, purified and amplified from LCM-procured carcinoma cells to assess relative gene expression. Biomarker results and de-identified clinical outcomes were examined using REMARK criteria in a CLIA licensed laboratory. Gene expression, quantified biomarkers, features of primary breast cancers and clinical outcomes were analyzed by univariable and multivariable Cox regressions, Fisher's Exact Test, Kaplan Meier plots and with R software v4.0.0. Clinical relevance of gene expression was externally validated with SurvExpress. (Aguirre-Gamboa et al. PLoS One e742502013). **Results:** Using the median value of relative AR expression in LCM-procured carcinoma cells as a cutoff, elevated AR mRNA, when considered independently, was associated with the following (given as the means): older patients (61.1 vs 55.8 yo), relative expression of either ESR1 (0.2 vs -3.1), PGR (0.4 vs 0.0) or ERBB2 (0.7 vs -0.1) as well as longer PFS (63.7 vs 52.6 mos) and OS (72.4 vs 61.8 mos). Also, carcinoma cells with increased AR mRNA exhibited higher levels of ER protein (242.4 vs 106.5 fmol/mcp) or PR protein (313.8 vs 90.2 fmol/mcp). Whereas, HER2 protein status was not significantly different between AR median bifurcated groups). Neither patient race nor tissue pathology was examined in these analyses. Significantly, Kaplan Meier analyses clearly indicated that addition of AR gene expression to TNBC status (so called QNBC, Quadruple Negative Breast Cancer) did not alter either PFS (5 yr = 0.78 vs 0.79 % probability) nor OS (5 yr = 0.57 vs 0.56 %) of patients. Similarly, Kaplan Meier analyses also indicated that addition of AR gene expression to TPBC status (so called QPBC, Quadruple Positive Breast Cancer) did not alter PFS (5 yr = 0.87 vs 0.87 % probability) nor OS (5 yr = 0.67 vs 0.66 %) of patients. Also, no differences were ascertained for PFS nor for OS of patients at 10 yrs of outcomes between TNBC and QNBC breast cancers clearly indicating that AR gene expression does not contribute to the assessment of a patient's clinical course. **Conclusions:** Collectively, when cancers were compared as TNBC versus TPBC status, expression results of ESR1, PGR and ERBB2 genes using LCM-procured carcinoma cells indicated poorer prognosis and overall survival of breast cancer patients with TNBC. However, inclusion of AR gene expression in either of these bifurcated groups ascertained from LCM-procured cells, did not alter patient PFS nor OS suggesting AR utility in clinical management appears to be unwarranted.
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# Oncological safety and patient journey with magseed™ localised breast conserving surgery

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**Introduction:** Wire localised wide local excision (W-WLE) has been the standard of care for impalpable breast lesions and requires insertion of the wire on the same day as the surgery. Logistics of same day localisation can lead to a chaotic morning for the patients with long uncomfortable waiting times prior to their surgery. Transporting patients across the hospital and at times between different sites can add to poor patient experience and inefficient theatre utilisation. Magseed localised wide local excision (M-WLE) is an alternative to W-WLE. Magseed is a 5mm non-radioactive paramagnetic seed inserted radiologically and in the UK it is licensed for insertion up to 30 days in advance. M-WLE was started for routine use in our Unit in July 2019. We compare the safety parameters and length of hospital stay (LOS) in patients undergoing M-WLE to W-WLE. **Methods:** All M-WLEs performed at a single institution over an 8 month period (Jul 19 - Feb 20) were included. These were compared to a historic matched cohort of W-WLEs performed over 8 months (Jan 18 - Aug 18) which would have been suitable for Magseed localisation. The suitability for Magseed localisation was decided by a breast radiologist based on local objective criteria. Intra-operative cavity shaves were performed based on specimen X-ray and re-excisions were performed where there was tumour at or < 1 mm from inked margin. Exclusion criteria for Magseed localisations included - i. multiple lesions requiring 2 or more wires and ii. Depth of lesion from skin (>3cm on ultrasound or >7cm deep in central breast on mammogram). Data including patient demographics, type of localisation, successful placements, pathology, re-excision rates, tumour size, and length of stay (LOS) was collected and analysed. **Results:** Over the 16 months, 319 patients underwent localised WLEs. 238 patients were included in the study and 81 excluded. Patient demographics and tumour characteristics are detailed in Table 1. There is no significant difference in the intra-operative cavity shaves between the two groups. A significant difference in the re-excisions rates favouring the M-WLE group despite no significant difference in the mean tumour to specimen ratio was seen. (Table 2) The median waiting time to surgery from the time of admission was observed to be significantly shorter in the M-WLE group (4h15mins *vs* 7h03mins, *p<0.01*). There was no significant difference in the median LOS between the two groups (M-WLE 13h44mins, W-WLE 13h56mins, *p=0.36*). The overall day surgery rates were comparable in the two groups (M-WLE 75.2%, W-WLE 75.1%, p=0.99). **Conclusion:** In the present series, M-WLE has been shown to be oncologically safe and non-inferior to W-WLE with a significantly lower re-excision rate. In addition to this, the reduced pre-operative waiting time on the day of surgery in the M-WLE group will have a positive effect on the patient journey. Further research should focus on the potential impact on day-bed utilisation and theatre efficiency.

**Table 1: Patient demographics and tumour characteristics**

| | | MagseedT | Wire | p value |
|---|---|---|---|---|
| n | | 105 | 133 | |
| Median age (years) | | 64 (34-87) | 60 (28-82) | 0.05 |
| Median BMI | | 28.2 (17-54.4) | 28.3 (18.8-43.1) | 0.62 |
| Pathology | Invasive+/-DCIS | 85 | 110 | 0.31 |
| | DCIS | 17 | 15 | |
| | Others | 3 | 8 | |
| Mean tumour diameter (mm) | Invasive+/-DCIS | 15.19 (3-55) | 15.52 (1-15) | 0.82 |
| | DCIS | 9.41 (3-45) | 17.12 (3-55) | 0.13 |

**Table 2: Tumour to specimen ratio, further intra-operative cavity shaves and re-excision rates**

| | | Magseed™ | Wire | p value |
|---|---|---|---|---|
| n | | 102 | 125 | |
| Mean Tumour/Specimen Ratio | Invasive+/-DCIS | 8.8% | 18.1% | 0.20 |
| | DCIS | 18.4% | 24.8% | 0.75 |
| Further intra-operative cavity shaves | Total | 48 (47.0%) | 68 (54.4%) | 0.27 |
| | Invasive+/-DCIS | 28/64 (43.7%) | 56/102 (54.9%) | 0.16 |
| | DCIS | 7/15 (46.6%) | 8/15 (53.3%) | 0.71 |
| | Oncoplastic procedures: Invasive+/-DCIS | 12/21 (57.1%) | 4/7 (57.1%) | 1 |
| | Oncoplastic procedures: DCIS | 1/2 (50%) | 0/1 (0%) | NA |
| Re-excisions of margins | Total | 3 (2.9%) | 13 (10.4%) | 0.03 |
| | Invasive+/-DCIS | 3/64 (4.6%) | 8/102 (7.8%) | 0.4 |
| | DCIS | 0/15 (0%) | 5/15 (33.3%) | NA |
| | Oncoplastic procedures: Invasive+/-DCIS | 0/21 (0%) | 0/7 (0%) | NA |
| | Oncoplastic procedures: DCIS | 0/2 (0%) | 0/1 (0%) | NA |

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Is inflammation a hero or a villain in human breast cancer?

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Inflammation has been linked with cancer, but whether it is part of the problem or part of the solution remains to be a matter of debate in breast cancer. Our group and others have demonstrated that inflammation aggravates cancer progression, however, some claim that inflammation may support immune cell infiltration and suppress cancer. We defined the gene set variation analysis of the Molecular Signatures Database Hallmark inflammatory response gene set as the inflammatory pathway score and analyzed 3632 tumors in total from 4 breast cancer cohorts (METABRIC, TCGA, GSE25066, and GSE21094). In the whole breast cancer cohort, high score tumors were associated with aggressive clinical characteristics, such as worse disease specific survival ($p = 0.002$), higher Nottingham histological grade ($p < 0.001$), as well as younger age (young < 65 yo, 65 yo < as elderly; $p < 0.001$). SphK1 high expression were associated with higher inflammatory score with the striking consistency in the two cohorts (both $p < 0.001$). Furthermore, inflammatory score was significantly elevated in tumors that express high levels of S1P receptor 1 (S1PR1) (both $p < 0.001$), and sphingosine kinase 2 (SphK2) low expression tumors were also associated with higher inflammatory score (both $p < 0.001$). Inflammatory score was significantly higher in Triple Negative (TNBC) ($p < 0.001$) as well as Basal and Normal subtypes ($p < 0.001$) compared with the other subtypes in both METABRIC and the TCGA cohorts, which suggest that the detrimental effect of high level of inflammation may be because it includes a more aggressive subtype. On the contrary, high score within TNBC was significantly associated with better survival (DSS; $p = 0.014$, OS; $p = 0.015$). TNBC with high score enriched not only IFN-α, IFN-γ response, IL-2/STAT5 signaling, Allograft rejection, Complement, p53 pathway, Reactive Oxygen, and Apoptosis, but also TNF-α signaling, IL6-JAK-STAT signaling, TGF-β signaling, Coagulation, Angiogenesis, EMT, KRAS signaling, and PI3K-AKT-MTOR signaling gene sets (all FDR < 0.25 in both cohorts). High score was associated with mainly favorable anti-cancerous immune cell infiltration, including CD8 T cell, CD4 memory T cell, M1 Macrophage, and dendritic cell (all $p < 0.001$ in both cohorts), as well as Leukocyte fraction ($p < 0.001$), TIL regional fraction ($p = 0.027$), Lymphocyte infiltration ($p < 0.001$), IFN-γ response ($p < 0.001$) and TGF-β response ($p < 0.001$) and cytolytic activity scores ($p < 0.001$ in both cohorts). Although the inflammatory pathway score was not associated with neoadjuvant treatment response, it associated with expressions of immune checkpoint molecules (all $p < 0.001$ in both cohorts). In conclusion, inflammation was associated with worse outcome in the whole breast cancer cohort, but with better outcome in TNBC, which was associated with favorable anti-cancerous immune response and immune cell infiltrations.

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# A first-in-human Phase 1/1b multicenter, open-label dose escalation study to assess safety and tolerability of PMD-026, a first-in-class oral RSK inhibitor, in metastatic breast cancer patients

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**Background:** Metastatic breast cancer (mBC) remains an aggressive disease with limited durable treatment options; the worst prognosis among the breast cancer subtypes is typically seen in metastatic triple-negative breast cancer (mTNBC). Given that unmet need, we sought to identify an actionable molecular target to combat mTNBC. Promising preclinical activity identified p90 ribosomal s6 kinase 2 (RSK2) as a key kinase in mTNBC. PMD-026 is a potent, oral, small molecular RSK inhibitor with high selectivity for the RSK2 isoform. RSK is a major convergence point in the important MAPK and PDK-1 signaling pathways, which drive TNBC cell survival, proliferation, and drug resistance.
**Methods:** The primary aim of this single-arm, open-label, first-in-human, phase 1/1b study (NCT04115306) is to evaluate the safety of single agent PMD-026 in patients with mBC. Secondary endpoints are clinical activity, pharmacokinetics (PK) and correlative biomarker expression on tumor specimens. Patients are dosed orally once or twice daily in 21-day cycles with measures to adapt the dosing schedule based on the PK data, as needed. In dose escalation, patients must have mBC with evaluable or measurable disease by RECIST v1.1. In dose expansion, patients must have mTNBC with measurable disease by RECIST v1.1. Patients must have progressed on or after standard of care therapy. Tumor tissue is required to retrospectively correlate RSK2 activity with clinical outcomes via immunohistochemistry using a CAP/CLIA certified companion diagnostic (CDx).
**Results:** Twelve mBC patients (ER+ mBC n=5, mTNBC n=7) who have failed standard chemotherapy as well as targeted therapies such as CDK4/6 inhibitors and immunotherapies have been enrolled to date. Patients have been treated in escalating cohorts of 25, 50, 100, 200, 400 (200 q12) or 600 mg (300 q12) of PMD-026 administered orally daily. At 400 mg the dose schedule was changed from daily to q12 hrs based on PK results to optimize drug exposure over a 24-hr timeframe in patients. The PK of PMD-026 showed linear exposure and a high volume of distribution. The AUC was ~9100 hr*ng/ml on Day 1 when PMD-026 was dosed at 200 mg qd demonstrating high exposure. In addition, when dosed at 200 mg q12 hrs, PMD-026 serum levels approached the preclinically established desired level of 1 µM over 24 hrs. In the 200 mg q12 hrs cohort, adverse events consisted of G2 GERD (n=1) and G2 neutropenia (n=1). Initial signs of activity were observed as CT-identified necrosis in a neck node metastasis (n=1) and transient decrease in CA 27-29 (n=1). While the 200 mg q12 hrs dose was generally well-tolerated, there were 2 dose limiting toxicities at 300 mg q12 hrs including syncope (n = 1) and vomiting with dehydration leading to reversible acute kidney injury (n = 1). To further understand the patient population, RSK2 activation was assessed in tumor samples from all patients. RSK2 was activated in all of the tumors and the H-Score ranged from 110 to 198 using the CDx platform.
**Conclusions:** Preliminary evidence indicates that PMD-026 is well-tolerated at dose levels up to 200 mg q12 with initial signs of activity; pharmacokinetics showed good linear exposure. Updated safety, clinical activity, pharmacokinetic and biomarker analyses will be presented; target accrual for Phase 1b Expansion is approximately 20 mTNBC patients. (clinicaltrials.gov NCT04115306).

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# Investigating oncogenic signaling pathways in inflammatory metastatic breast cancer (MBC) though circulating tumor DNA (ctDNA) next-generation sequencing (NGS)

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**Background**: Inflammatory breast cancer (IBC) has a distinctive and aggressive clinical behavior but its underlying biological characteristics have not been fully elucidated. The extended analysis of somatic alterations in The Cancer Genome Atlas (TCGA) highlighted canonical oncogenic pathways that were consistently represented across different tumor subtypes. The aim of this study was to translate such pathway-based characterization to the clinical setting through ctDNA NGS to dissect IBC's biology and prognosis.
**Methods**: The study retrospectively analyzed 255 metastatic breast cancer (MBC) patients (pts) treated and characterized for ctDNA at Northwestern University (Chicago, IL). ctDNA was analyzed using the Guardant360 NGS assay (Guardant Health). Only non-synonymous alterations were analyzed. Pathway classification was defined based on prior work (Sanchez-Vega F et al, Cell. 2018). Associations among clinical characteristics, pathway classification, and IBC were explored through uni- and multivariate logistic regression; survival was tested though uni- and multivariate Cox regression both for progression-free survival (PFS) and overall survival (OS).
**Results**: Of 255 enrolled pts, 124 (48%) were diagnosed with hormone receptor positive (HR pos) MBC, 75 (30%) with HER2-positive (HER2_pos) MBC and 56 (22%) with triple negative (TNBC) MBC. IBC was diagnosed in 74 pts (30%). Receptor-tyrosine kinase, RTK (130 pts, 51%), p53 (130 pts, 51%), PI3K/Akt (116 pts, 46%), and cell cycle (91 pts, 36%) were the most often altered pathways. The multivariate model highlighted the association of IBC with HER2_pos (OR: 2.19; 95%CI: 1.09 - 4.38; P=0.0276), an increased number of alterations in the p53 pathway (OR: 2.05; 95%CI: 1.12 - 3.75; P=0.0197) and a decreased number of alterations in the RAS pathway (OR: 0.34; 95%CI: 0.14 - 0.80; P=0.0137). Decreased alterations in the ER pathway were borderline significant (OR: 0.48; 95%CI: 0.22 - 1.03; P=0.0584). Only cell cycle alterations had an impact on PFS for IBC (HR: 2.20; 95%CI: 1.18 - 4.08; P=0.0127), while p53 and Wnt had an impact on nonIBC (respectively HR: 2.00; 95%CI: 1.23 - 3.25; P=0.0052 and HR: 3.40; 95%CI: 1.20 - 9.64; P=0.0212). The univariate model showed a significant impact on OS RAF, ER, and cell cycle pathways alterations for IBC, the role of ER and cell cycle pathways alterations was confirmed in the multivariate model (respectively HR: 6.19; 95%CI: 1.63 - 23.48; P=0.0073 and HR: 3.79; 95%CI: 1.04 - 13.75; P=0.0431). The multivariate model showed a prognostic impact only for p53 in the nonIBC subgroup (HR: 2.20; 95%CI: 1.11 - 4.36; P=0.0237)
**Conclusion**: The ctDNA-based oncogenic signaling pathway characterization showed different biological and prognostic features across IBC and nonIBC MBC patients. Alterations of the p53 pathway were more likely to be present in IBC pts, while alterations in the RAS pathway were less represented in this cohort. ER and cell cycle pathways' alterations impacted the OS of IBC MBC patients. Although preliminary, these results suggest a more comprehensive biological characterization based on ctDNA for treatment selection and clinical decision-making.

Main alterations and pathway

| Gene | Number of alterations | % | Pathway |
|---|---|---|---|
| TP53 | 188 | 15.58 | p53 |
| PIK3CA | 141 | 11.68 | PI3K/Akt |
| ERBB2 | 72 | 5.97 | RTK |
| ESR1 | 70 | 5.8 | ER |
| MYC | 57 | 4.72 | Myc |
| FGFR1 | 46 | 3.81 | RTK |
| EGFR | 45 | 3.73 | RTK |
| CCNE1 | 38 | 3.15 | Cell cycle |
| MET | 32 | 2.65 | RTK |
| NF1 | 32 | 2.65 | RAS |

**Publication Number:** PS8-33

Image-guided intraductal ablation with refined ethanol solution for primary prevention of breast cancer

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Breast cancer (BC) is the most prevalent cancer and the second-leading cause of cancer-related death for women in the USA. For moderate-risk and, especially, low-risk women with a 1-in-8 lifelong chance of developing BC, there are very few options available to reduce their risk. For high-risk women, prophylactic mastectomy is currently the most effective procedure for preventing BC. Prophylactic mastectomy completely removes the mammary epithelial cells from which BC arises along with surrounding tissue. This aggressive surgical procedure affects women physically, emotionally, psychologically, aesthetically, and socially. Therefore, there is a need to develop new strategies for primary prevention that focus on high-risk women, but that, at the same time, could be also applied to moderate- and low-risk women. Our overall hypothesis is that the local killing of mammary epithelial cells will be as effective as prophylactic mastectomy in preventing BC, but with minimal side effects. Preclinical and clinical research studies as well as clinical application of intraductal (ID) procedures such as ductography for diagnostic imaging strongly support the translational feasibility of our approach. EtOH has been long used clinically as an ablative or sclerosing agent for local treatment. We recently showed that ID injection of a 70% EtOH solution is effective at locally ablating mammary epithelial cells with limited collateral tissue damage and at preventing tumor formation in an aggressive and multifocal mouse model of BC. We also recently developed tantalum oxide ($TaO_x$) nanoparticles as a larger and higher radiopaque contrast agent with a much lower rate of outward diffusion than iodine-based contrast agents used in clinical ductography. Here, we investigated a refined EtOH formulation that consists of the addition of: i) $TaO_x$ nanoparticles as a high-resolution contrast agent to monitor in vivo filling of ductal trees and ablative effects of EtOH by computed tomography imaging; and ii) ethyl-cellulose (EC) as gelling agent to further minimize collateral tissue damage. This $TaO_x$-based imaging approach provided unprecedented resolution to visualize individual ducts and branches of the ductal tree network after initial ID injection and architectural changes over 7 d due to local retention of $TaO_x$ nanoparticles in both PBS and EtOH solutions. EC is used clinically to improve delivery of EtOH and to limit EtOH diffusion from the intended target area in the treatment of venous malformations. ID injection of 70% EtOH/3% EC in nontransgenic mice and rats achieved the same epithelial ablation rate as 70% EtOH alone, while significantly minimizing collateral tissue damage. These results demonstrate the compatibility, safety, and stability of this refined EtOH formulation and support its further investigation in cancer-prone rodent and larger animal models as an innovative primary intervention strategy for BC prevention.

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# Feasibility of a comprehensive monitoring protocol for the prevention and treatment of interstitial lung disease in patients undergoing treatment with fam-trastuzumab deruxtecan

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**Background**: Fam-trastuzumab deruxtecan (DS-8201) was recently approved in patients with advanced/metastatic HER2 positive breast cancer who have received two or more prior HER2-based regimens. In DESTINY-Breast01, an unprecedented response rate was observed in 61% of heavily pretreated patients; however, all-grade interstitial lung disease (ILD) developed in almost 14% of patients, which led to death in 2% of patients. Additionally, patients with a medical history of clinically significant lung disease were excluded which is not consistent with the standard community patient population that may receive fam-trastuzumab deruxtecan. Currently, there are no recommended protocols in place or guidance for monitoring patients for interstitial lung disease/pneumonitis while on fam-trastuzumab deruxtecan. This is a retrospective chart review to assess the feasibility of implementing an ILD monitoring protocol in a cohort of patients receiving treatment with fam-trastuzumab deruxtecan at the Duke Cancer Institute.
**Methods**: Patients with HER2-positive or HER2-low metastatic breast cancer who received ≥five cycles of fam-trastuzumab deruxtecan between Jan 1, 2020-June 30, 2020 were included. Chest imaging and pulmonary function testing with diffusing capacity for carbon monoxide (DLCO) were performed at baseline prior to initiation and every six weeks prior to cycle 3 and cycle 5 of fam-trastuzumab deruxtecan to monitor for ILD. DLCO was corrected for hemoglobin. Patients that experienced more than a 10% decrease in corrected DLCO (DLCOc) were recommended to have a pulmonology consult in which DLCOc was reviewed in combination with chest imaging and clinical history to evaluate for ILD and recommend continuance or cessation of the drug. Clinical pulmonary symptoms to include cough, shortness of breath, dyspnea, and new or worsening respiratory symptoms were monitored per chart review.
**Results**: Seven patients with HER2-positive (N=6) and HER2-low (N=1) metastatic breast cancer were monitored per predefined ILD monitoring protocol with 100% completion of chest imaging and pulmonary function testing at baseline and prior to cycle 3 and cycle 5 indicating feasibility. There were no confirmed cases of ILD/pneumonitis within the patient cohort. Two patients (28.6%) experienced DLCOc decreases >10% warranting a pulmonology consult. Upon further assessment, ILD/pneumonitis was ruled out based on chest imaging and/or asymptomatic presentation and both patients continued therapy without treatment delay or development of pneumonitis to date. Both patients with DLCOc decrease >10% had a history of lung disease or significant metastatic disease involvement including asthma and lymphangitic carcinomatosis, respectively. In these patients, DLCOc, imaging and clinical history were able to safely rule out ILD. .
**Conclusion**: Implementation of a comprehensive protocol to monitor and assess for ILD associated with fam-trastuzumab deruxtecan is feasible for patients receiving this therapy and may prevent treatment delay in patients with suspected ILD. In this small cohort, stable DCLOc suggests the absence of ILD onset in patients treated with fam-trastuzumab deruxtecan. DLCOc monitoring may be a reasonable measure to assess for ILD-related changes in patients. Further data collection is underway to understand the value of a comprehensive ILD monitoring protocol.

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# Androgen receptors are highly expressed in HER2-positive breast cancers that achieve pCR to anti-HER2 monoclonal antibodies

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**Background**Almost 50% of early HER2-positive Breast Cancer (BC) patients achieve pathological complete response (pCR) when treated with pertuzumab and trastuzumab in association with neoadjuvant chemotherapy (TPCT). Novel predictive factors are needed in order to improve the response rate by introducing innovative and less toxic combination regimens. We aimed to address this unmet clinical need by dissecting the role of Androgen Receptor (AR) expression in this subgroup of patients. **Methods**We quantified AR expression by Immunohistochemistry (IHC) in 59 untreated samples of patients enrolled in the ImmunHER trial. This is a non-comparative, phase II, neoadjuvant, randomized study that enrolled previously untreated patients with histologically confirmed, locally advanced, inflammatory, or early-stage HER2-positive BC. Patients were treated with FEC (fluorouracil 500 mg/m2; epirubicin 75 mg/m2; cyclophosphamide 500 mg/m2) q21 x 3 cycles. Then, they were randomly assigned (1:1) to receive: docetaxel (75 mg/m2) plus pertuzumab (840 mg loading dose (LD), then 420 mg) plus IV trastuzumab (8 mg/kg LD, then 6 mg/kg) q21 x 4 cycles (arm A) or, docetaxel plus pertuzumab plus SC trastuzumab (fixed dose of 600 mg) q21 x 4 cycles (arm B). After surgery, patients received trastuzumab q21 x 14 cycles using the same formulation (SC or IV) of the preoperative phase. The primary endpoint was the rate of stromal TILs (sTILs) on residual disease after surgery. ClinicalTrials.gov: NCT03144947. **Results**In 46 samples (78%), ARs were expressed in more than 10% of tumor cells. The median expression was 90%. ARs were more expressed in women older than 40 yo compared to younger (median expression: 90% vs 40% [*P*-value not provided for post hoc tests]) and in Estrogen Receptor (ER)-positive tumors compared to ER-negative (median expression: 90% vs 75%). ARs were more expressed in tumors that achieved pCR than in non-responder patients (median expression: 90% vs 60%) and in high sTILs tumors compared to low-intermediate sTILs tumors (median expression: 90% vs 80%). In our series, AR expression did not correlate with Ki67, CD3, CD56, PD1, PD-L1 expression. **Conclusions**ARs are highly expressed in early HER2-positive BC. The higher AR expression observed in patients with pCR and high-sTILs suggests the combined use of TPCT with Selective Androgen Receptor Modulator (SARM). We are currently testing the *in vitro* combination of SARM with trastuzumab and pertuzumab, and efficacy results will be presented at the meeting.

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National Clinical Trial Network Breast Trial mentions in electronic physician resources

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INTRODUCTION: Physicians look to various electronic resources to aid in management of patient treatment. While national guidelines encourage clinical trial participation for cancer patients, it is unclear if physician facing resources help guide physicians to appropriate trials in which to enroll their patients. If resources do not mention appropriate open clinical trials, physicians miss a major management strategy.
METHODS: A list of open breast cancer trials as of June 15, 2020 was obtained from the National Clinical Trial Network (NCTN). Physician facing electronic resources including UpToDate, DynaMed, WebMD, Medscape, theMedNet, WebMD, and ClinicalKey, were queried for each trial. The long name of the trial, trial name, any abbreviation associated with the trial, and definitive type of breast cancer characteristics qualifying for the trial were searched for in the database. Relevant management topics within each resource were also reviewed for mention of any open trial. A spreadsheet was constructed and trial mentions were tabulated.

Mentions of Trials within Physician Facing Electronic Resources

| Trial | Up to Date | DynaMed | WebMD | MedScape | MedNet | ClinicalKey |
|---|---|---|---|---|---|---|
| **EA1181** | No | No | No | No | No | No |
| **NRG-BR005** | No | No | Yes | Yes | No | No |
| **S1706** | No | No | No | No | No | No |
| **NSABP B-51** | Yes | No | No | No | Yes | No |
| **A011202** | No | No | No | No | Yes | No |
| **EA1131** | No | No | No | No | Yes | No |
| **S1418** | No | No | No | No | Yes | No |
| **NRG- BR003** | No | No | Yes | No | Yes | No |
| **CCTG MA.39** | No | No | No | No | Yes | No |
| **A011401 (BWEL)** | No | No | No | No | Yes | No |
| **A011502 (ABC)** | Yes | No | No | No | No | Yes |
| **EAI142** | No | No | No | No | No | No |
| **NRG- BR002** | No | No | Yes | No | Yes | No |
| **EA1183 (FEATURE)** | No | No | No | No | No | No |
| **NRG- BR004** | No | No | No | No | No | No |
| **EAY131 (MATCH)** | Yes | No | No | Yes | No | No |
| **S1609 (DART)** | Yes | Yes | No | No | No | No |
| **Percent mentioned** | **24%** | **6%** | **18%** | **12%** | **47%** | **6%** |

RESULTS: The 17 trials were found mentioned 19 times across all 6 resources resulting in clinical trials being mentioned an average of 18%, with a range of 6%-47%. A total of 47% of open NCTN breast trials were mentioned on the MedNet, the highest rate of any platform. Trials were mentioned the least on DynaMed and ClinicalKey at a rate of 6%. Clinical trial mentions did not always correlate with recommendation of enrollment or promotion of participation in the trial. The majority of mentions were found by searching the specific trial name.
CONCLUSION: Participation in clinical trials is almost always advised for breast cancer patients. However, access to open trial information is minimal within physician-facing electronic resources. Information on open or appropriate clinical trials rarely accompanies the recommendation for research participation. With extensive probing of physician facing databases, open clinical trials were mentioned only 18% of the time (range of 6%-47%). The lack of exposure of open clinical trials in physician facing electronic databases increases the difficulty of adherence to the recommendation of clinical trial enrollment as a management strategy. In addition to missing a major management strategy, the lack of representation of the trials may be a barrier to appropriate referrals.

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# A study to observe patients characteristics, treatment patterns and outcomes in patients with newly diagnosed breast cancer in Latin America - LATINA breast (LACOG 0615/ MO39485)

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**Background:** Breast cancer (BC) is the most common malignancy and one of the leading causes of cancer death in Latin American women, with an estimated age-standardized annual incidence of 38.3 and 56.8 and mortality rates of 10.1 and 13.4 cases per 100,000 females, in Central and South America respectively. However, BC incidence in Latin America (LATAM)is largely underestimated and lacks updated information. Furthermore, the shortage and quality of cancer registry data hinders a more reliable assessment of treatment and outcomes for these patients. The goals of LATINA Breast study is to build an electronic platform/database to allow a standardized collection of epidemiological data of BC in LATAMin addition to describe real world data on patients characteristics, treatment patterns and outcomes of this population. **Methods:** LATINA Breast (LACOG 0615) is a prospective, international, multicentre and non-interventional study of primary data collection designed to describe the diagnosis, oncologic treatment and outcomes of patients with BC in LATAM. Patients aged ≥ 18 years with stage I to IV newly diagnosed BC (i.e. <12 months since site activation) will be considered eligible for inclusion.Patient data will be collected from medical records at diagnosis and every 6 months for up to 5 years of follow-up. At baseline, data on socioeconomic, demographic, medical history and BC clinicopathological characteristics will be collected. Thereafter, information regarding treatment patterns, sequencing, response to treatment, adverse events, disease relapse/ progression and overall survival will be collected at each time-point. This study has a planned sample size of a minimum of 2.200 to a maximum of 4.500 patients accrued from approximately 30 sites in 10 LATAM countries: Argentina, Brazil, Cuba, Colombia, Chile, Dominican Republic, Ecuador, Mexico, Peru and Uruguay. The expected number of patients per country is based on age-standardize BC incidence rate by GLOBOCAN 2012 and not in a formal statistical estimation.Co-primary endpoints are (1) to describe patients' characteristics, prevalence of BC subtypes at diagnosis, local and systemic treatment patterns and outcomes; (2) to build an electronic platform/database of epidemiological data of BC in LATAM. Secondary endpoints are to evaluate regional differences in treatment strategies, to describe treatment efficacy parameters such as locoregional relapse, invasive disease-free survival, progression-free survival, overall survival and to evaluate treatment safety. The trial is registered at clinicaltrials.gov NCT04158258.**Results** The first site was activated for patient accrual on February 13, 2020, in Argentina. As of July 6, 2020, a total of 243 patients have been included in Argentina (*n*=81), Brazil (*n*=123), Colombia (*n*=37), and Guatemala (*n*=2) within 19 active sites. Regulatory approval and activation are ongoing in the other countries. Recruitment is estimated to last until December 2021 to achieve the planned sample size. Patients will be followed-up for 5 years, therefore we estimate the last follow-up data collection in December 2026. **Conclusion**LATINA Breast is the first multinational, prospective cohort study of BC in Latin America that will generate detailed information on diagnosis, treatment and outcome in real-world clinical practice. It will address important gaps in BC management and will likely single out some of the main inequities in this large and diverse population of BC patients and consequently support strategies for the improvement of BC cancer care in LATAM.

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# Sumo-modified androgen receptors support the metastatic phenotype of endocrine-resistant hormone receptor-positive breast cancer

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Background: Conventional endocrine therapy is the first-line treatment for hormone receptor positive (HR+) breast cancer (BCa) subtype. Frequently, intrinsic and acquired ET resistance (ET-R) persists to support a disease with poor prognosis and limited therapy than the ET-sensitive carcinoma. High levels of androgen receptors (AR) in HR+ BCa correlate with insensitivity to ET tamoxifen and greater susceptibility to cancer metastasis. However, targeting AR with antagonist enzalutamide (Enz) in ET-R HR+ BCa present conflicting results. In the current report, we present novel findings of a constitutively active modified AR population that accumulates in the ET-R HR+ BCa cells to drive cell migration and metastatic phenotype.
Methods: Cell-free protein modification tests, in-house SUMOylation assays, and PLA imaging were used to determine the AR protein profile in multiple ET-sensitive, intrinsic-, and acquired-ET HR+-BCa lines. Reporter assay and targeted transcriptome studies evaluate the genomic activity of native and modified-AR mimetic. Finally, the inhibitory effect of Enz with or without combination therapy was determined using migration and spheroid growth studies.
Results: In acquired and intrinsic ET-R BCa cell lines, a constitutively active, higher molecular weight SUMO-modified AR (SUMO-AR) persists at the chromatin. The SUMO-AR is resilient to ubiquitin-mediated proteasomal degradation. We now report that the canonical AR chaperone protein HSPB1/Hsp27 functions as a novel SUMO-E3 ligase for AR. SUMO-AR interacts with a unique repertoire of biomolecules as compared to unmodified AR in the same cell lines. An increase in the SUMO protein and global SUMO-modified proteome supports this multimeric complex. The ligand-independent SUMO-AR activity promotes a gene-expression profile that favors epithelial-mesenchymal transition. Treatment with Enz alone or in combination with a SUMO inhibitor attenuates migration and metastatic phenotype of ET-R HR+ BCa.
Conclusion: SUMO-AR dictates metastatic susceptibility and Enz responsiveness of ET-R HR+ BCa. Consistently, targeting both unmodified and SUMO-modified AR serves as a better therapeutic strategy for advanced HR+ BCa.

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Analysis of factors associated with pathological complete response (pCR) in patients with HER2+ breast cancer receiving neoadjuvant chemotherapy

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**Background:** Pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC) is associated with improved survival outcomes among women with HER2 positive (HER2+) breast cancer. We aimed to analyze the clinical, pathological and molecular factors associated with pCR in our series of HER2+ breast cancer patients. **Methods:** Between 2009 and 2019, breast cancer patients receiving NAC at our centre were enrolled in a prospective database. For this study we selected women with HER2+ unilateral breast cancer stages II or III who received anthracycline-taxane NAC regimens (with trastuzumab given concurrently with the taxane) and subsequently underwent breast and axillary surgery with curative intent. Medical charts of these 161 women were retrospectively reviewed to determine what clinical, pathological and molecular characteristics were associated with pCR using bivariate and multivariate analysis. **Results:** Of the 161 HER2+ women median age at diagnosis was 49 years (range 25-78) with 90 (56%) women under age 50. Total of 104 (65%) tumors were stage II, 108 (67%) expressed estrogen and/or progesterone receptors, 139 (86%) had HER2 3+ expression by immunohistochemistry (IHC) and 22 (14%) had HER2 IHC 2+ expression with amplified HER2 on fluorescence in situ hybridization (FISH) test. The NAC regimens were: Doxorubicin-Cyclophosphamide-*Paclitaxel* for 83 (52%) and Fluorouracil-Epirubicin-Cyclophosphamide-Docetaxel for 78 (48%) women. A total of 73 patients [45%; 44/108 HR+ (41%) and 29/53 HR- (55%)] achieved pCR (p=0.94). pCR rate among HER2 IHC 3+ tumors was 69/139 (50%), while for HER2 IHC 2+ tumors was 4/22 (18%). On bivariate analysis HER2 IHC 3+, absence of estrogen receptors and absence of progesterone receptors were predictive of pCR, while age, menopausal status, histologic subtype, tumor grade and NAC regimen were not. In the multivariate model only HER2 IHC 3+ expression remained a significant predictor of pCR (OR =4.443, 95% CI 1.376 - 14.344). **Conclusion:** Our analysis suggests that for HER2+ breast cancers treated with NAC with anthracycline-taxane and trastuzumab, HER2 IHC 3+ expression is associated with a higher rate of pCR compared to HER2 IHC 2+ expression with FISH amplification. Further analysis in a larger cohort is warranted.

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**Publication Number:** PS16-33

Niclosamide reverses cisplatin resistance by inhibiting Bcl-2 and Stat3 in HER2-positive breast cancer

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**Background:** Breast cancer is the second leading cause of cancer-related deaths. Chemotherapy resistant breast cancer is poorly differentiated and displays aggressive clinical behavior. These tumors become resistant to cytotoxic agents and tumor relapse has been attributed to the presence of epithelial-mesenchymal transition (EMT) and cancer stem cells (CSCs). Niclosamide has been shown to have broad clinical applications for the treatment of malignant tumors other than those caused by parasites. However, the specific functions and molecular mechanisms of niclosamide in chemo-resistant HER2 positive breast cancer are still unknown. **Methods:** HER2 positive breast cancer cell line, BT474, was continuously exposed to increasing concentrations of cisplatin (5-20 μM) to establish stable cell line resistant to cisplatin, BT-CR. Cell viability was determined by alamar blue. Apoptosis was determined by flow cytometry. Mammosphere formation assay was conducted to observe the self-renewal potential. Invasion ability was analyzed by transwell assay. Protein expression was determined by western-blot. **Results:** BT-CR had EMT and stem-like phenotype with higher invasion ability compared to naive sensitive cells. Alamar Blue assay showed combination of niclosamide with cisplatin could reverse cisplatin resistance. The combination index value of niclosamide combined with cisplatin was less than 1. Niclosamide in combination with cisplatin significantly enhanced apoptosis of BT-CR cells to over 50%. Western-blot showed niclosamide and cisplatin could reverse the EMT phenotype of BT-CR with E-cadherin up-regulated and N-cadherin and vimentin down-regulated. A significant reduction of Bcl-2 and Stat3 phosphorylation (Tyr705) levels was also confirmed. After treatment of niclosamide combined with cisplatin, the inhibition of mammosphere forming efficiency and capability of invasion was also observed in BT-CR. **Conclusion**: Our results revealed that niclosamide combined with cisplatin inhibited cell growth, invasion, EMT and stem-like phenotype in cisplatin resistant BT474 cells. The inhibitory effect of niclosamide was exerted by increasing apoptosis and down-regulated Bcl-2 expression, whilst inhibiting phosphorylation levels of STAT3. The results suggested that niclosamide combined with cisplatin appears to be a novel therapeutic way in chemo-resistant breast cancer.

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Cost-effectiveness of neratinib for the extended adjuvant treatment of adult patients with early-stage, HR+, HER2-overexpressed/amplified breast cancer who initiated neratinib within 1 year of completing trastuzumab in the US

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**Background:** Neratinib, an oral, irreversible tyrosine kinase inhibitor of multiple human epidermal growth factor receptors (HERs), is indicated for the extended adjuvant treatment of adult patients with, HER2-positive early-stage breast cancer (eBC) to follow adjuvant trastuzumab-based therapy in the United States (US). However, greater efficacy has been seen in patients with hormone receptor-positive (HR+) breast cancer and who initiated neratinib within 1 year of completing trastuzumab. **Objective:** This study explores the cost-effectiveness of neratinib versus placebo from a US third-party payer perspective in adult patients with HR+ HER2-overexpressed/amplified eBC and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy. **Methods:** A Markov model was constructed to model costs and health outcomes of neratinib and placebo over a lifetime horizon. The model consisted of five health states representing the primary stages of disease in eBC—disease-free, local recurrence, remission, distant recurrence, and dead—and corresponds to the primary and secondary endpoints in the neratinib ExteNET trial. Overall survival was modeled based on a combination of post-distant recurrence survival and general population mortality, assuming all cancer-related mortality would occur through the distant recurrence health state. Statistical extrapolation of invasive disease-free survival and post-distant recurrence survival were derived from the ExteNET clinical trial data as well as the proportion of local and distant recurrence and number of adverse events. Non-breast cancer-related mortality was derived from US life tables. Costs per treatment arm were calculated based on drug acquisition, administration, and monitoring costs as well as treatment costs for adverse events and health state-related medical resource use. Quality-adjusted life-years (QALYs) were estimated per health state, and disutilities were applied per adverse event independent of treatment. Utility values for the invasive disease-free survival health state and diarrhoea were estimated using the EQ-5D-3L data collected in ExteNET. Additional health state utilities and adverse events disutilities were identified from the literature. Costs were adjusted to 2020 US dollars. One-way (OWSA) and probabilistic sensitivity analyses (PSA) and scenario analyses were performed to investigate the robustness of the results. Further, analyses were performed to investigate the cost-effectiveness for the subgroup of patients who did not achieve a pathologic complete response (pCR) after neoadjuvant therapy. **Results:** The results of the base case analysis showed that, compared with placebo, neratinib treatment generated an additional 0.88 incremental QALYs, 0.99 incremental life-years, and a resulting cost per QALY gained of $56,367. The results were robust across multiple scenario analyses with incremental cost-effectiveness ratios (ICERs) below $70,000. OWSA showed that the parameters that most influenced the results were variations in treatment-related costs, efficacy, and health state utility values. The PSA indicated that the probability of neratinib being cost-effective at a $100,000 per QALY threshold was above 75%. The analysis for the subgroup of patients who did not achieve a pCR after neoadjuvant therapy resulted in an improved ICER. **Conclusions:** The current cost-effectiveness analysis shows that neratinib is a cost-effective therapy for treating adult patients with HR+ HER2-overexpressed/amplified eBC and who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy in the US and in patients who did not achieve a pCR after neoadjuvant treatment.

**Publication Number:** PS9-34

Initial experience using the SOZO bio-impedance device over a 2 year surveillance period for identifying subclinical breast cancer related lymphedema (BCRL) in patients attending a multidisciplinary breast clinic

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Lymphedema is a leading posttreatment complication for many cancer patients. Roughly 1 of 3 women treated for breast cancer with surgery, radiation, or taxane based chemotherapy will develop chronic lymphedema. Lymphedema is characterized by buildup of lymphatic fluid that causes painful and debilitating tightness and swelling of the extremity with decreased range of motion and increased risk of infection. Unfortunately, it is rarely diagnosed until it has become symptomatic due to fibrotic changes and lipid deposition caused by protein rich extracellular fluid stasis. If the condition is diagnosed when it is preclinical, stage 0, it is reversible with outpatient intervention. Traditional screening methods for lymphedema include limb measurements with a tape measure or by volume displacement however, these techniques can be inaccurate and require significant volume change in the affected limb for detection. The SOZO is a relatively new device that uses noninvasive bioimpedance spectroscopy (BIS) which can detect fluid changes as small as 36 cc. This allows detection of lymphedema at the preclinical stage allowing early intervention with decompressive therapy and compression garments which can reduce the progression of lymphedema by 95%. We reviewed our initial 2-year experience using the SOZO device for lymphedema screening in our multidisciplinary breast clinic. Of the 239 patients who were seen in the multidisciplinary breast clinic, 160 patients had a baseline measurement prior to intervention and 128 of those patients had posttreatment measurements. Of those patients, 35 (27%) were referred for lymphedema therapy. Of those patients referred, 62% were stage 0, 28% were stage I, and 6% were stage II. One patient with stage 0 lymphedema at the initial postoperative measurement progressed to stage I but returned to baseline after treatment. None of the remaining stage 0 patients developed disease progression. Of the 10 patients that had developed stage I lymphedema at the time of their initial postoperative measurement, 6 were down staged to stage 0 after appropriate treatment, 2 continue to receive lymphedema therapy but have not progressed beyond stage I, and 2 were lost to follow-up. It is important to note that 30 of the 35 patients referred for lymphedema therapy were also referred to physical therapy or occupational therapy for functional impairments including decreased range of motion, axillary cording, and scar restriction. These early results showed that a surveillance program using the SOZO bioimpedance technology with pretreatment and posttreatment measurements allows early detection of breast cancer related lymphedema in the preclinical and early clinical stages when therapeutic intervention is most effective. Early stage lymphedema was also found to be associated with an increased incidence of functional impairment including decreased range of motion, axillary cording, and scar contracture. Evaluation for those impairments should be considered in all patients who develop lymphedema.

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# The informed genetics annotated patient registry: The iGAP registry

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Background

Interest and knowledge about the genetics and biology of inherited risk of and progression of disease is growing. Physicians are increasingly using tests and technology, including germline genetic, genomic, and biomarker testing, to provide insight into a healthy individual's risk and an affected individual's disease characteristics, in order to provide personalized clinical management. However, many barriers to adoption of precision medicine still exist in the clinical setting, including rapid advances in technology and research, complex guidelines for eligibility, variable quality and cost, and adequate understanding of appropriate implementation by medical professionals.

Methods

Table 1: Eligibility Criteria

| | |
|---|---|
| Retrospective | 18 years or older;Is/was a patient at participating practice previously tested with germline, genomic, or biomarker tests; For germline patients, have a diagnosis of cancer or P/LP result. |
| Prospective | 18 years or older;?Presents consecutively to a participating practice and who has previously been screened and tested;Receives/has received germline, genomic, or other biomarker testing, either through a prior provider or a participating practice; Consents to be a part of the registry. |

Table 1: Eligibility Criteria

The iGAP Registry uses an innovative digital platform to collect genetic, genomic, biomarker data and correlates it with clinical, pathologic and outcome data to inform providers of an individual’s risk of developing cancer, guide them to appropriate clinical grade testing and provide clinical decision support to providers for prevention and management strategies over time. The iGAP Registry’s digital platform minimizes technological barriers to longitudinal research participation and is available in mobile and desktop formats, allowing for easy implementation in a wide variety of clinic and hospital settings.

The risk tool uses predictive analytics to identify and curate patients at risk who are eligible for initial and further testing. The tool additionally can generate letters of medical necessity, each individualized by personal and family history, for eligibility for genetic testing (based on national guidelines) and additional imaging (based on validated cancer risk calculators). The insights tool provides physicians with decision support on how to interpret and manage abnormal genetic testing results on an individual level and supports improved understanding across lab terminology through variant classification. The insights tool also supplies letters of medical necessity and supporting evidence across many specialties.

The platform connects the information stored in the risk and insights tools to a unique participant record and automatically feeds the data into a digital case report form for the research registry. Additional clinical data is entered for patients who consent to be a part of the Registry. This allows for seamless longitudinal data collection over time without disrupting typical clinical workflows, and is further enriched by emailed patient-reported outcomes and physician decision impact questionnaires. Follow-up occurs over 5 years after initial data entry for the 10,000 expected subjects in the Registry (Table 1).

Conclusion

The iGAP Registry is a multi-center longitudinal, observational research database with an integrated platform of clinically-useful tools designed to address gaps for providers specifically for identifying individuals at elevated risk based on clinical and pathologic factors, guiding them to appropriate genetic, genomic, and biomarker testing and providing clinical insights on actionable results for personalized management and prevention for the individual and their family members over time. The iGAP Registry is currently enrolling and accepting new sites at www.igapregistry.org or https://clinicaltrials.gov/ct2/show/NCT04419896.

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# Time to completion of breast cancer treatment and survival

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Background:Modern breast cancer (BC) treatment involves the use of multimodality therapy. Treatment delays are common and can be multifactorial. There are few studies examining the association between the duration of the time from diagnosis to completion of all acute BC treatment modalities and survival. This study is designed to determine if there is an association between time to complete treatment and survival. Study Design:A retrospective analysis was performed using data from The National Cancer Database (NCDB) to determine whether an association exists between the duration of time from diagnosis to completing all acute BC treatment (surgery, chemotherapy and radiation therapy) and survival. A second analysis was performed to determine if the association between treatment duration and survival varies by receptor status. Results:The NCDB data from BC patients diagnosed in 2010 was analyzed. The inclusion criteria included less than 80 years of age with a single cancer diagnosis, Stage I through III invasive breast cancer who required treatment with surgery, chemotherapy and radiation therapy. A total of 28,284 patients were included in the analysis. Median follow-up was 5.8 years. The order of treatment included 20,772 patients had treatment in the order of surgery, chemotherapy and radiation therapy and 7,512 patients had treatment order chemotherapy, surgery and radiation therapy. A Cox proportional hazards model was developed and identified a cut off showing the risk of delaying completion of all treatment beyond 38 weeks was associated with decrease in overall survival. This was statistically significant with an adjusted hazard Ratio of 1.21. This cut off of 38 weeks was found to be significant regardless of receptors type. The statistically significant Hazard ratios for receptor subtypes include: Triple negative (HR: 1.188, 95%CI: 1.06-1.34), ER+PR+Her2- (HR: 1.22, 95%CI: 1.09-1.36), ER-PR-Her2+ (HR: 1.29, 95%CI: 1.004-1.67) and ER+PR+Her2+ (HR: 1.32, 95%CI: 1.01-1.72). The patients with treatment duration greater than 38 weeks were comprised of 4768(63.47%) neo-adjuvant chemotherapy patients and 8191 (39.43%) of the surgery first group. Conclusion: Efforts to improve the efficiency of multimodality BC treatment and reduce treatment delays should be a priority to optimize BC patient outcomes.

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Identification of proteomics-based biomarkers for ER+/HER2- breast cancer stratification: Implications on clinical outcome

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**Introduction:** Improving stratification of breast cancer (BC) patients based on molecular signatures for treatment responses and clinical outcomes is a critical unmet need. Currently, endocrine therapy is first-line for hormone receptor positive (HR+) BC. Chemotherapy is added to patients with high-risk luminal BC. In practice, levels of Ki-67 are used to distinguish luminal tumors as low-risk luminal A (LA) and high-risk luminal B (LB) for adjuvant therapy decisions. Herein, proteomic tumor assessment from ER-positive HER2-negative (ER+/HER2-) BC patients was utilized to define molecular subtyping, estimate congruency between proteomic subtyping and traditionally used Ki67 marker, and define a new set of potential predictive and prognostic therapeutic biomarkers for ER+/HER2- BC patients.
**Method/Result:** Clinical immunohistochemistry (IHC) subtyping of core biopsies was used to select a cohort of 86 BC patients with ER+/HER2- primary tumors from flash-frozen surgical samples. The positive/negative status of ER/PR/HER2 was defined using updated ASCO 2020 guidelines. Ki-67 status was determined using the 2011 St. Gallen's International Expert Consensus recommendations. The cohort includes 28 LA (Ki67 < 14%) cases and 58 LB1 (Ki67 >= 14%) cases. Integrated consensus clustering algorithms with the most varying proteins in our cohort were applied to identify proteomic subtypes. Two distinct separations were observed from the analysis, resulting in one cluster enriched with LA (40 cases) and the other enriched with LB1 (46 cases) called by Fisher's exact test. These clusters matched 100% with the clusters generated using 900+ proteins common to the 1500+ proteins used in the CPTAC-BC proteomics-based subtyping analysis (Mertins et al. Nature 2016). The differential analyses demonstrated that there is no significant difference between Ki67-defined subtypes and proteomics-defined subtypes (LA-enriched vs. LA cases, LB1-enriched vs. LB1 cases),indicating they are consistent in the molecular profile. Differential analysis was performed to compare LB1-enriched versus LA-enriched cases, resulting in 672 significantly differentially expressed proteins defined at false discovery rate (FDR) < 0.05 and $|\log_2(\text{fold change})|>1$. 353 of the 672 proteins were correlated with mRNA at Pearson correlation > 0.39 as reported in the CPTAC-BC study or cBioPortal for Cancer Genome, and their coding genes were used for progression free interval (PFI) analysis based on TCGA RNA-seq data in the TCGA ER+/HER2- cases (662 cases, c.f. Huo *et al.* JAMA Oncology 2017). 90 of the 353 coding genes significantly associated with PFI were detected at p-value<0.05. Unsupervised hierarchical clustering method and principal component analysis (PCA) of the 90 genes were applied to our cohort to investigate the clustering performance and 94.2% of the cases were clustered correctly using support vector machine (SVM) method after PCA analysis. Biological process and molecular function GO term over-representation analyses of the 90 coding genes were performed separately. Some significant and biologically meaningful GO terms were identified at FDR<0.05.
**Conclusions:** We identified a set of biomarkers that can be potentially employed as proteomic or gene signatures to stratify ER+/HER2- BC into low risk and high-risk groups.
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Physician adoption and molecular landscape of next-generation sequencing in breast cancer patients from community-based clinics

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**Background:** Molecular biomarkers such as the expression status of hormone receptors (HR) and HER2 influence disease diagnosis, prognosis, and treatment decisions in breast cancer patients. Recent advances in genetic sequencing technologies and targeted therapies have revealed additional actionable biomarkers including PIK3CA, ESR1, and BRCA1/2; however, it remains unclear whether physicians in community-based clinics are universally adopting molecular profiling practices. Here, we describe the utility of next generation sequencing (NGS) in the care of breast cancer patients in community-based clinics with a focus on physician behaviors and molecular landscapes.
**Methods:** Sarah Cannon provides clinical research services to medical oncology practices who order NGS panels as part of standard of care. Genospace, Sarah Cannon's web-based precision medicine platform, links NGS test results with electronic medical records to identify and analyze clinico-genomic data of molecularly-profiled cancer patients. Here, a total of 2,673 NGS reports from 2,313 unique patients dated between January 2014 and December 2019 were analyzed. Hormone statuses were abstracted from physician notes using natural language processing capabilities and manual abstraction. Linear regression modeling was used for statistical analysis.
**Results:** Physician ordering of NGS tests for breast cancer patients increased 6.3-fold from 2014 to 2019. Ordering of plasma-based NGS tests increased from 0.6% (*versus* 99.4% tissue) in 2014 to 47.0% (*versus* 53.0% tissue) in 2019. The time from initial diagnosis to NGS results increased from a median of 1008 days in 2015 to 1296 days in 2019 ($p < 0.05$), while the time from specimen collection to NGS test results (tissue only) decreased from 53 days in 2015 to 28 days in 2019 ($p < 0.01$). The majority of NGS-tested breast cancer patients were HR+/HER2- (62.6%), followed by HR-/HER2- (21.5%), HR+/HER2+ (8.4%), HR-/HER2+ (4.4%), and HER2 equivocal (3.0%). Plasma-based NGS testing was utilized more commonly in HR+ cancers (43.4% of HR+; 25.3% of HR-). In agreement with published studies, BRCA1 alterations were enriched in HR- cancers (1.7% of HR+; 6.6% of HR-) and BRCA2 alterations were enriched in HR+ cancers (6.4% of HR+; 3.2% of HR-). Amplifications in CCND1 (21.7% of HR+; 2.2% of HR-) and FGFR1 (18.1% of HR+; 6.2% of HR-) were also enriched in HR+ cancers, as were mutations in ESR1 (18.9% of HR+; 1.0% of HR-). PIK3CA mutations occurred most frequently in HR+ cancers (45.0%), but were also present in HR- cancers (20.9%). TP53 mutations were comparatively high in HR- cancers (42.9% of HR+; 94.8% of HR-).
**Conclusions:** The usage of NGS for the care of breast cancer patients is increasing in community settings. Plasma-based NGS tests are ordered more frequently in HR+ cancers, likely as a result of difficult-to-biopsy and poor yield bone-only disease. Despite increased testing frequencies, NGS tests are ordered later-in-care which may be a reflection of earlier diagnosis or the development of more efficacious standard of care therapies in front line settings. The tissue specimens sent for sequencing are collected closer to the test date, indicating improved tissue processing systems and prioritization of fresh specimen collection for NGS testing. Overall, physicians are adopting NGS-testing as part of standard of care for breast cancer patients in the community setting and are discovering actionable mutations.

Frequency of detection of molecular biomarkers in NGS-tested breast cancer patients

| | | **Tissue** | **Tissue** | **Tissue** | **Tissue** | **Plasma** | **Plasma** | **Plasma** | **Plasma** |
|---|---|---|---|---|---|---|---|---|---|
| **Gene** | **Alteration** | **HR+/HER2-** | **HR-/HER2-** | **HR+/HER2+** | **HR-/HER2+** | **HR+/HER2-** | **HR-/HER2-** | **HR+/HER2+** | **HR-/HER2+** |
| ERBB2 | Amp | 1.1% | 0.5% | 45.4% | 67.9% | 0.0% | 0.8% | 10.4% | 45.5% |
| CCND1 | Amp | 21.3% | 1.7% | 21.8% | 5.1% | 7.5% | 1.7% | 5.2% | 0.0% |
| MYC | Amp | 9.3% | 15.5% | 18.5% | 17.9% | 1.3% | 5.8% | 1.3% | 9.1% |
| FGFR1 | Amp | 17.4% | 6.8% | 18.5% | 3.8% | 6.5% | 3.3% | 2.6% | 0.0% |
| PIK3CA | Mutation | 43.8% | 19.1% | 49.6% | 32.1% | 49.5% | 25.0% | 50.6% | 30.3% |
| ESR1 | Mutation | 19.4% | 1.2% | 13.4% | 0.0% | 41.7% | 4.2% | 31.2% | 0.0% |
| BRCA1 | Mutation | 1.9% | 7.2% | 0.8% | 3.8% | 5.1% | 5.0% | 2.6% | 9.1% |
| BRCA2 | Mutation | 6.7% | 3.6% | 5.9% | 1.3% | 8.8% | 5.8% | 14.3% | 3.0% |
| ERBB2 | Mutation | 3.4% | 1.4% | 11.8% | 6.4% | 9.5% | 1.7% | 15.6% | 12.1% |
| TP53 | Mutation | 42.2% | 94.7% | 51.3% | 93.6% | 65.8% | 96.7% | 68.8% | 93.9% |
| PTEN | Mutation | 8.8% | 10.6% | 2.5% | 3.8% | 12.6% | 10.8% | 7.8% | 6.1% |
| PALB2 | Mutation | 1.6% | 1.2% | 0.8% | 0.0% | 0.2% | 0.0% | 0.0% | 0.0% |
| MTOR | Mutation | 0.7% | 0.2% | 0.8% | 0.0% | 2.7% | 0.0% | 0.0% | 0.0% |
| ARID1A | Mutation | 9.0% | 4.8% | 12.6% | 2.6% | 11.0% | 11.7% | 7.8% | 3.0% |
| KRAS | Mutation | 3.2% | 3.1% | 0.8% | 2.6% | 6.5% | 8.3% | 5.2% | 6.1% |
| AKT1 | Mutation | 6.5% | 3.4% | 2.5% | 1.3% | 7.5% | 6.7% | 1.3% | 0.0% |
| | | n=856 | n=414 | n=119 | n=78 | n=602 | n=120 | n=77 | n=33 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS16-34

Phenotype and prognosis of patients with breast cancer and pathogenic *TP53* variants

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**Background:** The lifetime risk of cancer in individuals with Li Fraumeni syndrome (LFS) is more than 70% for men and more than 90% for women. Breast cancer (BC) is the most common type of cancer in premenopause women with pathogenic allelic *TP53* variants (PVs). However, little is known about the BC response to systemic therapy and the prognosis in these patients. We aim to analyze the phenotype and the outcomes of patients with LFS and BC. **Methods:** We evaluated a cohort of patients with PVs or likely PVs of TP53 with BC diagnosis treated from December 1999 to June 2020 from a single tertiary cancer center. Our primary objective is to evaluate the outcomes of these patients. Secondary objective is to describe the BC phenotype, characterizing the clinical and the pathological features.**Results:** Among 56 patients with PVs or likely PVs of TP53, 25 were diagnosed with BC. Median age at BC diagnosis was 39.2 years (range 23.4-57.4 years). The majority (N= 18, 72%) harbored a germline PV *TP53* p.R337H in heterozygosity status. The most common histology type was an invasive carcinoma of no special subtype, 73% were hormone receptor-positive, and 32% were HER2-positive. Three (12%) patients were metastatic at diagnosis. Seven (28%) of the patients with localized disease at diagnosis received neoadjuvant chemotherapy, and other 7 (28%) received adjuvant chemotherapy. Among patients treated with neoadjuvant chemotherapy, 5 (71%) had a tumor response, while 2 (29%) presented with disease progression. No pathologic complete response was achieved. After a median follow-up of 52.6 months, no deaths secondary to breast cancer occurred. Only 1 patient died due to another neoplasm (jaw osteosarcoma), and 3 (12%) patients developed radiotherapy-induced malignancies in the irradiated field. Conclusions: BC in patients with LFS is mainly the invasive carcinoma of no special subtype, enriched in hormone receptor and HER2 positivity. Although response to neoadjuvant chemotherapy is high, no pathologic complete response occurred in this cohort. Favorable outcomes were observed, with a high BC specific survival. Secondary malignancies remain a major concern. Larger cohorts should test whether new genes act as modifiers of p53 function and breast cancer susceptibility.

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**Publication Number:** PS4-34

# Multi-country study of the use of genomic assays in HR+, HER2- early breast cancer and characteristics of patients tested

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**Background** Recognized prognostic factors associated with increased risk of recurrence in patients (pts) with HR+, HER2- early breast cancer (EBC) are higher histologic grade, larger primary tumor size, and greater lymph node involvement. Genomic assays like Oncotype DX obtain prognostic information to indicate benefit of adjuvant therapy. The objective was to examine use of genomic assays and describe demographic, clinical, and pathological characteristics of pts tested.

**Methods** Real-world data was drawn from the Adelphi EBC I Disease Specific Programme, a cross-sectional observational study in France, Germany, Italy, Spain, United Kingdom (UK), United States (US) and Japan. 765 consulting physicians were surveyed, including questions on use of genomic assays to assess risk of recurrence. In each country, 20-64 of the physicians also completed patient record forms from Mar-Sep 2019 for up to 8 eligible pts with HR+, HER2- EBC.

**Results** Physicians in US (n=176), UK (n=52) and Spain (n=100) reported highest use of genomic assays to categorize patients from low to intermediate risk (US 61%; Spain 57%; UK 65%) and from intermediate to high risk of recurrence (US 64%; Spain 67%; UK 65%). Lowest use was in Japan (n=134), 13% and 20%, respectively. Oncotype DX was consistently reported as the most frequently used genomic assay to assess the risk of recurrence (see table). Patient record forms were completed for 2447 pts (98% female, mean age 59.6 years, SD 13.0). Frequency of Oncotype DX testing varied by stage, with less testing in stage III pts (stage I 26% (194/755); stage II 20% (221/1130); stage III 11% (56/505) p<0.0001). Similar patterns were seen across most countries, but often not statistically significant. Germany had similar use across stages (~20%). Oncotype DX testing was less frequent in pts with grade 3 tumors (grade 1 21% (100/484); grade 2 22% (203/908); grade 3 12% (44/384); p<0.0001). Similar patterns were seen across countries except UK and Spain where testing was less in pts with grade 1 tumor, but not statistically significant. Oncotype DX testing was less frequent in large tumors (size <2cm 19% (161/865); size 2-5cm 20% (254/1265); size >5 cm 11% (11/105); p=0.0503). Similar patterns were seen across countries except Italy, but generally not significant. Oncotype Dx testing was less frequent in pts >50 years (age ≤50 25% (161/657); age >50 18% (318/1790); p=0.0003). Similar patterns were seen across countries, and significant in Germany (p=0.0029) and Italy (p<0.0001), except for US and Japan where testing was very similar between age groups. Oncotype DX testing was less frequent in node +ve pts, 14% of 733 pts, compared with 23% of 1593 node -ve patients (p<0.0001). Similar patterns were seen in most countries, with some statistically significant differences. Germany and Japan were exceptions, Oncotype DX testing was used for node +ve pts more than node -ve pts. Difference was statistically significant in Japan (p=0.032).

**Conclusion** Use of genomic assays to assess pt risk of recurrence varied across countries. The most commonly used assay was Oncotype DX. Oncotype DX testing was less frequent amongst stage III, grade 3, large, node +ve tumors or age >50, although there were some important country variations. These data contribute to the understanding of drivers in adopting multi-gene assays within clinical practice.

| Genomic Assay | Total(n=729)* | US (n=171) | Japan (n=122) | France (n=93) | Germany (n=97) | Italy (n=96) | Spain (n=100) | UK (n=50) |
|---|---|---|---|---|---|---|---|---|
| Oncotype DX | 67% | 91% | 45% | 54% | 64% | 60% | 63% | 94% |
| Adjuvant! Online | 30% | 23% | 25% | 29% | 29% | 34% | 43% | 42% |
| Mammaprint | 29% | 37% | 30% | 17% | 24% | 21% | 52% | 0% |
| Breast Cancer Index | 17% | 29% | 25% | 13% | 14% | 17% | 2% | 4% |
| EndoPredict | 13% | 8% | 20% | 20% | 12% | 11% | 8% | 18% |
| Prosigna | 11% | 8% | 11% | 22% | 4% | 6% | 21% | 8% |

* 729/765 physicians who assessed all or some of their patients with EBC for risk of recurrence

**Publication Number:** PS17-34

Proto-oncogene PELP1 interactions with SETDB1 contribute to aberrant activation of AKT1 in breast cancer

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**BACKGROUND:** Hyperactivation of PI3K/Akt signaling is implicated in breast cancer (BCa) progression. SETDB1, a methyltransferase, is also implicated in BCa, however, the mechanism remains elusive. Recent studies have shown SETDB1 can methylate non-histone substrates such as Akt1 and contribute to its aberrant activation, thus leading to tumor progression. PELP1 is a proto-oncogene which is overexpressed in BCa and participates in both the nuclear and extra nuclear functions of various nuclear receptors. In a subset of BCa, PELP1 uniquely localizes in the cytoplasm and contributes to endocrine therapy resistance. The objective of this study is to characterize the significance of PELP1 in SETDB1 mediated Akt signaling in BCa progression.
**METHODS:** Using yeast two-hybrid screening, we identified PELP1 as a novel interacting protein of SETDB1. Functional significance of cross-talk was tested using MTT, proliferation, stemness and colony formation assays. Mechanistic studies were conducted using immunoprecipitation, RNA-seq, shRNA, overexpression, Western blotting, and RT-qPCR. Biological significance of PELP1 and SETDB1 in endocrine therapy resistance was also examined.
**RESULTS**: Analyses of TCGA databases showed that SETDB1 is highly expressed in BCa and associated with poor clinical outcome. Further, SETDB1 expression is positively correlated with PELP1 expression in BCa ($r=0.30$, $p<0.0001$). Immunoprecipitation assays using multiple BCa cell lysates confirmed the interaction of SETDB1 with PELP1. Using two different shRNAs targeting SETDB1 and multiple BCa model cells, we provided evidence that SETDB1 plays an important role in the proliferation of BCa cells. SETDB1 upregulation is sufficient to accelerate proliferation and PELP1 knockdown attenuated SETDB1 oncogenic functions. SETDB1 overexpression contributed to resistance to tamoxifen treatment, while PELP1 knockdown re-sensitized cells to therapy. RNA-seq identified Akt signaling pathways were activated by SETDB1 in BCa. Mechanistic studies showed that SETDB1 overexpression increased Akt phosphorylation and its downstream signaling, while PELP1 knock down attenuated SETDB1 mediated Akt activation in both MCF7 and ZR75 models. Furthermore, in BCa model cells that uniquely express PELP1 in cytoplasm, knockdown of SETDB1 reduced activation of Akt and its downstream pathways.
**CONCLUSIONS**: Our study results suggest that the PELP1/SETDB1 interactome plays an important role in aberrant Akt activation. Drugs that target PELP1/SETDB1 axis may be useful in modulating aberrant Akt signaling. Supported by VA grant I01BX004545.

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# Differential efficacy of pegfilgrastim (Peg) in patients (pts) with breast cancer (BC) versus other cancer types for the prevention of docetaxel (Doc) chemotherapy-induced neutropenia (CIN)

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**Introduction**: Peg and other G-CSFs are widely used in BC patients receiving myelosuppressive chemotherapy. We previously reported that Peg's mechanism of action (MoA) for CIN -prevention protects in week 2 of the cycle. BC pts receiving Doc/Doxorubicin/Cyclophosphamide (TAC) are unprotected in week 1. [Study BPI-2358-106 (NCT03102606) Blayney, St Gallen 2019]. In this study, the novel CIN agent Plinabulin (Plin), with a MoA different, yet complimentary to Peg CIN, prevented severe CIN in week 1 of the Cycle (C), and given in combination with Pegflgrastim, offered superior protection throughout the entire cycle. Other Study 106 results indicated that monotherapy Peg is a sub-optimal CIN prophylaxis strategy in TAC-treated BC pts. In Study BPI-2358-105 (NCT03102606) we evaluated Peg monotherapy as CIN preventive therapy in BC pts.
**Methods**: In Study 105, BC, lung (NSCLC) and prostate cancer (HRPC) pts with at least 1 risk factor as per NCCN guidelines, received Doc 75 mg/m2 with either Peg 6mg (n=53) or Plin 40 mg (n=52), and had frequent blood draws in C1 for Neutrophil count assessment. Grade (Gr) 4 Neutropenia (N) frequency in C1, Duration of Severe Neutropenia (DSN) in C1, and frequency of clinical sequelae of N (Hospitalizations, Infections, FN, antibiotic use, chemotherapy dose reductions) in C1 to C4 were calculated in BC (n=27) and NSCLC/HRPC (n=26) pts receiving Doc 75 mg/m2. There were 9 pts in the HRPC group in the Peg arm.
**Results:**No HRPC and 4% (1pt) NSCLC pts of peg-treated developed Gr 4 N, whereas 16% of Peg-treated BC pts developed Gr 4 N. Gr 4 N frequency over time in C1 was significantly higher in BC pts vs NSCLC/HRPC pts ($p<0.016$; Cochran-Mantel-Haenszel test; see table below) with Peg. DSN in BC pts was >5 times longer ($p<0.005$; NBR test) in BC pts vs NSCLC/HRPC pts. DSN was 0.36 Day (D) (95% CI: 0.28; 0.49) in BC pts vs 0.076 Day (95% CI: 0.03; 0.12) in NSCLC/HRPC pts with Peg. Numerically more BC pts vs NSCLC/HRPC pts had clinical sequelae of N with Peg.

| Gr4N % | Baseline | C1D1 | C1D2 | C1D6* | C1D7 | C1D8 | C1D9 | C1D10 | C1D15 |
|---|---|---|---|---|---|---|---|---|---|
| BC | 0% | 0% | 0% | 16% | 12% | 4% | 4% | 4% | 0% |
| NSCLC/ HRPC | 0% | 0% | 0% | 4% | 4% | 0% | 0% | 0% | 0% |

*On C1D6, Gr 4 frequency in the Plin arm was 0% in BC pts
**Conclusions**: In BC pts treated with Peg monotherapy after Doc 75 mg/m2, Peg is significantly less effective for CIN prevention compared to NSCLC/HRPC pts. The sub-optimal efficacy of Peg was due to its protection occurring in week 2 of the Cycle, leaving a significant number of pts unprotected in week 1 of the Cycle. The demonstrated effectiveness of Plinabulin in week 1 of the Cycle in BC pts, when combined with Peg could offer superior CIN protection vs Peg alone in BC pts receiving Doc.

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The association of race and socioeconomic status with overall survival in women with breast cancer in the southern community cohort study

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**Background:**Breast cancer outcomes in minority and low socioeconomic status populations are not clearly defined due to underrepresentation of these underserved populations in breast cancer clinical trials and population-based studies. The Southern Community Cohort Study (SCCS), a prospective cohort of underserved, predominantly Black participants, provides a unique opportunity to evaluate disparities in breast cancer outcomes. We sought to examine the association between race and socioeconomic status (SES) and *overall survival (OS) in women with localized breast cancer* in the SCCS.
**Methods:**The SCCS enrolled approximately 86,000 participants aged 40-79 from 12 Southeastern states between 2002-2009, 86% of whom were enrolled at Community Health Centers. This analysis includes women diagnosed with incident localized breast cancer (stage I-III) identified through annual cohort linkage with 12 state cancer registries through December 20, 2017. Demographic data including participant age, self-reported history of diagnosed diabetes, body mass index (BMI), race, annual household income, and insurance coverage were obtained from baseline surveys. Tumor grade and stage were obtained from state cancer registries, and survival data were obtained from death registry records. Immunohistochemical (IHC) subtype was determined from tumor estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status obtained from cancer registry records and pathology reports. Survival time was defined as the number of months between initial breast cancer diagnosis and death from any cause. Descriptive analyses including mean (standard deviation) and number (%) were used to summarize clinical and sociodemographic characteristics by race. Multivariable Cox survival analysis was used to evaluate OS by race and annual household income, adjusting for age, insurance, stage, IHC subtype, diabetes, and BMI.
**Results:**Of the 1347 women diagnosed with incident breast cancer, 1016 had localized disease (stage I-III) and comprised our analytic sample. Compared to White women, Black women were more likely to have lower income, higher prevalence of triple negative breast cancer (TNBC), grade III tumors and stage III breast cancer (Table 1). After adjusting for clinical and sociodemographic factors, Black women had similar OS compared to White women (HR 0.67; 95% CI 0.42-1.07). However, after adjusting for race, women with a household income ≥ $25,000 had an improved OS compared to those with annual household income < $25,000 (HR 0.53; 95% CI 0.30-0.93).
**Table 1**. Patient characteristics overall and by race

| **Patient Characteristics** | **Total(N=1016)** | **Black(N=667)** | **White(N=349)** | **P-value*** |
|---|---|---|---|---|
| **Age at diagnosis, years (Mean, SD)** | 61 (9) | 60 (9) | 63 (9) | |
| **Income, annual household (N, %)** < $25,000 ≥ $25,000 | 719 (71)297 (29) | 503 (75)164 (25) | 216(62)133 (38) | <0.001 |
| **Insurance (N, %)** Private insurance Medicare Medicaid Uninsured | 220 (29)331 (43)178 (23)34 (5) | 152 (29)209 (40)139 (26)26 (5) | 68 (29)122 (51)39 (16)8 (3) | 0.005 |
| **Diabetes (N, %)** No history of diabetes History of diabetes | 736 (74)258 (26) | 469 (72)183 (28) | 267 (78)75 (22) | 0.04 |
| **BMI, kg/m$^2$ (N, %)** 18.5-30.0 kg/m$^2$ 30.0+ kg/\\ | 411 (40)605 (60) | 239 (36)428 (64) | 172 (49)177 (51) | <0.001 |
| **IHC subtype (N, %)** HR+,HER2- HR+,HER2+ HR-,HER2- TNBC | 392 (69)55 (10)34 (6)86 (15) | 255 (65)38 (10)26 (7)75 (19) | 137 (79)17 (10)8 (5)11 (6) | 0.001 |
| **Grade (N, %)** I II III | 188 (20)383 (41)372 (39) | 111 (18)239 (38)277 (44) | 77 (24)144 (46)95 (30) | <0.001 |
| **Stage (N, %)** I II III | 460 (45)383 (38)173 (17) | 278 (42)261 (39)128 (19) | 182 (52)122 (35)45 (13) | 0.003 |

HR = Estrogen receptor (ER) and/or progesterone receptor (PR)* denotes p-value for White compared Black women
**Conclusion:** In a low-income, medically underserved population, Black women with localized breast cancer had similar OS compared to White women. However, socioeconomic disparities were observed, with worse OS for women with low annual household income. Future studies focused on minority, underserved groups are imperative to better understand the non-biological and biological factors contributing to disparities in survival among women with breast cancer.

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High rates of *BRCA1* and *BRCA2* germline mutations among Arab patients with triple-negative breast cancer

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**Background**: Patients with triple-negative (TN) disease, which represent 10-15% of all breast cancer cases, is associated with the worst prognosis among all breast cancer subtypes. Because of higher risk for *BRCA* mutation, patients diagnosed at age ≤60 years with triple-negative disease should undergo genetic testing. Identification of *BRCA1* or *BRCA2* mutation has clinical impact on breast and ovarian cancer prevention and treatment. Many drugs were recently approved for patients with *BRCA* mutation carriers. We here investigate the patterns and prevalence of *BRCA1* and *BRCA2* mutations among Arab patients diagnosed with this breast cancer subtypes and treated at our institution. **Patients and Methods**: We utilized our database of all breast cancer patients, from Jordan and neighboring Arab countries, tested for *BRCA* mutations (n=1302) as per the NCCN guidelines. Patients with no expression of estrogen (ER) or progesterone (PR) receptors and negative for HER2 (triple-negative) were enrolled regardless of their age or family history. Following a detailed genetic counselling in a clinic established for this purpose, *BRCA* testing was then performed at 3 reference labs in UK and USA. *BRCA1* and *BRCA2* mutations were classified as pathogenic/likely pathogenic and variant of uncertain significance (VUS). **Results**: During the three-year study period, a total of 171 (13.1%) of all patients in database fulfilled our inclusion criteria. Twenty-two (12.9%) patients were from Palestine, Syria and Iraq. Median age was 41 (range, 19-77) years and all were females. Among this group, a total of 45 (26.3%) were tested positive for *BRCA1* (n=32, 18.7%) or *BRCA2* (n=13, 7.6%) while 12 (7.0%) others had VUS. Mutations were detected in 26 (31.7%) of 82 patients who were triple-negative and diagnosed at age 40 years or younger. Additionally, 26 (36.6%) of 71 patients with triple-negative disease who had one or more close relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) had positive *BRCA1* or *BRCA2* mutation, too. In multivariate analysis, the impact of younger age on mutation rates was considered insignificant (OR: 1.86; 95%CI: 0.89-3.91; p=0.10). However, breast cancer diagnosis at any age with 2 or more close relatives with breast cancer have is associated with a significantly higher *BRCA* mutation rate (OR: 2.76; 95%CI: 1.13, 6.71; p = 0.03). **Conclusions**: Arab patients with triple-negative breast cancer subtype have very high *BRCA1* or *BRCA2* mutation rates. Family history of breast cancer in close relatives further increase this risk.

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**Publication Number:** PS2-34

Concordance of breast cancer biomarker testing in core-needle biopsy and surgical specimens: A single institution experience

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Accurate diagnostic biomarker testing, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2) expression profile, is crucial to appropriate management decisions in breast cancer. Receptor status testing is typically performed on the initial core needle biopsy (CNB) and surgical specimen (SS). The rate of concordance between CNB and SS is unclear as is the impact this has on clinical decision making. The current guidelines on retesting are vague, which results in individual institutions and providers determining retesting policies. Several studies worldwide have assessed the concordance of receptor testing with mixed conclusions. We aim to determine concordance between CNB and SS, and whether this leads to clinically relevant management changes. A retrospective analysis was performed on patients with invasive breast cancer with available CNB and SS pathology at our institution between January 2010- May 2020. Patients who were treated with primary surgical resection and neoadjuvant chemotherapy with residual disease were included. Concordance rates between CNB and SS were assessed for ER, PR, and Her2 IHC/ FISH amplification. ER and PR status were defined per NCCN guidelines as “positive,” “low-positive (ER)” or “negative.” Major discrepancy was defined as a change in label of “positive” or “negative”. Minor discrepancy was defined as change >10% without a “positive” or “negative” label change. Major discordance in Her2 was defined as change in label of “positive” or “negative” based on IHC or FISH amplification results. A minor discrepancy was a change in Her2 IHC (0-3) or FISH amplification without change in label of “positive” or “negative.” The clinical impact of discordant results was determined by investigator review. 748 patients met the eligibility criteria, and 64 of these patients received neoadjuvant therapy. For ER, there was 90.6% concordance, 2.2% major discordance, and 7.8% minor discordance between CNB and SS. For PR, there was 59.64% concordance, 11.9% major discordance, and 28.46% minor discordance. For Her2, there was 54.7% concordance, 1.6% major discordance, and 43.8% minor discordance. Of major discordance, ER (43.8%) led to the most change in management compared to Her2 and PR (12.5% and 2.2%, respectively). Retesting Her2 on SS did not change management when initial CNB was Her2 positive. For major discrepancies, patient demographics, tumor characteristics, treatment course, recurrence, and survival were reviewed. Although discordance was more common in PR and Her2 than ER biomarker profiles, major discordance leading to treatment changes were more common in ER and Her2. Retesting ER and Her2 on CNB and SS may be more clinically beneficial than retesting PR. Guidelines for retesting receptor profiles on CNB and SS are needed to best guide patient care management decisions that maximize clinical benefits while minimizing healthcare costs.

**Table: Concordance of ER, PR, and HER2 Expression Profile**

| | **Concordance** | **Major Discrepancy** | **Minor Discrepancy** | **# Patients with Change in Treatment with Major Discrepancies** |
|---|---|---|---|---|
| **ER** | 90.6% | 2.2% | 7.8% | 7/16 (43.8%) |
| **PR** | 59.6% | 11.9% | 28.5% | 2/90 (2.2%) |
| **Her2** | 54.7% | 1.6% | 43.8% | 5/12 (12.5%) |

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**Publication Number:** PS6-34

# Real life impact of TAILORx trial in a multi-center healthcare system: A comparison of management practice one year before and after the release of the trial

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Introduction: Oncotype DX is a 21 gene assay which has been shown to be useful in predicting the risk of breast cancer recurrence. TAILORx trial compared survival with the use of hormonal therapy (HT) vs. chemo-hormonal therapy (CHT) in early-stage, Hormone receptor-positive, HER2-negative, axillary lymphnode-negative breast cancer who had an Oncotype DX recurrence score in the intermediate range (11-25), The study found HT to be non-inferior to CHT in that group, especially in women older than 50. **Materials and methods:** We studied 1084 patients with hormone receptor-positive, HER-2 negative early stage breast cancer at a multi-center setting in South Dakota and North Dakota who were diagnosed one year before and after the results of the TAILORx trial were presented. We aimed to identify any change in practice after the trial was published as compared to the year prior. Chi-square analysis was used to compare demographics of patients and management practices before and after the TAILORx trial publication. **Results:** We did not find any statistically significant change in Oncotype DX testing frequency across various age groups, tumor sizes, tumor grades or amongst patients who had lymphnode negative or one axillary lymph node positive disease (Table-1).We also did not find any statistically significant difference in management of early stage breast cancer patients (Table-2) that matched our inclusion criteria and had an intermediate risk Oncotype Dx score of 11-25(n=266). **Conclusion:** Our results indicate that management of early stage breast cancer at our center was not significantly impacted by the results of TAILORx. Rare use of CHT prior to TAILORx reporting suggests that practice prior to this trial was largely based on earlier trials suggesting minimal benefit for CHT in the intermediate risk group. Larger studies may be able to identify smaller changes in practice resulting from this study and should be pursued.

| | | Before TAILORx□ (N=512) | After TAILORx□ (N=572) | p-value |
|---|---|---|---|---|
| | | n (%) | n (%) | |
| **Overall** | | 204 (40) | 234 (41) | 0.7212 |
| **Age** | | | | |
| < 50 | | 44 (46) | 31 (37) | 0.2254 |
| 50 - 69 | | 121 (46) | 146 (49) | 0.4519 |
| Equal or > 70 | | 39 (26) | 57 (30) | 0.3986 |
| **Tumor Size** | | | | |
| < 1 cm | | 41 (25) | 50 (28) | 0.5388 |
| 1 - 1.9 cm | | 97 (51) | 122 (53) | 0.6055 |
| 2 - 2.9 cm | | 40 (44) | 44 (42) | 0.7728 |
| 3+ cm | | 24 (39) | 18 (32) | 0.4161 |
| **Tumor Grade** | | | | |
| | 1 | 56 (39) | 63 (42) | 0.6200 |
| | 2 | 113 (48) | 135 (47) | 0.8542 |
| | 3 | 34 (26) | 35 (27) | 0.9768 |
| **LN Positive** | | 31 (33) | 36 (32) | 0.9403 |

Table-1: Frequency of Oncotype Dx testing one year before and after the TAILORx trial was released overall and in various sub-categories based on age of the patient, tumor size and tumor grade. Last row indicates the frequency comparison in patients who had one axillary lymph node positive status.

| | **Before TAILORx** | **After TAILORx** |
|---|---|---|
| **HT + CT** | n=15 | n=13 |
| | 5.91% | 5.12% |
| **HT Alone** | n=108 | n=118 |
| | 42.52% | 46.46% |

Table-2: Comparison of treatment received by patients in the intermediate risk group (score:11-25) based on Oncotype Dx test before and after the release of TAILORx trial , Chi sq p-value=0.5635, HT (Hormonal Therapy), CT (Chemotherapy).

**Publication Number:** PS10-34

Clinical outcomes in *de novo* metastatic HER2-positive inflammatory breast cancer

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**Background**: Advances in HER2-directed therapy have significantly improved survival in HER2+ metastatic breast cancer. Approximately 30% of *de novo* metastatic inflammatory breast cancer (mIBC) is HER2+, though there has been limited IBC representation in clinical trials evaluating the role of HER2-directed agents as first-line metastatic therapy. Elevated rates of locoregional progression or recurrence (LRPR) with systemic therapy alone also raise the question of whether trimodality therapy (TMT) may improve outcomes in IBC patients (pts) with limited metastatic disease, particularly in the setting of increasingly effective anti-HER2 therapy. **Methods**: Pts diagnosed with *de novo* HER2+ mIBC were identified from an IRB-approved IBC registry at Dana-Farber Cancer Institute. Clinical, pathology and treatment data were manually abstracted by chart review. Progression-free survival (PFS) was defined as time from IBC diagnosis to LRPR, distant progression/relapse or death (in the absence of event, censored at date of last follow-up). Overall survival (OS) was defined as time from IBC diagnosis to death from any cause or censored at date last known alive. For pts who underwent surgery of the primary tumor, pathologic complete response (pCR) was defined as no residual invasive carcinoma in the breast and axilla and survival was estimated from date of surgery. Median PFS and OS were estimated by Kaplan-Meier method; cumulative incidence of CNS metastasis and LRPR were estimated with death as competing risk. **Results**: 78 pts diagnosed between 1998-2019 with *de novo* HER2+ mIBC (41 hormone receptor (HR)-positive; 37 HR-negative) were identified. Median age at diagnosis was 53 years (yr; range: 24-91). Sites of metastatic disease at presentation included bone only (n=12), lymph node/contralateral chest wall only (n=17), bone and lymph node (n=5), visceral (n=40) and CNS with extracranial disease (n=4). As initial HER2-directed therapy, 37 pts received trastuzumab (H), 40 H plus pertuzumab and 1 T-DM1. At a median follow-up of 2.7 yr in the overall cohort, median PFS was 1.0 yr (IQR: 0.5-2.8 yr; 60 events) and median OS was 4.6 yr (IQR: 2.9-8.7 yr; 39 deaths). 34 pts had CNS metastasis with a cumulative incidence of 20% and 28% at 1 and 2 yr, respectively. LRPR developed in 26 pts, of which 16 occurred within 12 months (mo) of diagnosis. Cumulative incidence of LRPR at 1 and 2 yr was 21% and 29%, respectively. In 41 pts (53%), mastectomy was performed after receipt of systemic therapy. Median time from IBC diagnosis to surgery was 7.5 mo (IQR: 6.0-9.9 mo). Radiation was administered in 33 pts, 3 pre- and 30 post-mastectomy. Median OS from surgery was 5.2 yr (IQR: 3.1-8.4 yr). 9/41 pts (22%) achieved pCR; all pCR pts were alive at 1.3-8.9 yr since surgery. To investigate the value of therapy for locoregional control, a landmark analysis was performed in the subset of pts alive and LRPR free at 12 mo from diagnosis (n=56). 27 had surgery within 12 mo from diagnosis and 29 did not. LRPR occurred in 10/56; 9 were among pts who did not undergo surgery. Cumulative LRPR incidence at 1 and 2 yr since the 12 mo landmark was 21% and 29%, respectively, in pts who did not undergo surgery, and 0% at both time points in pts who had surgery (1 LRPR at 8 yr). **Conclusion**: Long-term outcomes in *de novo* HER2+ mIBC are overall similar to those reported in metastatic HER2+ non-IBC. More than half of pts underwent systemic and local therapy with good locoregional control and prolonged survival, suggesting a potential role for aggressive local therapy in this mIBC subset with favorable prognosis and effective systemic therapy. The high incidence of early CNS involvement in *de novo* HER2+ mIBC prompted us to explore this group in detail (Warren SABCS 2020 abstract). Larger studies are needed to better understand the effectiveness of TMT in HER2+ mIBC, highlighting the importance of collaborative research efforts in this rare subset.

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**Publication Number:** PS1-35

Combined primary site resection and metastasectomy in patients with metastatic breast cancer

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**Background**: We previously reported a significant survival benefit of surgery in patients with *de novo* stage IV breast cancer. However, prospective trials, focusing predominantly on the impact of lumpectomy or mastectomy in metastatic breast cancer (mBC) (versus metastatic resection, i.e. 'metastasectomy'), have yielded inconclusive results. We sought to assess whether a combination of surgical approaches may be associated with optimal survival.
**Methods**: This is a retrospective analysis of patients diagnosed with mBC between 2004 and 2016 using the *National Cancer Database*. We identified a cohort of patients undergoing both primary site resection and metastasectomy, describing them using frequency and distribution statistics. Subsequently, we conducted a multivariate Cox regression survival model to understand whether this surgical approach was associated with better overall survival (OS) compared to patients undergoing lumpectomy/mastectomy alone, metastasectomy alone, or no surgery. This model controlled for relevant sociodemographic and clinicopathologic factors. Finally, we used the Kaplan-Meier method to demonstrate the utility of surgery in: 1) patients with mBC involving only 1 site, stratifying by tissue type as bone, brain liver, or lung and 2) patients with mBC involving >1 site.
**Results**: A total of n=55,125 patients with mBC were included in this analysis. N=13,478 patients underwent lumpectomy/mastectomy alone, n=2116 underwent metastasectomy alone, n=912 underwent combined lumpectomy/mastectomy + metastasectomy, and n=38,619 did not undergo surgery. Of those that underwent *combined* resection, n=713 (78.2%) were White; n=132 (14.5%) were Black, and n=47 (5.2%) were Asian. Multivariate Cox regression survival modeling showed mBC patients undergoing combined resection exhibited the best OS (median OS: 50 months, HR 0.882, p=0.012) compared to patients undergoing lumpectomy/mastectomy alone (median OS: 43 months – reference category); while patients undergoing metastasectomy alone had worse OS (median OS: 30 months, HR 1.327, p<0.0001), and those who did not undergo surgery had the worst OS (median OS: 21 months, HR 1.824, p<0.0001). Kaplan-Meier modeling corroborated this survival benefit when mBC involved 1 site *and* when it involved multiple sites (log-rank p<0.001). In further subgroup univariate analysis of patients with metastasis to 1 site, patients undergoing combined lumpectomy/mastectomy + metastasectomy exhibited superior survival compared to lumpectomy/mastectomy alone, when metastatic disease involved the liver or lung (log-rank p<0.001), but not when it involved bone or the brain. Additionally, in patients with mBC involving only the lung, metastasectomy alone was also associated with a superior survival benefit to lumpectomy/mastectomy alone (log-rank p<0.001), highlighting the potential impact of pulmonary metastasectomy.
**Conclusions**: Patients with newly-diagnosed mBC undergoing primary site resection in combination with metastasectomy exhibited longer survival compared to those undergoing only lumpectomy/mastectomy and those not undergoing surgery, particularly when metastasis involved only the liver or lung.

**Table 1:** Multivariate Cox regression model for overall survival in *de novo* stage IV patients

| | De Novo Stage IV Patients (n=55,125)[a] | | | |
|---|---|---|---|---|
| Variable | No. (%) | Median OS (95% CI)[#] | HR (95%CI) | *p*-value |
| Surgical approach | | | | <0.0001 |
| Lumpectomy/mastectomy alone (ref) | 13,478 (24.4%) | 43 (42-44) | 1 | |
| Metastasectomy alone | 2116 (3.8%) | 30 (28-32) | 1.327 (1.249-1.410) | <0.0001 |
| Lumpectomy/mastectomy + metastasectomy | 912 (1.7%) | 50 (45-54) | 0.882 (0.799-0.973) | 0.012 |
| No surgery | 38,619 (70.1%) | 21 (21-22) | 1.824 (1.774-1.875) | <0.0001 |
| Age | | | | <0.0001 |
| <50 (ref) | 10,057 (18.2%) | 39 (38-41) | 1 | |
| 50-70 | 29,437 (53.4%) | 29 (28-29) | 1.203 (1.166-1.242) | <0.0001 |
| >70 | 15,631 (28.4%) | 16 (15-17) | 1.623 (1.566-1.681) | <0.0001 |
| Race | | | | <0.0001 |
| White (ref) | 40,128 (72.8%) | 27 (27-28) | 1 | |
| Black | 9476 (17.2%) | 21 (21-22) | 1.097 (1.067-1.128) | <0.0001 |
| Hispanic | 3038 (5.5%) | 38 (36-40) | 0.733 (0.696-0.772) | <0.0001 |
| Asian | 1492 (2.7%) | 35 (33-38) | 0.812 (0.755-0.874) | <0.0001 |
| Other | 991 (1.8%) | 32 (28-36) | 0.805 (0.738-0.878) | <0.0001 |
| Charlson/Deyo comorbidity index | | | | <0.0001 |
| 0 (ref) | 44,069 (79.9%) | 29 (29-30) | 1 | |
| 1 | 7982 (14.5%) | 19 (18-20) | 1.274 (1.238-1.312) | <0.0001 |
| 2+ | 661 (1.2%) | 11 (10-12) | 1.644 (1.576-1.715) | <0.0001 |
| Molecular subtype | | | | <0.0001 |
| TNBC (ref) | 6721 (12.2%) | 12 (12-12) | 1 | |
| HR+, HER2- | 27,905 (50.6%) | 32 (31-32) | 0.610 (0.588-0.632) | <0.0001 |
| HR-. HER2+ | 4171 (7.6%) | 30 (28-31) | 0.556 (0.529-0.585) | <0.0001 |
| HR+, HER2+ | 7394 (13.4%) | 40 (38-41) | 0.592 (0.566-0.619) | <0.0001 |
| Radiation therapy | | | | <0.0001 |
| No (ref) | 36,848 (66.8%) | 24 (24-25) | 1 | |
| Yes | 17,715 (32.1%) | 31 (31-32) | 1.036 (1.012-1.060) | 0.004 |
| Hormonal therapy | | | | <0.0001 |
| No (ref) | 24,662 (44.7%) | 14 (14-15) | 1 | |
| Yes | 28,635 (51.9%) | 37 (36-37) | 0.449 (0.438-0.462) | <0.0001 |
| Chemotherapy | | | | <0.0001 |
| No (ref) | 25,360 (46.0%) | 21 (20-21) | 1 | |
| Yes | 28,342 (51.4%) | 32 (31-32) | 0.632 (0.616-0.649) | <0.0001 |
| Immunotherapy | | | | <0.0001 |
| No (ref) | 48,276 (87.6%) | 25 (25-25) | 1 | |

| | | | | |
|---|---|---|---|---|
| Yes | 6616 (12.0%) | 41 (40-43) | 0.668 (0.639-0.698) | <0.0001 |

[a]Number of cases with documented surgical status and survival data included in this model. [#]Median OS in months.

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Volumetric assessment of lymphedema with 3D sensor

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Volumetric assessment of lymphedema with 3D sensor: A new practical method
Secondary lymphedema of the upper extremities is an important quality-of-life issue for around 40% of patients who were treated for breast cancer and required axillary nodal dissection and radiotherapy. Volume measurement is an important aspect of diagnosis, follow up, and evaluation after conservative or surgical treatment for lymphedema. Until now, there have been complex techniques to assess volume of affected limbs: bioimpedance, liquid-displacement volumetry, CT, MRI. There is a need for a practical method of volumen assessment in lymphedema patients. The objective of the present study is to confirm whether or not 3D scanning for volumetric assessment is useful and correlates with direct perimeter measurement and indirect volume calculation. Methods: A 3D sensor (Structure Sensor, Occipital Inc) mounted on an Ipad (Apple, Inc.) was used to make a 3D model file of the affected limb, that was later analyzed by 3DsizeME software (TechMed 3D, Inc.) in a desktop computer. 3D model analysis allows to measure perimeters and volumes. Fifteen patients were measured, lymphedema and normal limbs (30 extremities) by this technique and were also measured with tape, as traditional method; results were compared to assess correlation. Results: There were not statistical difference between the two techniques (p 0.05). Table attached. Discussion: volumetric assessment by 3D sensor allows consistent and reproducible measurements. It is practical as we only need the space of an ipad, it can be performed in the clinic visit, by any doctor, nurse or physical therapist. It is not expensive, as the software charges US$10 by each analysis. It do not expose the patient to any harmful radiation, as is obtained by and infrared camera. Allows electronic records of all measurements. Average time to capture 3D model is 5 minutes. We think this new method is a valuable tool for any lymphedema clinic as volume measurement is important for disease evaluation and now, more important, with a growing field of surgical treatment for this disease.

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# Disparities in reporting of race and participation by race in genomic studies

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**Background:** Black/African American(B/AA) women are more likely to die of breast cancer as compared to White (Wh) women but are underrepresented in genomic research. Current genomic research that aims to classify breast cancer in order to personalize treatment in early breast cancer or to identify targets for therapy in advanced breast cancer fails to adequately represent B/AA women and other minority groups. This negatively impacts our current knowledge of breast cancer in non-Wh women and raises questions about the applicability of such testing in minority groups.
**Objective:** To evaluate the frequency of race reporting and representation of non-White women in genomic studies.
**Methods:** This a database study of all PubMed reported genomic testing studies to classify breast cancer for prognostic or predictive purposes. A PubMed search was conducted with articles from inception to the present with the following keyword search terms: “Breast Cancer Gene Expression Assay” AND “Race”, “PAM50” AND “Race”, “MammaPrint” AND “Race”, “Oncotype Dx” AND “Race”, “76 gene prognostic score” AND “Race”, Intrinsic Subtype” AND “Breast Cancer” AND “Race”. This search yielded 129 articles. 31 articles were removed due to lack of relevance.
**Results:** Of the 98 articles remaining after applying inclusion/exclusion criteria, 39 (40%) failed to report race in their analysis. Of the remaining 59 articles, 57 (96.61%) included Wh participants in their study, 54 (91.53%) included B/AA participants, 13 (22.04%) included Hispanics/Latinos, and 20 (33.90%) included Asians. Two of the major clinical trials of widely used testing such as Oncotype Dx and MammaPrint but did not report race in the pivotal studies. The genomic studies that included B/AA women were more likely to be health services research studies. The genomic studies that focused on triple-negative breast cancer (TNBC) were also more likely to have B/AA participants that ranged from 6%-52% of participants. For Oncotype Dx testing, B/AA women were more likely to have a later stage at diagnosis. While the number of patients with low risk was similar in all race groups, B/AA women were more likely to have high Ki-67 with uncertain significance of these findings.
**Conclusions:** A significant number of genomic studies did not report race and ethnicity. Racial and ethnic minorities continue to be under-represented in genomic research and this raises questions about the wider applicability of this research in these populations. Large clinical studies should specifically report the race and ethnicity of participants to inform decision making. In addition, funders should require reporting of race in genomic studies.

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**Publication Number:** PS13-35

Evaluation of age as a risk factor for CINV in breast cancer patients: Post-hoc analysis of the German real-world AkyPRO study

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**Background:** The primary objective of the prospective, non-interventional study (NIS) AkyPRO was the evaluation of quality of life (QoL) in adult cancer patients (pts) receiving NEPA as antiemetic prophylaxis. Secondary endpoints were efficacy and safety of NEPA. NEPA is administered as an oral fixed dose combination of 300 mg of the neurokinin-1-receptor antagonist - ($NK_1RA$) netupitant and 0,5 mg of the 5-hydroxytryptamin-3-receptor antagonist ($5\text{-}HT_3RA$) palonosetron once per chemotherapy cycle as primary prophylaxis for chemotherapy-induced nausea and vomiting (CINV) associated with moderately (MEC) or highly (HEC) emetogenic chemotherapy. In modern antiemetic guidelines, anthracycline/ cyclophosphamide (AC) - containing chemotherapy (AC-CT) is classified as HEC requiring triple antiemetic prophylaxis with a $5\text{-}HT_3RA$, a $NK_1RA$ and dexamethasone. Pts with breast cancer (BC) have additional risk factors for nausea and vomiting, like female sex and younger age, thus representing a high-risk group for CINV. Here, we present a post-hoc analysis of quality of life data and effectiveness of NEPA in the subgroup of BC pts in two age groups ≥ and < 60 years (y), who were treated with AC-CT in the AkyPRO NIS. **Methods:** The AkyPRO NIS has been conducted to evaluate quality of life and effectiveness of antiemetic prophylaxis with NEPA in cancer pts with various cancer entities receiving single day or two day MEC or HEC in a real life situation. Quality of life (QoL) was recorded by FLIE questionnaires. Effectiveness of NEPA as indicated by complete response (CR: no vomiting, no rescue medication), additional medication, and adverse events were recorded in patient diaries over three consecutive chemotherapy cycles. Patients and physicians documented overall antiemetic control on a 4-point scale (very good, good, satisfactory, poor). **Results:** In total, the AkyPro NIS enrolled 2,427 pts. 1,428 pts (65.7 %) had breast cancer. In this post hoc analysis 1,197 BC pts receiving AC-CT (83 % of all BC pts) were evaluated. 782 pts (65%) were <60y, 415 (35%) ≥ 60y old. Most pts received AC-CT in the adjuvant or neoadjuvant setting. Pts ≥ 60y reported a higher CR rate in the overall phase over 3 cycles (c1 88%, c2 90%, c3 88%) than pts <60y (c1 78%, c2, 78%, c77%). Pts ≥ 60y also experienced moderate or severe nausea less frequently, with the non-significant nausea (NSN) rate being 67, 67, 70% c1-c3 in these pts vs. 57, 59, 58% in c1-c3 in younger pts. QoL data confirmed this observation. Older pts reported more often to have no impact on daily life (NIDL) due to nausea (58-62% in c1-c3) than younger pts (50-54% in c1-c3). Comparison of patients' and physicians' perception of antiemetic treatment effectiveness revealed that in both groups the majority estimated the effectiveness of antiemetic prophylaxis with NEPA high and comparably well and good or very good.
**Conclusion:** This real-life study confirmed the effectiveness of NEPA in preventing CINV in the subgroup of BC pts receiving AC-chemotherapy. Pts ≥ 60y experienced less CINV compared to pts <60y, confirming that younger age represents a risk factor for CINV and indicating that the choice of an adequate antiemetic prophylaxis is crucial in this group of pts.

**Publication Number:** OT-12-01

# The FLEX real-world data platform explores new gene expression profiles and investigator-initiated protocols in early stage breast cancer

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**Background:** Genomic expression profiles have implications for the personalized treatment of breast cancer beyond clinical and pathological features by enabling the classification of breast cancers into molecular subtypes and providing prognostic information about the metastatic potential of tumors. However, full genome expression data should be combined with comprehensive clinical information to precisely stratify tumors into clinically actionable subgroups. The FLEX Registry aims to aggregate a large, real-world dataset, which will enable the discovery of novel genomic profiles to improve precision in the management of breast cancer, particularly in underrepresented patient subsets in traditional clinical trials. **Trial Design:** The FLEX Registry (NCT03053193) is a multi-center, prospective, observational trial for patients with stage I-III breast cancer whose primary tumor is analyzed by MammaPrint, with or without BluePrint.The primary objective of FLEX is to create a large scale, population-based registry that links comprehensive clinical data with full genome expression data to elucidate new prognostic and/or predictive gene associations in a real-world setting. The FLEX Registry employs a shared study infrastructure to develop and investigate hypotheses for targeted subset analyses and/or clinical trials based on full genome expression data. The adaptable protocol is designed to be amended with the inclusion of additional targeted sub-studies. Patients enrolled in the initial study are eligible for inclusion in sub-studies for which they meet all eligibility criteria and additional consent is not required. Data will be collected on patients from diagnosis through10 years of follow-up and any necessary additional clinical data will be collected as specified in the appendix protocols. The target enrollment of FLEX is a minimum of 10,000 patients; over 5,000 patients have enrolled sinceApril 2017 at more than 85 sites, including eight National Cancer Institute-designated comprehensive cancer centers. The FLEX collaborative platform allows participating investigators the opportunity to author their own sub-study protocols, as approved by the FLEX Review Committee. Sub-study research categories include: Age and Breast Cancer, Optimizing Therapy Strategies, Breast Cancer and MetabolicSyndrome, ctDNA and Liquid Biopsy, Genomics and Subtypes, Social and Ancestry, and Neoadjuvant Therapy and Surgery. To date, twenty-five investigator-initiated sub-studies have been approved.**Trial contact information:** NCT03053193FLEX@agendia.com

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**Publication Number:** PS5-35

Detection of PI3K pathway activation in circulating tumor cells in PIK3CA mutated metastatic breast cancer as a putative predictive biomarker for PI3K inhibitor therapies

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**Background:** Somatic genomic alterations that activate the phosphatidylinositol-3-kinase (PI3K) pathway signaling are found in 30-50% of breast cancers, and the p110a-specific inhibitor alpelisib is approved for use in combination with fulvestrant in PIK3CA mutated hormone receptor-positive (HR+) metastatic breast cancer. However, preclinical and clinical data has demonstrated significant variability in response to alpelisib and other PI3K inhibitors even in the presence of hotspot PIK3CA activating mutations, likely reflecting functional differences between somatic alterations, bypass signaling mechanisms, and intratumor clonal heterogeneity. Thus, there is an ongoing need for novel predictive biomarkers to help guide patient selection for these therapies. Circulating tumor cells (CTCs) represent an accessible source of tumor derived analytes that allow for the interrogation of protein level readouts of PI3K pathway activation, may better reflect the biologic heterogeneity of metastatic disease than single site solid tumor biopsy, and are amenable to longitudinal analysis. Here, we report the development of an assay to evaluate the expression of activated AKT (AKT pS473) in CTCs as a putative biomarker of sensitivity to PI3K inhibitor therapies in metastatic breast cancer. **Methods:** Peripheral blood for CTC isolation was collected serially from patients with metastatic breast cancer and known somatic PI3K pathway mutation status. Samples were processed using VERSA (Versatile Exclusion-based Rare Sample Analysis), a microfluidic technology that integrates CTC capture and downstream analysis. Following fixation, CTCs were captured immunomagnetically with antibodies for EpCAM and Trop2, permeabilized and stained on chip for pan-AKT plus AKT pS473. Quantitative fluorescent microscopy was used to enumerate CTCs, defined as cytokeratin positive cells with intact nuclei and negative for a group of normal blood cell markers (CD45/CD11b/CD34/CD66b), and to quantify activated AKT protein expression in CTCs and matched peripheral blood mononuclear cells (PBMCs). **Results:** 100% of patients with somatic PIK3CA mutations in our pilot cohort had CTCs with detectable phospho-AKT expression, and in 50% of patients, the median phospho-AKT/pan AKT ratio was higher in CTCs compared to matched peripheral blood cells, suggestive of increased PI3K pathway activity. All patients demonstrated heterogeneity in phospho-AKT expression and phospho-AKT/pan-AKT ratio among individual CTCs at a single timepoint and across timepoints in longitudinal analysis. **Conclusion:** We report here the feasibility of quantitative and longitudinal detection of activated AKT in EpCAM/Trop2 captured CTCs from metastatic breast cancer with somatic PIK3CA mutations. Future work will prospectively evaluate multiple clinical applications of this assay in patients receiving alpelisib plus endocrine therapy for PIK3CA mutated HR+ metastatic breast cancer, as well as expanding the assay to include the detection of additional phospho-protein readouts of PI3K pathway activity in CTCs. In addition to the potential to complement solid biopsy PIK3CA mutation status as a predictive biomarker of sensitivity to PI3K therapies, this assay has the unique potential to provide a pharmacodynamic assessment of PI3K inhibitor activity in CTCs while on treatment, which may serve as an early biomarker of clinical response or resistance.

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**Publication Number:** PS4-35

# The E2F cell cycle pathway score to predict treatment response among patients with breast cancer

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Cell cycle progression is a critical component of cell proliferation, and continuous proliferation is one of the hallmarks of cancer. Components regulating the E2F pathway have been identified in nearly every human malignancy and many of them including E2F transcription factors themselves play major roles in cancer progression, metastasis and treatment response of breasts cancer. Their activity therefore is expected to reflect tumor aggressiveness and responsiveness to therapy. We scored 3,905 tumors of nine breast cancer cohorts for this activity based on their 200 gene expression for the Hallmark E2F targets gene set. As expected, tumors with a high score had increased expression of cell proliferation-related genes, including G2M checkpoint, MYC targets v1 and v2, MITOTIC spindle, MTORC1 signaling, UNFOLDED protein response, and DNA repair in both the TCGA and METABRIC cohorts (false discovery rate < 0.001 in both cohorts). A high score was significantly associated with greater MKI67 expression ($p < 0.001$ in both cohorts), histological grade ($p < 0.001$ in both cohorts), and AJCC pathological stage ($p < 0.001$ in both cohorts). And Indel and single nucleotide variation neoantigen loads were associated with a high E2F pathway score ($p = 0.006$ and 0.047 respectively). Furthermore, the E2F pathway score correlated positively with copy number alteration (Spearman $r = 0.55$, $p < 0.001$). Intra-tumoral genome heterogeneity and proliferation score were significantly associated with the E2F pathway score as well ($p < 0.001$). The high E2F pathway score group demonstrated significantly higher fractions of not only pro-cancerous regulatory T cells, helper T cell (Th2), but also anti-cancerous CD4 memory T cell, helper T cell (Th1), and M1 macrophage as well as B cells compared to the low score group in the TCGA cohort ($p < 0.001$). Similar trends were observed in the METABRIC cohort. Furthermore, metastatic tumors had higher E2F scores than the primary tumors from which they arose especially luminal and normal subtype ($p = 0.006$ and $p < 0.001$). Interestingly, metastases with a high E2F score were associated with significantly worse PFS in the whole cohort, as well as patient sub-groups with local recurrence and with liver metastasis ($p = 0.018$, $p = 0.025$ and $p = 0.027$). Additionally, the E2F pathway score was significantly decreased with good response to chemotherapy ($p < 0.001$) and demonstrated higher pCR rate after neoadjuvant therapies in the high E2F pathway score group of estrogen receptor (ER)-positive/HER2-negative cancer ($p < 0.001$). The E2F score was significantly associated with expression of cyclin-dependent kinase (CDK)-related genes, including CCNE1, CDKN2A, CDKN2D, CDK2, CDK4 and CDK6 (all $p < 0.001$), and immune checkpoint molecule-related genes including PD-L1/2, CTLA4, IDO1, LAG3 and TIGIT ($p = 0.013$, 0.014, < 0.001, < 0.001, < 0.001 and 0.002, respectively). These results were validated by other cohort. Finally, the E2F score was strongly correlated with sensitivity to CDK inhibition in ER+/HER2- breast cancer cell-lines (Spearman $r = 0.90$, $p = 0.04$). In conclusion, the E2F score is a marker of breast cancer aggressiveness and predicts responsiveness of ER+/HER2- patients to neoadjuvant chemotherapy and possibly to CDK and immune checkpoint inhibitors.

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**Publication Number:** PS6-35

Real world outcomes in elderly women with HER2 positive advanced breast cancer

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Background The development of anti-human epidermal growth factor receptor 2 (HER2) therapies has significantly improved disease outcomes in patients with HER2-positive advanced breast cancer (ABC). However, elderly patients are persistently under-represented in clinical trials, with only 2.4% of patients aged ≥75 years in the pivotal CLEOPATRA study. Despite a lack of research addressing treatment outcomes in elderly patients, advanced age at diagnosis is associated with a greater likelihood of receiving no initial systemic therapy for de novo metastatic breast cancer. Studies have also shown that older women diagnosed with metastatic breast cancer have a poorer prognosis and shorter life expectancy. We examined treatment patterns and outcomes in an elderly (defined as ≥70) 'real world' Australian population.

Methods Data was extracted from the Treatment of Advanced Breast Cancer in the HER2-positive Australian Patient (TABITHA) multi-site clinical registry, and patients stratified according to age (<70 and ≥70 years). Descriptive statistics were used to report baseline characteristics and compared using T-tests and Chi square analyses. Treatment duration and overall survival were calculated via the Kaplan-Meier method using GraphPad Prism 8.0 software.

Results We identified 319 patients, including 67 patients (21%) aged ≥70 years. Older patients were more likely to have an Eastern Cooperative Oncology Group performance status of ≥2 (16% vs 3%; p<0.001) and a Charlson Comorbidity Index of ≥2 (13% vs 7%; p<0.001). There were no significant differences in hormone receptor status, de novo metastatic presentation, or presence of visceral disease between groups. A similar proportion of patients in each group received first line HER2-directed therapy (85% vs 93%; p=0.054), and the duration of therapy was not significantly different between groups (16 vs 22 months; p=0.70). Despite no difference between groups in the proportion of patients who received first-line chemotherapy, older patients demonstrated shorter chemotherapy durations (2.7 months vs 3.5 months; p<0.02). Median overall survival was significantly longer in younger patients (82 months vs 42 months; hazard ratio, 0.50; 95%CI, 0.29-0.87; p<0.001). In the first-line setting, overall adverse events rates were higher in the older group (34% vs 20%; p=0.04), including cardiotoxicity (7% vs 0.9%; p=0.02), and on-treatment deaths (5% vs 0%; p=0.01).

Conclusion Elderly patients with HER2-positive ABC demonstrated shorter chemotherapy durations, poorer overall survival, and increased rates of adverse events despite having similar disease characteristics and treatment patterns. Prospective studies are required to improve outcomes in the elderly HER2 positive population.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number:** PS7-35

Geicam/2014-03 (registem): A prospective registry of advanced breast cancer: A subset of triple negative breast cancer patients with her2 low expression

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**Background:** The RegistEM study will provide prospective data from advanced breast cancer (ABC) patients (pts). Understanding the real distribution of BC subtypes is its primary objective. A new nomenclature has been proposed for those cases with HER2 1+ or 2+ by immunohistochemistry and negative *in situ* hybridization, HER2-low BC. In clinical practice, these tumors are reported as HER2 negative. **Methods:** This is a non-interventional study that will enroll approximately 1,867 pts with ABC diagnosed from January 2016 to December 2019, either after recurrence or as 1$^{st}$ diagnosis, in 38 Spanish sites. Biological samples (primary and/or metastatic tumor lesions, and blood) collection is part of its procedures. In this analysis (cut-off date 01/April/2020, database ongoing), we describe the characteristics of pts with Triple Negative (TN) subtype and HER2-low expression (as mentioned above). Biomarkers, including HER2, were determined in either primary tumor (PT), M1 or in both, PT and M1. **Results:** This subset of pts make up 37.4% (n=49) of TN pts considered for this analysis (n=131). Their distribution within the three groups (PT, M1 and PT/M1), was 46.9% (n=23), 42.9% (n=21) and 10.2% (n=5), respectively. These pts were diagnosed with early BC (EBC) and at recurrence, 91.7% presented distant metastases. Median time from EBC diagnosis until recurrent disease in terms of ABC was 29.8 months (mo), with the majority of pts recurring at >12 mo (95.9%), similar to the whole TN subset. Most pts were Caucasian (98%), and at diagnosis of ABC, the median age was 60 years (range 31-84) and 65.3% were postmenopausal. A change of BC subtype was documented in 15/49 (30.6%) pts, with the higher rate in M1 group (52.4%); as opposed to the TN subset, a change to HER2+ disease was reported in 6/15 (40.0%) pts and just after the TN subtype in all cases. Family history of BC and/or ovarian cancer was reported in 42.9% pts and any genetic test to assess the hereditary risk was performed in 30.6% pts. Similarly to TN subset, lung (36.7%), lymph nodes and bone (34.7% each) and liver (24.5%) were the most frequent metastatic locations; central nervous system metastases were developed by 14.3% pts. Visceral involvement was present in 66.7% pts, being this rate lower in M1 compared to PT and PT/M1 groups. The most frequent 1$^{st}$-line therapies were chemotherapy (CT) (44.9%) and CT/biological therapy (BT) (36.7%). Type of CT mainly included capecitabine (36.4%), taxanes (27.3%), eribulin (13.6%) and platinum-based combinations (13.6%). Most pts received CT as monotherapy (86.4%). Bevacizumab (BVZ) was the most frequent BT associated to CT (77.8%), mainly with capecitabine and/or paclitaxel (72.2%). Progressive disease to 1$^{st}$-line therapy in the whole group was reported in 73.5% pts (higher than in TN subset), with a median time to progression (TTP) of 5.7 mo (range 1.7-15.0); PT was the group with a higher PD rate. A 2$^{nd}$-line therapy was reported in 63.3% pts. Similarly to 1$^{st}$-line setting, the most frequent 2$^{nd}$-line therapies were CT (74.2%) and CT/BT (12.9%) (with BVZ in 75.0% pts). CT in monotherapy was reported in 69.6% pts (capecitabine 31.3%, eribulin 25.0%). Median duration of this line therapy was 3.0 mo (range 0.6-15.8), PD has been reported in 96.8% pts (similar between groups), and 3$^{rd}$-line therapy in 25/49 (51.0%) pts.

**Conclusions:** In TN/HER2-low ABC pts, lung, lymph nodes and bone were the most frequent metastatic locations. As opposed to TN subset, HER2+ disease is part of the subtype changes reported. Although the main 1$^{st}$- and 2$^{nd}$-line therapies were CT and CT/BT, similarly to TN subset, the rate of pts with PD to 1$^{st}$- and 2$^{nd}$-line therapies is higher, and also those pts treated in the 3$^{rd}$-line setting.

**Publication Number:** PS11-35

Mipra, a window of opportunity study evaluating mifepristone treatment for postmenopausal breast cancer patients with higher levels of progesterone receptor isoform a than b

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**Background**: Different antiprogestins have been clinically evaluated in gynecological andbreast cancers. Mifepristone (MFP), as well as onapristone and telapristone acetate, showedpartial responses in breast cancer clinical trials. Preclinical data indicates that antiprogestinsinhibit cell proliferation of luminal breast carcinomas expressing higher levels of progesteronereceptor isoform A (PRA) than those of isoform B (PRB) evaluated by western blots (WB). Thus,we designed a pre-surgical window trial to determine the therapeutic effects of oral MFP oncell proliferation and on differential gene expression in 20 breast cancer patients selected bytheir high PRA/PRB isoform ratio.**Methods**. MIPRA is an open-label, one-arm, prospective interventional study (NCT02651844).We interviewed 140 naive breast cancer patients and 133 accepted to participate. Four coreultrasound-guided biopsies were performed, two were formalin-fixed for diagnosis, ER, PR,HER2, and Ki67 evaluation and two were snap-frozen for WB and molecular studies. Patientsthat met the inclusion criteria, with ER+, PRA/PRB>1.5 and total PR ≥50% determined by WBand immunohistochemistry (IHC), respectively, were included for MFP treatment. Plasma wasobtained before and after treatment for future studies. Patients were treated with oral MFP(200 mg/day) for 14 days before surgery which was performed on day 15. Clinical examinationwas performed at days 7 and 14 to register possible adverse effects and to measure tumorsize. During surgery, samples were formalin-fixed for IHC studies, and others were snap-frozenfor further molecular studies. One patient had a bilateral breast cancer, and both tumorsmatched with the inclusion criteria and were included. The primary endpoint was Ki67labeling, comparing diagnostic core needle biopsy to post-therapy surgical specimens.Considering previous studies performed with tamoxifen, we pre-specified that 30% of relativereduction in Ki67 would be considered as a positive response. Differences in Ki67 expressionwere quantitated by an expert pathologist counting at least ten 40x fields per slide. Theseresults are currently being validated by a second pathologist. One patient, with a core biopsywith less than 500 total cells, was excluded. Ongoing experiments include secondary and otherendpoints: comparison of apoptotic, proliferative and hormone receptor markers by IHC,measurement of MFP plasma levels and, RNAseq analysis in samples pre- and post-treatment. Ki67 changes from baseline were tested with paired Wilcoxon matched-pairssigned-rank test.**Results:** The median (range) Ki67 value of biopsies was 11.87% (2.70- 34.56) and for surgicalspecimens was 6.45% (0.48-23.77). A 45.67% of decrease in the median % Ki67 (41.63%comparing the arithmetic mean values and 50.83% comparing the geometric mean values) wasregistered in all surgical specimens compared to baseline (p= 0.003). Using the pre-specifiedresponse parameter (30% relative reduction in Ki67), we identified 15/20 (75%) responders.Considering only responsive tumors, a 49.87% decrease in the median % Ki67 (50.83%,arithmetic mean; 62.34% geometric mean) was observed (p<0.0001) between baseline andsurgical specimens. In those cases with the highest response, the decrease in Ki-67 wasaccompanied by a decrease in tumor volume (ultrasound measurements).**Conclusion**: Our results show that MFP treatment may be effective in patients showing a highPRA/PRB ratio. The magnitude of the inhibition was similar or higher to that reported fortamoxifen in ER+ breast cancer patients in short-term treatment studies. Ongoing analysis willdetermine if there are changes in other markers that may help to further define MFP-responsive patients.

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# Outcomes and management of positive and close anterior margins following skin-sparing mastectomy

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**Background:** Skin-sparing mastectomy (SSM) has emerged as a safe oncologic technique for extirpation of breast tissue in the context of immediate breast reconstruction (IBR). Documented rates of local recurrence are comparable for SSM and conventional mastectomy and attention to the plane of dissection is essential with removal of skin overlying the tumor when clinically indicated. The incidence of positive or close margins is greatest for peripheral tumors at the breast boundaries and will influence rates of local recurrence. Management of positive or close margins is inconsistent and this audit aimed to determine the incidence of compromised margins and their impact on local recurrence and overall survival in SSM patients.
**Methods:** A retrospective analysis was undertaken of breast patients with invasive or non-invasive breast cancer undergoing SSM and IBR at a single tertiary referral centre between January 2006 and December 2009. A total of 150 patients were included and all underwent resection of breast tissue with a peri-areolar incision. Clinical information was extracted from a prospectively maintained database. Data was collected on patient demographics, tumor characteristics, non-surgical treatment and outcome events (recurrence and death). The definition of a negative margin on histology during the study period was tumor ≥2mm from the edge of the specimen with close margins <2mm but no ink on tumor.
**Results:** The mean age of patients was 51 years (range 24 - 75) and median duration of follow up 140 months (range 10 - 167). Amongst these 150 SSM patients, 25 (17%) had positive or close anterior margins (<2mm) with 125 patients having negative anterior margins (>2mm). None of these patients with close or positive margins underwent re-excision following initial SSM. Twenty-four patients (16%) developed either loco-regional (n=9) or distant recurrence (n=15) with 126 patients (84%) alive at 10 years. Although more patients with positive/close compared with negative margins had recurrence (20% versus 15%), this did not reach statistical significance (p=0.55) Similar proportions of patients in each margin category received post-mastectomy radiotherapy (p=0.66) and adjuvant/neo-adjuvant chemotherapy (p=0.66). There were no statistically significant differences in rates of local recurrence or survival between patients with positive/close and negative margins but the number of events is small and may represent a type II error.
**Conclusion:** Twenty percent of patients (5/25) with positive or close margins after SSM develop local or distant recurrence with reduction of risk by PMRT of <50%. None of the patients with positive/close margins who developed recurrence survived for 10 years. Close/positive margins after SSM may portend a worse outcome from recurrent disease and further research is required to optimize management of this group of patients in an era of skin-preserving mastectomy.

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**Publication Number:** PS2-39

# A peninsular experience - developing a non-biopsy protocol for the female cohort 25-29 years with clinically typical fibroadenoma conforming to maxwell criteria on ultrasound

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| Intro | Aim: The aim of this study was to introduce a non -biopsy protocol in our department for benign breast lump referrals confirmed as typical U2/3 fibroadenoma on imaging. The cohort of women between 25-29 years of age with sonographic features (Maxwell non-biopsy criteria) U2/3 typical of fibroadenoma does not miss malignancy. Current UK guidance is not to biopsy sonographically typical fibroadenomas in women under 25 years. We have studied our population extending the radiological Maxwell criteria reflecting histologically benign outcomes even in this group of 25-29 years. |
| Methods | Methods: Retrospectively data was collected of all women between 25-29 years of age undergoing core biopsy for ultrasound confirmed both simple and complex fibroadenomas at Clatterbridge General Hospital between 2014 and 2019 over a period of five years. The number of cancers picked up was compared with the number of referrals and the discordance between radiological diagnosis of fibroadenoma and histopathological confirmation of malignancy was recorded. |
| Results | Results: We saw increment in referrals in this group of young women from n=260 to n=386 over the five year study period. A total of 1707 referrals were made across five years. n=175 image guided core biopsies were carried out for U2,U3,U4 lesions appearing as fibroadenoma on ultrasound. Out of these (n=175), all lesions coded U2/3 (n=165) based on Maxwell criteria on ultrasound were negative for cancer. U4 lesions on ultrasound were confirmed as cancers mimicking fibroadenoma(n=10). |
| Conclusion | Conclusion: This retrospective audit of 1707 patients provides sound evidence for safe non-biopsy of typical fibroadenomas in women 25-29 years when clinical and sonographic features meet strict criteria. We started using the non-biopsy protocol using Maxwell criteria for U2/3 lesions. We discharged women in this group if they met all the protocol criteria, i.e., their lesion does not appear suspicious clinically, has all the ultrasound appearances typical of a fibroadenoma U2/3 , and they do not have any compounding circumstances (e.g., family history, genetic predisposition). As routine, we advise all women who are discharged without follow-up to examine their breasts regularly and return if they detect any changes including increase in lesion size. We need data to be audited prospectively and provide level 1 evidence to the same effect. |

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Early intervention for and management of alpelisib (ALP)-induced hyperglycemia: Case studies from the phase III SOLAR-1 trial

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**Background:** In the Phase III SOLAR-1 trial (NCT02437318), ALP (PI3Kα inhibitor) + fulvestrant (FUL) significantly improved progression-free survival vs FUL alone in patients (pts) with HR+/HER2− advanced breast cancer with *PIK3CA* mutations (André et al. *N Engl J Med*. 2019;380:1929-1940). Hyperglycemia was identified as an expected adverse event (AE) with ALP and was the most frequent grade (G) 3/4 AE in SOLAR-1 (G3, 32.7%; G4, 3.9%). A protocol amendment was implemented during the study to provide additional detailed guidance on hyperglycemia and rash management. Additionally, conditions at baseline such as prediabetic or diabetic glycemic status, body mass index (BMI) ≥30, and age ≥75 years have been identified as risk factors for ALP-induced hyperglycemia. Here we present a case report highlighting 4 examples of early intervention and different management approaches for ALP-induced hyperglycemia in SOLAR-1. **Methods:** According to the protocol, glycemic status was assessed at baseline and over time using fasting plasma glucose and glycated hemoglobin. Hyperglycemia was regularly assessed per the National Cancer Institute CTCAE v4.03. In addition to concomitant medications for hyperglycemia, dose interruptions or reductions by one level were recommended for both G3 and G4 hyperglycemia, per protocol. If G4 hyperglycemia had not improved within 24 hours and confounding factors could be excluded, pts should be permanently discontinued from ALP. Pts from this case report were selected on the basis of hyperglycemia events of interest to the community: (1) not well controlled on metformin alone; (2) required hospitalization; (3) no risk factors for hyperglycemia at baseline; (4) no action taken at initial presentation of hyperglycemia. **Results:** In SOLAR-1, 284 pts were randomized to ALP + FUL and 187 (66%) developed hyperglycemia; 163 of these pts received concomitant medications for hyperglycemia, and most received metformin as part of their treatment (87%). Three cases exhibited examples of early intervention for ALP-induced hyperglycemia. The first pt was prediabetic and had a BMI >30. She presented with G2 hyperglycemia on day 8 and received metformin and a DPP-4 inhibitor but then had a G3 event 2 weeks later, managed by an ALP dose interruption. Another G2 event led to addition of an SGLT2 inhibitor and a sulfonylurea, which allowed her to stay on ALP treatment (>43.3 mo). The second pt was prediabetic and had a BMI >30. She had G3 hyperglycemia leading to hospitalization on day 8, started metformin, and then received rescue insulin. She continued to be managed with dose adjustments of metformin and addition of a sulfonylurea until disease progression (11.2 mo). The third pt had a normal glycemic status at baseline and a BMI <25. She presented with G2 hyperglycemia at 197 days of treatment and immediately received metformin. A DPP-4 inhibitor was also later added, allowing her to stay on treatment (>40.5 mo). A case example of late intervention for ALP-induced hyperglycemia was a pt who had a normal glycemic status at baseline and a BMI <30. She demonstrated G1 hyperglycemia at day 8, no action was taken, and then she presented with G4 hyperglycemia 8 days later, requiring hospitalization leading to discontinuation of ALP. **Conclusions:** These cases from SOLAR-1 suggest that ALP-induced hyperglycemia is manageable with close monitoring, early detection, and prompt intervention, including concomitant medications and dose modifications where appropriate. This case report should be interpreted with caution due to the limited number and type of pts.

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# B7-H3 and B7-H4 expression in triple-negative breast cancer subtypes detected by RNA in situ hybridization and immunohistochemistry: Association with clinicopathological features and T-cell infiltration

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**Background**: Triple-negative breast cancer (TNBC) is a heterogeneous group of cancer with dismal prognosis. B7 families can be promising targets for cancer immunotherapy in TNBC. Previously we have found increased expression of B7-H3 and B7-H4 mRNA and protein in breast cancer including TNBC. In an effort to discover therapeutic targets, TNBC has been further stratified into molecular subtypes. However, little is known about the clinical impact and value of B7-H3 and B7-H4 in TNBC subtypes. The purpose of this study was to evaluate the clinicopathologic characteristics of the B7-H3 and B7-H4 mRNA and protein expression according to the TNBC subset. **Materials and methods:** A tissue microarray was constructed from 186 patients with TNBC. B7-H3 and B7-H4 mRNA and protein expression were assessed by the RNAscope in situ hybridization (ISH) and immunohistochemistry. Immunohistochemistry for the TNBC molecular subtype-surrogate markers [cytokeratin 5/6 (CK5/6), CK14, epidermal growth factor receptor (EGFR), and androgen receptor (AR)], CD3, and CD8 was also performed. TNBC subtypes were classified into three subtypes: basal-like (BL), luminal AR (LAR), and unclassifiable type (UN). **Results:** Based on the immunohistochemical results, 186 TNBCs were classified into BL (n=120, 64.5%), LAR (n=10, 10.8%), and UN (n=46, 24.7%) subtypes. BL and UN subtypes were associated with younger age than the LAR subtype. B7-H3 mRNA and protein expressions were expressed in the tumor and stromal cells of the TNBCs. On the contrary, B7-H4 mRNA and protein expressions were only observed in the tumor cells. High tumor mRNA and protein expression of B7-H3 and B7-H4 were found in 49 of 175 (28.0%) and 121 of 176 (68.8) cases, and 92 of 174 (52.9%) and 66 of 176 (37.5%) cases, respectively. High stromal B7-H3 mRNA and protein expression were observed in 22 of 175 (12.6%) and 43 of 176 (24.4%) cases. High stromal B7-H4 mRNA and protein expression were not observed. B7-H3 and B7-H4 protein expression were closely correlated with their mRNA expression according to the tumor compartment. Tumor B7-H4 mRNA expression was associated with younger age at the initial diagnosis and molecular TNBC subtypes. Expression of B7-H3 mRNA and protein in the tumor cells negatively correlated with CD3+ and CD8+ T cell infiltration density in the tumor and/or stromal compartment of the TNBCs and its subtypes. High stromal B7-H3 mRNA expression was associated with poor disease-free and overall survival in the TNBCs and overall survival in the UN subtype. Stromal B7-H3 mRNA expression was independently associated with overall survival in the TNBCs and disease-free survival in the BL subtype. **Conclusions:** As prognostic factors, our results point to the importance of the expression of B7-H3 mRNA by the stromal cells in the TNBCs and the BL subtype. The inverse relationship between B7-H3 expression and CD3+ and CD8+ T lymphocyte infiltration may represent a promising target in the immunotherapy of the TNBCs, irrespective of its molecular subtypes.

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**Publication Number:** PS8-35

Use of a web-based decision aid to promote chemoprevention uptake among racially/ethnically diverse women at high-risk for developing breast cancer: A qualitative study

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**Background:** Chemopreventive agents such as selective estrogen receptor modulators (SERMs; tamoxifen and raloxifene) and aromatase inhibitors (AIs; exemestane and anastrozole) have proven efficacy in reducing breast cancer risk by 41%-79% in high risk women. Women at high risk of developing breast cancer face the complex decision of whether to take SERMs or AIs for breast cancer chemoprevention. Underserved racial/ethnic minority women are less likely to take chemoprevention, contributing to higher rates of advanced tumors, and poorer clinical outcomes compared to non-Hispanic whites, which could exacerbate health disparities. *RealRisks* is a patient-centered web-based decision aid (DA) that was designed to promote understanding of breast cancer risk and to engage diverse women in planning a preference-sensitive course of decision-making about taking chemoprevention. We aimed to understand perceptions of women at high-risk for developing breast cancer regarding their use of *RealRisks.*
**Methods:** We completed enrollment to a randomized controlled trial (RCT) among 300 racially/ethnically diverse high-risk women assigned to standard educational materials alone or in combination with *RealRisks*, with the primary endpoint of chemoprevention uptake at 6 months. We conducted a qualitative study using semi-structured interviews with a subset of 27 high-risk women enrolled in the intervention arm of the RCT to understand how they interact with the DA. All interviews were audio-recorded, transcribed verbatim, and compared against the digital recordings to ensure accuracy of the content. Content analysis was used as a method to analyze the data and to generate themes.
**Results:** The mean age of the participants was 60.9 years (SD, 10.3). Our sample was racially and ethnically diverse with 59.3% non-Hispanic white, 18.5% non-Hispanic black, 14.8% Hispanic/Latina, and 3.7% Asian. Most participants had a family history of breast cancer (70.4%) and most (78%) reported using *RealRisks* after being granted access to the DA. Three overarching themes emerged from the qualitative analyses: (1) acceptability of the intervention, (2) usability of the intervention, (3) and information needs. *RealRisks* was found to be acceptable among the women who used the DA (n=21/27). Most women (n=18/21) felt that *RealRisks* improved their knowledge about breast cancer risk and chemoprevention options and informed their decision-making about whether or not taking chemoprevention was the right choice for them (n=17/21). Most women reported that *RealRisks* was easy to navigate, user-friendly, and easily accessible online. Alternatively, a subset of women (n=9/21) shared challenges with using the DA, as they wanted more tailoring based on user characteristics; felt that the DA was specifically targeting multi-ethnic populations that did not reflect them; used difficult terminology; and had a strong emphasis on chemoprevention drugs. Participants offered recommendations for improving the DA and shared their information needs, which mainly focused on wanting to learn about guidelines for mammography screening and lifestyle modification.
**Conclusions:** With this qualitative study, we demonstrated the acceptability of the *RealRisks* web-based DA among diverse high-risk women with a few caveats and recommendations for improvement. These results emphasize the need for more tailoring of the DA based on user characteristics and a holistic approach to reducing breast cancer risk, to include information on breast cancer screening, as well as lifestyle risk factors. Next steps include incorporating feedback from this study to further enhance the DA and to optimize the modular architecture within *RealRisks* to include additional modules to meet the needs of diverse high-risk women.

**Publication Number:** PS16-35

Microbiota and breast cancer in mexican women

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Microbiota and breast cancer in Mexican womenStudy Type: ObservationalTime Perspective: Cross-SectionalThe human microbiome refers to the genes of the universe of microbes that inhabit our skinand mucosal surfaces. Epidemiological studies implicated that human microfloracontributes to 16% more of malignant neoplasms worldwide, either as a risk factor orcausative agent.Although hereditary and genetic factors represent 5% to 10% of breast cancer cases, 70%of them are due to a host of environmental factors. Migrant studies demonstrated that non-hereditary factors are the main drivers of international and inter-ethnic differences in theincidence and mortality of breast cancer. The environment contributes to the developmentof the disease; although, the factors involved are not well known, among the latter is theinfluence of microorganisms and, therefore, attention is recently being paid to themammary microbiota. This study hypothesizes that women with breast cancer havedifferences in the composition and functionality of breast microbiota compared to womenwithout breast disease.Inclusion and exclusion criteria. Women's age range of 25-70 years. Women with confirmedbreast cancer diagnosis scheduled for surgery as primary treatment (mastectomy orconservative surgery) surgically intervened with breast augmentation or reduction withoutbreast cancer and signed informed consent. Women with antecedents of cancer, or whohave received antibiotic treatment one month before recruitment, or any neoadjuvanttherapy, without breast surgery in the past for any reason. Immunocompromised patients.Pregnant patients or with the use of implants were excluded from the study.Sample size. Sixty women with confirmed breast cancer matched with 30 women withoutcancer, and 30 with benign breast disease. Three hospitals participated in the recruitment:Instituto Nacional de Cancerología , Centro Oncológico Estatal ISSEMYM and Centromedico ABC.Method: DNA total of tissue samples was extracted using the Quick-DNA Miniprep Plus Kit(Zymo research Cat. D4068). 5 uL of DNA isolated of tissue samples were amplified with16S™ Metagenomics Kit (Thermo Fisher Scientific, Cat. A26216) and were marked with IonXpress Barcode Adapter (Thermo Fisher Scientific cat. no. 4471250), purified with AMPureXP reagent (Beckman Coulter cat. no. A63881) and quantified with Ion Universal LibraryQuantitation Kit (Thermo Fisher Scientific cat. no. A26217). After that, emulsion PCR wasprepared in the Ion OneTouch 2 System (Thermo Fisher Scientific). For sequencing, we usedthe Ion PGM Hi-Q view Sequencing kit (REFA30044) with chips 318 in the Ion torrent PGMinstrument (Thermo Fisher Scientific).
Results: In this study, we employed 16s rRNA sequencing to analyze the bacterial profiles ofnormal, benign, and breast tumor tissues. We observed that the beta diversity between thethree types of tissues is similar, although patients showed significant differences in theabundance of specific bacteria genera depending on the tissue of origin. We determinedthat bacteria from the genera *Burkholderia* had a lower relative abundance in benign tissuesthan normal tissues, although these genera had a higher relative abundance in tumortissues. We found a more significant difference in the amount of bacteria between benignand tumoral tissues; we observed that the seven genera (*Aeromonas, Alcanivorax, Burkholderia, Corynebacterium, Finegoldia, Pseudomonas and Staphylococcus*) are greaterintumortissueswhereasfivegenera: Cupriavidus, Microbacterium, Ralstonia, Renibacterium and Sphingomonas had alower relative abundance in tumoral tissues. This study suggests that bacterial beta-diversity does not change much among the analyzed tissues; however, it is specific bacterialgenera that change their relative abundance during tumor progression.

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**Publication Number:** PS9-36

# Exercise therapy to reduce breast cancer fatigue: Results from the EXPECT study

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**Background.** Breast cancer fatigue (BCF) is a complex and multidimensional condition characterized by a persistent sense of physical and/or mental stiffness, resulting in a substantial impairment of health-related quality of life in breast cancer patients and survivors. Several therapeutic approaches have been proposed for BCF. Among them, supervised exercise therapy is a valuable non-pharmacologic option. However, the optimal exercise scheme (i.e. type, combination, frequency, intensity, and duration) remains controversial. Here, we sought to evaluate the effects of a specific therapeutic exercise protocol on BCF and muscle performance. **Methods.** This is a still-recruiting pilot prospective cohort study including women with a diagnosis of BCF up to two months after breast surgery. Exclusion criteria: Hb <9 g/dl, platelets <150,000/mm3, and brain and/or bone metastases. Intervention: all participants were subjected to a physical exercise rehabilitative protocol consisting of 10 minutes of warm-up, 40 minutes of aerobic exercise (e.g. walking, cycling, rowing) and strength training (e.g. light weightlifting), and 10 minutes of cool-down. Each session was repeated 2 times/week with >2 days of rest for 4 weeks, under the supervision of an experienced physical therapist. Primary outcome evaluation: brief fatigue inventory (BFI). Secondary outcomes: the European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30); hand grip strength test (HGS); short physical performance battery (SPPB); 10 meter walking test (10MWT); 6 minute walking test (6MWT). All outcomes were assessed at baseline (T0), after 1 month (T1), and after 3 months (T2). **Results.** Of the 102 patients assessed, 48 did not meet the inclusion and exclusion criteria and 18 refused to sign the informed consent. Finally, 36 BC women (mean age: 55.17 ±7.76 years; body mass index: 25.15 ±5.52 kg/m2) were enrolled. BFI showed a statistically significant reduction both at T1 (5.4 ±1.6 vs 4.2 ±1.7; p=0.004) and T2 (5.4 ±1.6 vs 4.4 ±1.6; p=0.004). Furthermore, we found significant differences at T1 in terms of HGS (20.1 ± 5.8 vs 22.5 ± 5.2: p<0.001), SPPB (9.3 ± 2.0 vs 11.3 ± 1.2; p<0.001), 10MWT (1.5 ± 0.3 vs 1.8 ± 0.3; p<0.001), 6MWT (464.5 ± 62.9 vs 554.1 ± 71.6; p<0.001), EORTC QLQ-C30 Functional score (69.2 ± 14.9 vs 76.9 ± 15.7; p<0.001), EORTC QLQ-C30 Symptoms score (29.2 ± 14.9 vs 21.2 ± 16.0: p<0.001), and EORTC QLQ-C30 Global Health score (40.7 ± 12.5 vs 67.6 ± 14.8; p<0.001). At 2 months (T2), all the outcome measures significantly differ from the baseline (p<0.05), including FFM (43.2±6.4 vs 45.5±6.6; p<0.001) and FM (24.0±10.6 vs 21.7±10.0; p<0.001), as showed by Table 3. Moreover, the GPE score measured at T1 was 2.20 considering patients' perspective and 2.40 considering physical therapists' perspective.**Conclusions.** The physical exercise rehabilitation protocol proposed herein might be a feasible, safe, reliable and effective intervention in reducing BCF and improving muscle mass, function, and health-related quality of life in breast cancer survivors. Further studies are needed to define the role of physical rehabilitation in the multidisciplinary management of BCF.

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# Reduction mammoplasty in the setting of neoadjuvant chemotherapy

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Background: Oncoplastic reduction mammoplasty is an accepted method of breast conserving surgery that also allows for potentially improved symmetry and aesthetics compared to other techniques and allows for larger tissue volumes to be removed with acceptable cosmetic outcomes. Neoadjuvant systemic chemotherapy (NAC) is increasingly used for the treatment of patients with breast cancer. While there is some data that oncoplastic reduction may delay timing of adjuvant radiation, we sought to examine this in our patients, and specifically to compare complications and time to radiation in patients who received NAC to those that didn't.
Methods: A retrospective analysis was done of all patients with DCIS or invasive cancer who underwent a reduction mammoplasty and received adjuvant radiation at our single institution from 2009-2018. Patients who received NAC were compared to those that did not.
Results: A total of 114 patients underwent reduction mammoplasty as part of their oncologic surgery and received adjuvant radiation at our institution. Of those, 40.4% received neoadjuvant chemotherapy and 49.1% received no neoadjuvant treatment. A total of 38 patients (33.3%) had some postoperative complication with 8.8% having a serious complication that required intervention. Adjuvant radiation started after 8 weeks in 74.6% of patients and after 12 weeks in 38.6% of patients, with the majority of these delays due to non-clinical factors. A total of 29.4% of patients had a delay due to wound healing issues. There was no association between NAC and delayed radiation due to wound healing ($p=0.18$).
Discussion: Oncoplastic reduction mammoplasty is a safe option for breast-conserving surgery in patients who have received NAC. The receipt of NAC in itself does not delay timing of adjuvant radiation or lead to increases in delayed wound healing. We are additionally examining other factors and their possible interaction with NAC, including diabetes, smoking, BMI and breast reduction size. In those with larger tumors receiving NAC who would otherwise not be candidates for breast conserving surgery, oncoplastic reduction should be considered as an appropriate option for surgical management. Reduction also allows for wider excision which may mitigate the impact of the longer time from surgery to radiation.

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Why is neoadjuvant treatment for patients with triple negative breast cancer of T1cN0 required ?

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Background) Patients with early stage triple negative breast cancer(TNBC) are typically treated with surgery and chemotherapy, and sometimes radiotherapy. Despite effective neoadjuvant and adjuvant chemotherapies, the relapse rate is high and up to 50% of patients will experience disease recurrence including 10% of patients with stage I disease, and pCR is useful surrogate marker for patients with neoadjuvant treatment. Currently Neoadjuvant treatment is recommended for patients with TNBC of 2cm or larger at diagnosis. However, patients with T1 disease at diagnosis are mostly recommended with upfront surgery because uncertain clinical meaning of pCR and potential escalation of treatment for patients with non-pCR in this group. The aim of this study is to see whether patients with T1c of TNBC has different prognosis from T1a /b of same or different subtype and the potential benefit of neoadjuvant treatment exist or not. Material and methods) From 2000 to 2015, female patients treated with upfront surgery for stage I-III breast cancer were included. Patients of estrogen receptor positive disease and TNBC were further stratified according to the tumor size. The primary objective of this study was to see the different incidence of disease recurrence, for which chi-square test or Fisher's exact tests were used. The secondary objective was recurrence free survival and distant disease free survival, for which Kaplan-Meier(K-M) graphs were generated and compared with log-rank test. Results) None of the TNBC patients experienced disease recurrence when they have T1a/b disease. However, patients with T1c disease showed similar incidence of disease recurrence with patients with T2 or T3 stage (89% vs. 86%), suggesting conventional T staging might not reflect real characteristics of TNBC. On the other hands, patients with ER positive disease less affected by tumor size, showing incidence of recurrent disease of T1a/b, T1c and T2 or over as 96.7%, 93.1% and 91.5% respectively. K-M graphs were generated and log-rank test showed worse survival of patients with T1c of TNBC than T1a/b and rather similar prognosis with patients with T2 or over. Conclusion) Effective adjuvant treatment, such as capecitabine had been proposed for patients with non-pCR. However, mixed results are reported, suggesting appropriate selection of patients is critical. While we need to define TNBC better, patients also need appropriate biomarker to decide whether they need escalated treatment after completion of neoadjuvant treatment. Given the dismal prognosis of T1c of TNBC, we propose this group of patients might benefit from preoperative systemic treatment with using pathologic result as surrogate marker.

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Treatment patterns and clinical outcomes among patients (pts) with HER2- advanced breast cancer (ABC) and somatic *BRCA1/2* mutation(s) (s*BRCA1/2*mut): Results from a US real-world study

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**Background:** Recently, poly ADP-ribose polymerases inhibitors (PARPi) have been approved as treatments for pts with germline (g*BRCA1/2*mut) HER2- ABC. Real-world evidence suggests that these agents are utilized in pts who have s*BRCA1/2*mut. Limited information is available on the effectiveness of these agents in pts with s*BRCA1/2*mut and establishing a reference point is necessary to assess the potential clinical benefit of these agents in pts with s*BRCA1/2*mut. We assessed real-world treatment patterns and clinical outcomes among pts with s*BRCA1/2*mut with g*BRCA* wild type (wt) genes receiving ABC treatment.
**Methods:** Oncologists retrospectively reviewed charts (July 2019-June 2020) of quasi-random selected pts ≥18 y, with s*BRCA1/2*mut and g*BRCA1/2*wt genes who received ≥1 cytotoxic chemotherapy (CT) regimen(s) for ABC between Jan 2013-April 2018. Descriptive analysis was performed for treatment patterns and safety events for the 1$^{st}$ 3 lines of ABC therapy. Clinical outcomes (progression free survival [PFS] and survival rates) were estimated using the Kaplan-Meier method for 1$^{st}$ line of therapy. Given the relatively recent launch of PARPi, clinical outcomes for these agents were immature.
**Results:** This is a placeholder abstract. Results will be provided during the final submission.
**Funding:** Pfizer

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# Dysregulation of soluble immune checkpoint proteins in newly - diagnosed early breast cancer patients

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**Background:** Checkpoint proteins regulate the immune system. Breast cancer (BC) cells exploit the up-regulation or down-regulation of these proteins to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (ICM) can be measured in human plasma. However, their biological and clinical significance remains mostly unknown. The aim of the present analysis was to measure the levels of pre-treatment ICM in newly diagnosed BC patients (pts) and compare them to healthy controls. **Method:** Soluble forms of ICM, as well as cytokines and chemokines, were measured using Multiplex® bead array and ELISA technologies. Plasma samples from 98 BC pts and 45 healthy controls were analyzed for each protein. Data was prospectively obtained. Measured levels were compared between BC pts and healthy controls using a non-parametric test (Mann-Whitney). **Results:** Soluble stimulatory molecules GITR ($p < 0.000002$), GITRL ($p < 0.007$), CD27 ($p < 0.002$), CD28 ($p < 0.003$), CD40 ($p < 0.003$), CD80 ($p < 0.009$), ICOS ($p < 0.0006$) as well as inhibitory molecules PD-L1 ($p < 0.0000001$), CTLA-4 ($p < 0.005$), TIM-3 ($p < 0.00006$), HVEM ($p < 0.00002$) and TLR-2 ($p < 0.05$) levels were significantly lower in early BC pts compared to healthy controls. When analyzed according to BC characteristics (TNBC vs. non-TNBC, tumor size, stage, nodal status and age) no significant difference was detected between the soluble levels of these ICM and between the different subsets. Additionally, serum levels of CXCL5 ($p < 0.000001$), CCL23 ($p < 0.04$), IL-16 ($p < 0.00005$), interferon-α ($p < 0.03$) and IL1-RA ($p < 0.03$) were significantly lower compared to healthy controls. Serum CX3CL1 or fractalkine ($p < 0.024465$) was significantly higher compared to healthy controls. **Conclusion:** In the current study, we identified low levels of both stimulatory and inhibitory soluble immune checkpoint molecules in newly diagnosed, non-metastatic BC pts compared to healthy controls. These results indicate that early BC is associated with a down-regulation of both soluble stimulatory and inhibitory immune-checkpoint pathways. Newly diagnosed early BC pts have a generalized immune-suppression independent of subtype and stage, which, to our knowledge, is the first study to describe soluble immune checkpoints in early BC pts.

**Publication Number:** OT-13-01

# A phase I study of preoperative ipilimumab, nivolumab, and talimogene laherparepvec for localized breast cancer

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**Background:** Immunotherapy has emerged as a novel therapeutic strategy in many solid malignancies. In breast cancer, treatment with checkpoint inhibitors alone showed minimal response rates, likely because breast cancers are not sufficiently immunogenic to induce adequate baseline T cell activation. Talimogene laherparepvec (T-VEC) is an attenuated herpes simplex virus 1 (HSV-1) engineered to introduce the GM-CSF gene selectively into tumor cells to thereby enhance the immunogenicity of transduced tumor cells. T-VEC has been approved in the treatment of patients with advanced melanoma and injectable tumors. In a phase 1b clinical trial, T-VEC was well tolerated in combination with immunotherapy in patients with advanced melanoma. We evaluated the safety and tolerability of T-VEC, nivolumab, and ipilimumab in the preoperative treatment of early stage localized triple-negative breast cancer (TNBC) and hormone receptor (HR)-positive breast cancer.
**Trial design and eligibility criteria:** This is a single site open-label phase 1b window of opportunity trial of neoadjuvant T-VEC in combination with nivolumab and ipilimumab in patients with localized breast cancer. Twenty patients with localized TNBC or HR-positive breast cancer with palpable tumors will be included. T-VEC is administered intratumorally in week 1 ($10^6$ plaque-forming units/mL [pfu/ml]) and then every 3 weeks ($10^8$ plaque-forming units/mL [pfu/ml]) for a total of 3 injections. Nivolumab (240 mg) is administered intravenously in week 1 and every 2 weeks for a total of 4 infusions. Ipilimumab (1 mg/kg) is administered intravenously in week 1 and week 6 for a total of 2 infusions. Breast cancer surgery will be carried out after completion of study treatment. Neoadjuvant chemotherapy could be administered before or after study treatment.
**Study objectives:** The primary objective is to evaluate the safety and tolerability of T-VEC in combination with nivolumab and ipilimumab in this population. The secondary objectives are 1) to assess tumor response to T-VEC, nivolumab, and ipilimumab and 2) to descriptively analyze surgical specimens for evidence of tumor necrosis and inflammatory infiltration on histopathological examination.
**Present accrual:** To date, 5 patients have been enrolled. As described above, the projected sample size is 20 patients.
Clinical trials identification: NCT04185311

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# Prevention of chemotherapy-induced alopecia: A prospective study in breast and ovarian cancer patients

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**Background:** Scalp cooling minimises chemotherapy-induced alopecia (CIA) which may reduce distress, improve quality of life and body image. This study assesses scalp-cooling efficacy in women receiving chemotherapy for early and advanced breast and ovarian cancer. **Methods**: Women with breast or ovarian cancer undergoing chemotherapy and scalp cooling at two intuitions were enrolled prospectively. Data collected included demographics, chemotherapy agent(s), hair loss and reasons for discontinuing scalp cooling. Successful hair preservation (SHP) was defined as Dean's scale grade 0-2 (<!--=50%) hair loss without desire for head-cover use at the completion of chemotherapy. Results were analysed using descriptive statistics. **Results: 188 patients were enrolled, mean age 54 [28-83] . 90 women (48%) achieved SHP. 120 (64%) completed scalp cooling. Reasons for discontinuation included: intolerance 34 (49%), perceived loss of hair in 28 (41%) and extra chair time in 6 (9%). 14% continued scalp cooling despite significant hair loss (>50%) SHP was significantly higher in non-anthracycline regimens; 62% (70/112) compared with anthracycline-containing regimens; 24% (18/74), p<0.0001. Single-agent taxane regimen achieved highest SHP in 70% (31/44)and in carboplatin/Paclitaxel regimen; 80% (16 of 20). SHP was lower in Docetaxel-Cyclophosphamide; 48% (21/44), in FEC-D; 27% (20/74) and in AC-T; 26% (16 of 62). SHP rates did not differ between ethnicities; 47% (15/32) in Asian and 47% (75/156) of non-Asian ethnicities, p=0.90. In non-anthracycline regimens SHP was numerically, but non-significantly higher in younger age (<65) 65% (52/81) compared with older age (>/=65) 57% (17/29)Conclusion: Among women receiving chemotherapy for early or advanced breast and ovarian cancer, scalp cooling offers a chance to prevent CIA with most success in taxane +/- carboplatin regimens.**
**Further study is warranted into patients views on the trade-off of benefits and costs in this limited, resource intensive intervention.**

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# First-in-human chimeric antigen receptor t cells target muc1 transmembrane cleavage product

**Cynthia Bamdad[1], Andrew K Stewart[1], Pengyu Huang[1], Benoit J Smagghe[1], Scott T Moe[1], Tyler E Swanson[1], Thomas G Jeon[1], Danica M Page[1], Trevor J Grant[1] and Jennifer M Specht[2]. [1]Minerva Biotechnologies, Waltham, MA;[2]Associate Member, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA**

**huMNC2-CAR44 is a second generation CAR that recognizes the growth factor receptor form, MUC1*, does not bind to full-length MUC1, hits a wide range of cancers and shows to little or no binding to normal tissues and is the first therapeutic tested in humans targeting the MUC1 transmembrane cleavage product called MUC1*. A 1st-in-human clinical trial of huMNC2-CAR44, NCT04020575, for metastatic breast cancers is underway at the Fred Hutchinson Cancer Research Center.**

**MUC1 biology has historically been poorly understood. Several flawed reports are still widely cited in the literature. We will present data that de-bunks current MUC1 dogma. Namely, we will demonstrate that full-length MUC1 plays no role in tumorigenesis. The cleaved tandem repeat domain does not form a heterodimer with the remaining transmembrane portion. We demonstrate that elimination of full-length MUC1 greatly accelerates tumor growth *in vitro* and *in vivo*.**

**MUC1* is a Class I growth factor receptor that is activated by ligand-induced dimerization of its truncated extra cellular domain, which activates the MAP kinase signaling pathway as well as survival pathways. Onco-embryonic growth factor $NME7_{AB}$ binds to an ectopic site on MUC1* that is only unmasked after MUC1 is cleaved and the tandem repeat domain is shed from the cell surface. $NME7_{AB}$ looks like a single chain dimer of pseudo-identical domains that each can bind to a MUC1* extra cellular domain. Because it can dimerize MUC1* as a monomer, it renders the MUC1* growth factor receptor constitutively active. Adult forms of $NME7_{AB}$ limit self-replication by changing multimerization state from the active dimer to the inactive hexamer. Antibodies such as 5E5 and SM3 bind to aberrant, trapped glycans on O-linked glycosylation sites that are only in the tandem repeat domain, which is shed from the tumor after MUC1 cleavage. Unlike full-length MUC1, MUC1* has no sites for O-linked glycosylation, so MUC1* is missed by antibodies that target aberrant glycans. Importantly, therapeutics that target full-length MUC1 could increase tumorigenesis by enriching for cells expressing the tumorigenic MUC1* growth factor receptor.**

**Minerva's anti-MUC1* antibody, huMNC2, binds to the conformational epitope that is unmasked when MUC1 is cleaved to MUC1*. MMP9, which has been linked to poor prognosis and metastasis, cleaves MUC1 to a tumor-associated growth factor receptor form of MUC1*. huMNC2 and onco-embryonic growth factor $NME7_{AB}$ compete for binding to the same conformational epitope created when MUC1 is cleaved to MUC1* by MMP9. Neither huMNC2 nor $NME7_{AB}$ binds to full-length MUC1. IHC studies of thousands of human tissues – both normal and cancerous – show that the tumor associated antigen is MUC1* and not full-length MUC1. Patient-match primary and metastases show that as cancer stage progresses the amount of MUC1* increases. huMNC2-scFv bound robustly to 95% of the breast cancers, 83% ovarian, 78% pancreatic and 71% of lung cancer tissues (specimens n>2,800). There was minimal staining of normal tissues, primarily on apical surfaces which are expected to be less accessible to immune cells. *In vivo*, huMNC2-CAR44 T cells inhibited or completely obliterated a variety of MUC1* positive solid tumors in NSG mice (n>500).**

**Minerva has developed next-gen CARs designed to increase persistence, and intends to file for additional INDs.**

**Conclusions: MUC1* is the predominant form of MUC1 on cancerous tissues. Antibodies that target a conformational epitope in the membrane-proximal MUC1* extra cellular domain are tumor selective. CAR T cells targeting MUC1* extra cellular domain are highly effective against solid tumors in animals. Robust staining of cancerous tissues and minimal staining of normal tissues predicts a promising therapeutic window for huMNC2-CAR44 T cell dosing.**

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# Paracrine signalling with stromal fibroblasts drives recovery of cancer cells after chemotherapy treatment

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Introduction: The main cause of death for cancer patients is the development of metastasis. These arise mainly due to irresponsiveness of cancer cells to the administered therapy, which then fails to eliminate all cancer cells present in the patient. To overcome this problem, it is essential to understand which mechanisms are involved in the lack of treatment response. We are investigating how the tumour microenvironment (TME) affects the response of cancer cells to chemotherapy (CTX) and how it can be modulated to improve the outcome of patients to therapy. Materials and Methods: Co-culture of chemotherapy-treated breast cancer cell lines with primary fibroblasts isolated from breast cancer patients was performed to investigate if fibroblasts affect the response of tumour cells to commonly used agents, such as epirubicin and paclitaxel. Recovery of cells was assessed using colony formation assays (CFA) and cell cycle profiling by EdU and the FUCCI system. To further explore the complex crosstalk between cancer cells and fibroblasts in the context of CTX, gene expression analysis of both cell types was done using next generation sequencing. Validation and evaluation of the biological impact of the identified pathways was done using RT-qPCR, western-blot and perturbation experiments. Lastly, publicly available datasets for breast cancer were used to investigate the clinical relevance of our findings. Results and Discussion: We show that cancer cells utilize paracrine signalling with stromal fibroblasts to drive their recovery after treatment withdrawal. Cell cycle analysis and RNA-sequencing revealed an increase in cell cycle re-entry of CTX-treated cancer cells in co-culture with fibroblasts. In addition, we have successfully shown that treated cancer cells upregulate an important secreted factor that modulates fibroblasts into a pro-tumorigenic state. Moreover, analysis of human breast carcinomas supported the proposed role of the identified factor since its expression is inversely correlated with recurrence free survival (RFS). Moreover, expression of the gene signature identified in stromal fibroblasts in co-culture with CTX-treated cancer cells was equally associated with higher recurrence rates and a worse outcome in breast cancer patients. Conclusion: CTX-induced secretory profile of cancer cells orchestrates the reprogramming of stromal fibroblasts into a pro-tumorigenic state, which drives the expansion of cancer cells. Our study unravels a novel paracrine communication between cancer cells and stromal fibroblasts that ultimately results in the escape of malignant cells to treatment, highlighting the importance of the TME in drug response. Targeting of this axis could potentially improve the outcome of breast cancer patients to CTX treatment.

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**Publication Number: PS2-40**

# Analytical and clinical validation of the trucheck$^{TM}$ platform for diagnostic triaging of symptomatic cases suspected of breast cancer

**Dadasaheb Akolkar, Darshana Patil, Pradip Fulmali, Pooja Fulmali, Revati Patil, Kiran Bendale, Archana Adhav, Shoeb Patel, Shabista Khan, Raja Dasarathan, Vishal Ranjan, Rohit Chougule, Pradyumna Shejwalkar, Akshay Ainwale, Mohini Garte, Rahul Sonawane, Madhav Purane, Yogeshwar Chaudhari, Prajakta Sagar, Shubhangi Nerkar, Vineet Datta, Cynthe Sims, Prashant Kumar, Ajay Srinivasan and Rajan Datar. Datar Cancer Genetics Limited, Nasik, India**

**Background:** trucheck$^{TM}$ is a non-invasive micro-biopsy-like approach for diagnostic triaging of symptomatic individuals suspected of Breast Cancer. trucheck$^{TM}$ is based on the detection of Circulating Ensembles of Tumor Associated Cells (C-ETACs: EpCAM$^{+}$, Pan-CK$^{+}$, CD45$^{\pm}$) of Breast Cancer origin (GCDFP15$^{+}$, GATA3$^{+}$); such C-ETACs are ubiquitous in blood samples of patients with Breast Cancer and unexpected in asymptomatic individuals as well as in individuals with Benign Breast conditions.. **Methods:** Analytical validation was performed using control cell lines for EpCAM (SKBR-3), Pan-CK (SKBR-3), CD45 (PBMCs), GCDFP15 (SKBR-3) and GATA3 (MCF-7) respectively. Known amounts of control cells were spiked into healthy donor blood and their recovery rates determined by immunocytochemistry (ICC) to establish Sensitivity, Specificity, Accuracy, Limit of Detection, Linearity and Precision. Clinical Validation was performed using 15 mL peripheral blood collected from 1,527 participants. An initial Retrospective Clinical Pre-validation was performed using blood samples collected from 547 known cases of Breast Cancer and 19 known cases of other (non-Breast) solid organ Cancers. In a subset of 20 Breast Cancer cases with metastases to the Lungs or Liver, C-ETACs were evaluated for markers associated Lung (Napsin-A, TTF-1, p40) and Liver (Hep-Par 1, Glypican-3) primaries. Prospective Clinical Validation was performed on blood samples collected prior to any invasive procedure from 961 symptomatic cases suspected of Breast Cancer. **Results:** Analytical Validation based on recovery of spiked control cells indicated 94.0% Sensitivity, 100% Specificity, 97.0% Accuracy, 93.2% - 96.7% Precision and significant linearity ($R^2 \geq 0.99$) for all ICC markers. Clinical Pre-validation indicated 89.4% Sensitivity and 100% Specificity. C-ETACs from the known Breast Cancer cases with Lung and Liver metastases were negative for Lung- and Liver-cancer specific ICC markers, respectively, while C-ETACs from non-Breast Cancer samples were negative for Breast Cancer-specific ICC markers. In the Prospective Clinical Validation, histopathological evaluation (HPE) of biopsied tumor tissue indicated Breast Cancer in 848 cases and benign conditions in 113 of the 961 suspected symptomatic cases. C-ETAC-based trucheck$^{TM}$ approach had 91.9% Sensitivity, 98.3% Specificity and 96.9% Accuracy. **Conclusion:** Analytical and Clinical Validation data establish the viability of C-ETAC-based trucheck$^{TM}$ for diagnostic triaging of symptomatic individuals suspected of Breast Cancer. Individuals positive for Breast Cancer-specific C-ETACs can be prioritized for further clinical procedures whereas C-ETAC negative individuals can be considered for alternate diagnoses.

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**Publication Number: PS7-36**

# Subtype-dependent locoregional recurrence patterns in different subtypes of breast cancer: A retrospective analysis of 16,505 patients over 10 years of follow-up

**Jong Ho Cheun, Han-Byoel Lee, Wonshink Han, Dong-Young Noh and Hyeong-Gon Moon. Seoul National University Hospital, Seoul, Korea, Republic of**

**Background While numerous studies have consistently reported that the molecular subtypes of breast cancer are associated with different patterns of distant metastasis, the impact of molecular subtypes on the locoregional recurrence has not been thoroughly investigated. Currently, major guidelines in breast cancer recommend annual mammography for locoregional surveillance. In the present study, we investigated the patterns of locoregional recurrence in a large cohort of breast cancer patients who underwent standardized treatment at a single institution.**

**Methods We retrospectively reviewed the clinical records of all patients who underwent breast cancer surgery for stage I-III diseases between January 2000 and December 2018. The patients with ductal carcinoma in situ who underwent standard treatment were also included. The events were classified into ipsilateral breast cancer recurrence (IBTR), locoregional recurrence (LRR) and contralateral breast cancer (CBC). All IBTR events were included in the LRR events. The patients with initial stage IV breast cancer, with recurrence breast cancer previously treated at elsewhere, or patients with insufficient follow-up period were excluded.**

**Results A total of 16,505 patients were identified and included in the analysis. For all patients, the rate of IBTR, LRR, and CBC at 10 year was 2.6%, 4.9% and 1.9%, retrospectively. There was no significant association between the IHC-based molecular subtype and tumor recurrences in the 1,535 patients with ductal carcinoma in situ. For 14,970 patients with invasive disease, we observed significant differences in IBTR, LRR, and CBC between different molecular subtypes. For all events, HR-/HER2+ subtype and HR-/HER2- subtype showed worst recurrence-free survival compared to other subtypes ($p<0.001$). However, when each event-types was separately analyzed, we observed a unique subtype-specific outcome differences according to different types of events. For IBTR, HR-/HER2- subtype showed significantly worse outcome compared to HR+ tumors ($p<0.001$) but HR-/HER2+ subtype showed significantly higher number of events even compared to HR-/HER2- ($p=0.026$). For LRR, HR-/HER2+ and HR-/HER2- subtypes showed similar degree of worsening outcome compared to other subtypes ($p<0.001$). For CBC, HR+/HER2- subtype showed significantly better outcome compared to other subtypes ($p<0.001$). Interestingly, while the risk of development of LRR in HR+ subtypes was steady over time, the HR- subtypes showed increased risk of developing LRR during the first three years of follow-up. After that, all subtypes showed constant risk of developing LRR. In HR-/HER2+ subtype and HR-/HER- subtype, 68.2% and 75.5% of LRR events were manifested during the first three years, respectively. In contrast, HR+/HER2- and HR+/HER2+ subtypes had 43.5% and 56.5% of LRR events during the same period. In terms of CBC, all subtypes showed consistent annual risk of developing CBC during the follow-up period. The HR-/HER2- showed significantly increased risk of developing CBC compared to HR+/HER2- subtype until seven years of follow-up.**

**Conclusions We propose a subtype-specific locoregional and contralateral breast recurrence patterns in operable breast cancer patients by using a large cohort of breast cancer patients with sufficient long-term follow-up. These findings suggest a subtype-based tailored approach for locoregional and contralateral breast recurrences after curative treatment**

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# Computational modeling of androgen receptor (AR) and estrogen receptor as predictive biomarkers of response to AR agonists and antagonists

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**Background: Androgen receptor (AR) is expressed in 60%-90% of breast cancers. The role of AR in breast cancer largely depends on estrogen receptor (ER) status and remains controversial. In ER+ cancers, AR expression is associated with improved prognosis. Enzalutamide (ENZ), an AR antagonist, impairs AR signaling, inhibits ER+/AR+ breast cancer cell proliferation and has been shown to mitigate resistance to anti-estrogen therapies. A recent study identified that RAD140, an AR agonist, suppressed the growth of ER+/AR+ breast cancer via stimulating AR signaling, resulting in down regulation of ERα. Both AR agonists and antagonists are effective in treating ER+ breast cancers. Identifying the subgroup of patients who most likely will benefit from an individual drug is important in clinical practice. Here, we sought to characterize the relative AR to ER levels and their relationships to drug response in ER+ breast cancers.Methods: We evaluated AR and ER expression levels among 68 samples with ER+ breast cancers. On each tumor, IHC staining for AR and ER were performed and results were scored by multiplying the percentage of positive cells by the intensity. TCGA-RPPA (reverse phase protein array) dataset was used to verify AR protein distribution in ER+ cancers. We created MCF7 and T47D cells with doxycycline-inducible AR and ER expression system to manipulate the relative AR to ER ratios and determined the antitumor activity of ENZ and RAD140 by cell proliferation assays. The levels of AR and ER in cells were measured by western blot. Linear regression was used to test the association between dose-response area under curve (AUC) and AR, ER levels. Drug preference was modeled against AR/ER expression levels (AR/ER ratios) using logistic regression.Results: Among 68 ER+ breast cancers, 69.12% were AR-positive. More than 2/3 cases (48 of 68) had more ER than AR expressed. The AR to ER ratios varied from 0 to 6. In the TCGA cohort, 84.15% of 347 ER+ patients had AR/ER ratios less than 1.The range of AR to ER ratios in TCGA dataset were comparable with our data (0.004 to 4.210). In our cell line models, the AR/ER ratios were controlled between 0.19 to 4.05. We found that the AUC of RAD140 was negatively associated with AR protein levels (P=0.008) and AR/ER ratios (P=0.013), and not significantly associated with ER expression levels. On the other hand, the AUC of ENZ was significantly negatively associated with ER protein (P=0.0016) but postiviely associated with AR/ER ratio (p=0.037). Preferred treatment comparing efficacy of the two drug can be best determined at extremes of AR/ER ratios. Using clinically relevant dosages, our model predicted that ENZ (10μM) would be a preferred treatment choice and have a better treatment efficacy compared with RAD140 when the AR/ER ratio was ≤ 0.42, whereas RAD140 (1μM) would be the preferred choice with a better treatment efficacy compared with ENZ when AR/ER ratios were ≥ 3.1 The efficacy preference of the two drugs are equivocal for AR/ER ratios between 0.42 and 3.10.**
**Conclusion: We developed preclinical models using AR and ER expression levels to predict AR-targeting drug response. The results support the use of RAD140 in AR high patients and those with an AR/ER ratio ≥3.10, and enzalutamide in AR low patients and those with an AR/ER ratio ≤0.42. Equipoise on choice of drug was found for AR/ER ratios of 0.42-3.10. RAD140 and enzalutamide are compelling candidates for monotherapy or combination with anti-estrogen therapies in ER+/AR+ breast cancer. Future clinical validation of the models and therapeutic effect is warranted.**

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**The formation of GCs in cancer-free ALNs, a non-monotonic prognostic factor in HR-negative invasive breast cancer patients**

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**Purpose: To assess the frequency and prognostic relevance of germinal centres (GC) in cancer-free axillary lymph nodes (ALNs), in relation to stromal tumour-infiltrating lymphocytes (sTILs) and the presence of tertiary lymphoid structures (TLS) in the primary carcinoma, in LN-positive Hormone Receptor (HR)-negative invasive breast cancer patients.**
**Patients and methods: A cohort of 161 patients with HR-negative invasive breast cancer of no special type (NST) and LN-positive status treated between 2005-10 at Tianjin Medical University (China) was identified. sTILs and TLS at the primary tumour site and GC in 2,841 involved and cancer-free ALNs were evaluated on H&E stained sections. Markers were tested for prognostic value for invasive Disease-Free Survival (iDFS), distant Disease-Free Survival (dDFS) and Overall Survival (OS), using Cox regression models adjusted for clinico-pathological factors.**
**Results: Among the 161 HR-negative breast cancers, 47% (n=75) had >=20% sTILs and 24% (n=38) peritumoural TLS. 75% (121/161) and 76% (122/161), respectively, displayed GCs in their cancer-free and involved ALNs. Significantly higher numbers of GCs were seen in both cancer-free and involved ALNs when the primary tumours showed >=20% sTILs. The presence of TLS was significantly associated with increased GC numbers in involved but to a lesser extend in cancer-free ALNs (Kruskal-Wallis rank sum test, p<0.001 and *P_value*=0.07, respectively). As expected, increased sTILs and presence of TLS were associated with improved outcome for all endpoints.**
**Using an iterative process to determine an optimal cut off point by a minimal P value approach, a non-monotonic relationship between the frequency of GC in cancer-free ALNs and all endpoints was observed. Patients with >2 GC but less than the top 5% (= 62 GC) in cancer-free ALNs showed improved iDFS, dDFS and OS, whilst patients with <=2 GC or >62 GC across all assessed cancer-free ALNs had poorer iDFS, dDFS and OS (see Table). In the multivariate models, the frequency of GC in cancer-free ALNs added independent prognostic information for all endpoints across all patients.**
**In patients with >=20% sTILS, cancer-free ALNs within the top 5% for GC remained associated with a worse dDFS and iDFS (see Table). Cancer-free ALNs with <=2 GC in total identified a subgroup of patients with <20% sTILs tumours having the worst iDFS, dDFS and OS in multivariate models.**
**Five-year iDFS, dDFS and OS in patients with <20% sTILs were 39%, 39% and 48% respectively for those with <=2 GC in total, in comparison those with >2 GC whose five-year iDFS, dDFS and OS were 65%, 65% and 69%, respectively.**
**Conclusions: The prognostic importance of GC assessment in cancer-free ALNs in women with LN-positive HR-negative breast cancers is demonstrated. A better outcome in patients with GC formation in their cancer-free ALNs, despite low sTILs in the primary carcinoma, may suggest a systemic anticancer immune response. High sTILs but with extreme GC formation in the cancer-free ALNs could potentially reflect an overdriving but less effective immune response. The assessment of the combination of primary and nodal immune response in HR-negative breast cancers is imperative in these high-risk patients.**

Table 1. Univariate and Multivariate Cox Regression Analysis of Outcome by GC in Cancer-Free ALNs

| iDFS | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Univariate | All cases | | | | <20% sTIL | | | | >=20% sTIL | | | |
| Total GCs number - binned | Model P | | HR | CI | Model P | | HR | CI | Model P | | HR | CI |
| <=2 | | | 3.58 | 1.95 - 6.57 | | | 2.87 | 1.48 - 5.57 | | | 1.31 | 0.15 - 11.26 |
| 2>GC<62 | 4.86E-05 | | reference | | 7.64E-03 | | reference | | 4.66E-03 | | reference | |
| >62 | | | 4.63 | 1.75 - 12.4 | | | 1.93 | 0.26 - 14.56 | | | 12.79 | 3.34 - 48.97 |
| Multivariate | Corrected for: pNstage, sTILS & TLS | | | | Corrected for: pTstage & TLS | | | | Corrected for: pNstage | | | |
| Total GCs number - binned | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI |
| <=2 | 2.90E-02 | 2.00E-08 | 2.10 | 2.08 - 4.10 | 3.13E-03 | 7.00E-04 | 2.83 | 1.42 - 5.65 | 8.45E-01 | 1.00E-03 | 1.24 | 0.14 - 10.62 |
| 2>GC<62 | NA | | reference | | NA | | reference | | NA | | reference | |
| >62 | 4.15E-05 | | 9.58 | 3.25 - 28.20 | 1.94E-01 | | 4.07 | 0.49 - 33.87 | 6.62E-03 | | 8.86 | 1.83 - 42.82 |
| dDFS | | | | | | | | | | | | |
| Univariate | All cases | | | | <20% sTIL | | | | >=20% sTIL | | | |
| Total GCs number - binned | Model P | | HR | CI | Model P | | HR | CI | Model P | | HR | CI |
| <=2 | | | 4.76 | 2.48 - 9.14 | | | 3.68 | 1.82 - 7.43 | | | 2,13 | 0.22 - 20.44 |
| 2>GC<62 | 2.46E-06 | | reference | | 1.10E-03 | | reference | | 2.19E-03 | | reference | |
| >62 | | | 5.87 | 2.14 - 16.08 | | | 2.49 | 0.32 - 19.07 | | | 18.43 | 4.04 - 84.03 |
| Multivariate | Corrected for: pTstage, pNstage, sTILS & TLS | | | | Corrected for: Age, pTstage, TLS | | | | Corrected for: pNstage | | | |
| Total GCs number - binned | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI |
| <=2 | 4.30E-03 | 3.00E-09 | 2.91 | 1.40 - 6.05 | 9.01E-04 | 2.00E-05 | 3.45 | 1.66 - 7.16 | 5.51E-01 | 1.00E-03 | 1.99 | 0.21 - 19.13 |
| 2>GC<62 | NA | | reference | | NA | | reference | | NA | | reference | |
| >62 | 2.49E-06 | | 15.30 | 4.91 - 47.63 | 5.19E-02 | | 8.61 | 0.98 - 75.55 | 3.11E-03 | | 13.30 | 2.39 - 73.89 |
| OS | | | | | | | | | | | | |
| Univariate | All cases | | | | <20% sTIL | | | | >=20% sTIL | | | |

| Total GCs number - binned | Model P | | HR | CI | Model P | | HR | CI | Model P | | HR | CI |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <=2 | | | 4.14 | 2.03 - 8.41 | | | 2.93 | 1.38 - 6.22 | | | 3.13 | 0.28 - 34.51 |
| 2>GC<62 | 2.62E-04 | | reference | | 1.78E-02 | | reference | | 7.52E-02 | | reference | |
| >62 | | | 4.13 | 1.18 - 14.4 | | | 2.57 | 0.33 - 19.83 | | | 11.89 | 1.65 - 85.45 |
| Multivariate | Corrected for: Age, pTstage, pNstage, sTILS & TLS | | | | Corrected for: Age & TLS | | | | Corrected for: pNstage, LVI & TLS | | | |
| Total GCs number - binned | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI | Covariate P | Model P | HR | CI |
| <=2 | 1.50E-01 | 3.00E-09 | 1.82 | 0.80 - 4.12 | 2.28E-02 | 4.00E-04 | 2.41 | 1.13 - 5.12 | * | 3.00E-04 | * | * |
| 2>GC<62 | NA | | reference | | NA | | reference | | NA | | reference | |
| >62 | 8.62E-05 | | 16.06 | 4.02 - 64.24 | 7.01E-02 | | 7.05 | 0.85 - 58.34 | 2.80E-01 | | 2.97 | 0.41 - 21.43 |
| | | | | | | | | | *too few events | | | |

2020 San Antonio Breast Cancer Symposium®

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# Proteomic profiling of specific tumor clones using spatially resolved mass spectrometry technologies for precision oncology

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**Background**
Breast cancer (BC) remains a leading cause of cancer-related death among women worldwide. The complexity of this disease, especially its heterogeneity, have prevented its eradication and driven resistance to treatments. To reach precision oncology to eradicate BC, therapy needs to be specific to each tumor clone. Yielding enough molecular information from tumor clones to identify new drug targets represents a technical challenge due to sample size limitation or loss of spatial resolution. Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry combined with microproteomics enables a spatially-resolved unlabeled tumor imaging of its protein distribution, thus revealing proteomic clones. Our aims were to analyze the clonal proteome of luminal breast cancers, and explore its potential to expand new drug target discovery and drug repurposing.

**Methods**
A retrospective study at the Comprehensive Cancer Centre Oscar Lambret (Lille, France) was conducted to analyze 76 FFPE luminal HER2 negative tumors: 52 primary tumors from patients with early BC and 24 BC metastases. Patients gave their informed consent and the study was approved by the local institutional review board. MALDI mass spectrometry imaging and spatially-resolved on-tissue shotgun microproteomics were performed on FFPE slides of tumor tissue to determine the proteomic profile of selected clones using nanoLC-MS & MS/MS. Protein identification was performed using MaxQuant software against the Uniprot database. Functional annotation and characterization of the identified proteins were performed using Panther software. Candidate druggable targets were searched using DrugCentral druggable genome database, and their druggability level was assessed using the classification by the Illuminating the Druggable Genome Knowledge Management Center. The clonal proteome dataset was compared to publically available TCGA, BC360, and CDx datasets.

**Results**
The clonal proteome analysis identified a total of 2868 different proteins; 780 proteins were found in more than 50% of the patients. Panther analysis showed that 22% of the proteins were classified as enzymes, 15% were related to DNA processes, 6% were structural proteins, and less than 2% were related to immunity. Panther identified 139 pathways in the clonal proteome dataset. The clonal proteome analysis yielded the highest number of pathways compared to TCGA, BC360, and CDx datasets. 41 pathways (mainly metabolic pathways) were exclusive to the clonal proteome dataset. 1495 proteins of this dataset had an entry and were druggable in DrugCentral database, with 52% of them with known mechanisms of action and drug interaction. The main target classes were enzymes (60%), kinases (23%) and transporters (7%), whereas kinases were dominant in TCGA, BC360, and CDx datasets (46% to 77%). To explore the clonal proteome potential for repurposing anticancer drugs in luminal breast cancers, protein targets matching approved antineoplastic agents were searched using DrugCentral database. 97 approved anticancer drugs were identified, mostly chemotherapy (33%) or protein kinase inhibitors (28%), of whom only 17 were approved for breast cancer treatment. Compared to publically available TCGA, BC360, and CDx datasets, the clonal proteome analysis yielded the highest number of drug target candidate.

**Conclusion**
Mass spectrometry-based analysis of BC proteomic clones provides the technological means to access large functional molecular information at a clonal level to develop clone specific strategies for drug target discovery and drug repurposing in BC.

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# Non-invasive evaluation of chemoresistance in breast cancers using circulating tumor associated cells

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**Background: Despite the development of Checkpoint Inhibitor Treatments (Immunotherapy) and Targeted anticancer agents, cytotoxic (chemotherapy) agents remain the mainstay of breast cancer treatments. However, treatment failure is often encountered in breast cancers owing to innate or acquired chemoresistance. Real time monitoring of inherent or incipient chemoresistance is an unmet need to minimize or prevent treatment failures and improve outcomes. However, prior efforts to determine chemoresistance have used tumor tissue or explants and are hence not suitable for repetitive monitoring. We present findings from a large cohort perspective observational study which shows that Circulating Tumor Associated Cells (CTACs) be isolated in sufficient numbers from peripheral blood and can be profiled in vitro for chemoresistance characteristics. Methods: 15 ml of peripheral blood was obtained from 1410 breast cancer patients, of whom 719 were treatment naïve and 691 had received prior systemic therapies. Matched tumor tissue was obtained by a biopsy (post-blood collection) in a subset of 68 cases. Peripheral blood mononuclear cells (PBMCs) were isolated from all blood samples and treated with an epigenetically activating treatment medium which exerts selective cytotoxicity towards non-malignant hematolymphoid cells and allows survival of apoptosis resistant malignant CTACs, which were defined as cells which were EpCAM+, PanCK+ and CD45+/-. Viable Tumor Derived Cells (TDCs) were harvested from biopsied tumor tissue (N=68). CTACs and TDCs were treated in vitro with cytotoxic chemotherapy agents that are used in Standard of Care (SoC) treatment protocols for breast cancer as single agents or in combinations. In 68 cases, concordance in Chemoresistance Profiles (CRP) was determined between CTACs and corresponding TDCs. In 681 pretreated cases, CRP of CTACs evaluated cumulative (innate and acquired) resistance following prior exposure to chemotherapy agents. In 685 therapy naïve cases, CRP of CTACs evaluated innate chemoresistance towards chemotherapy agents. Results: Among the 68 paired samples of CTACs and TDCs, there were 733 unique combinations of CTAC-TDC-drug, among which 366 pairs (50%) were concordant for chemo-resistance, 336 pairs (46%) were concordant for absence of resistance, and 31 pairs (4%) showed absence of concordance leading to a cumulative concordance of 96% in CRP between TDC and CTACs. Among the 681 pretreated cases, resistance towards ≥1 anticancer agents was observed in 67% of the samples. Among the 685 therapy naïve cases, resistance towards ≥1 anticancer agents was observed in 39% of the samples. Conclusion: The present study shows that sufficient CTACs can be harvested from peripheral blood for meaningful non-invasive chemoresistance profiling and that the resistance profiles of CTACs are concordant with that of tumor tissue. The present approach can identify innate as well as acquired chemoresistance and can guide selection of appropriate therapies. This approach can facilitate real time monitoring of chemoresistance and therapeutic course correction to minimize the risk of treatment failures.**

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# Loss of Trop2 protein in metaplastic carcinoma of breast by IHC

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Background: Trop2 (trophoblast cell surface antigen) is a transmembrane calcium transducer which has been associated with tumor growth, aggressiveness and metastasis. Compared to normal tissue, Trop2 is expressed at much higher levels in many epithelial tumors, which makes it an excellent target for ADCs (antibody-drug conjugates). Sacituzumab govitecan-hziy, an ADC that combines Trop-2 antibody with a SN-38 payload has been recently approved for treatment of refractory metastatic triple-negative breast cancer, and several other TROP2 targeted therapies are in development. To better understand Trop 2 expression in breast tumor that may help to identify patients who could benefit most from Trop2-targeted therapy, we aimed to screen Trop2 protein in multiple types of breast tumor. Design: Using chromogenic immunohistochemistry (IHC), Trop2 protein was examined in 42 formalin fixed paraffin embedded (FFPE) specimens from surgically resected breast tumors, including 21 TNBC, 16 HR+, 4 HER2+ (3 HR+/HER2+ and 1 HR-/HER2+), and 1 sarcoma. Sections were stained on an automated staining system (BOND-MAX; Leica Microsystems) using anti-TROP2 antibody (clone ERP20043, Abcam, cat# 214488). Membrane staining was assessed. The percentage of positivity (0% to 100%) and the staining intensity (0 = no staining, 1+ = weak staining, 2+ = moderate staining, and 3+ = strong staining) were evaluated and multiplied to generate H-score (0-300). Results: Among of 41 breast carcinoma cases, 38 (92.6%) cases expressed Trop2 protein in tumor cells, with a median H-score of 162.5, including 18/21 TNBC, 16/16 HR+, 4/4 HER2+ cases. Trop2 was expressed in several breast cancer histopathology subtypes, including 32 invasive ductal carcinomas (H score ranged from 29 - 290), 2 invasive lobular carcinomas (H score 140 and 145), 1 invasive papillary carcinoma (H score 70), 1 invasive micropapillary carcinoma (H score 210), 1 invasive squamous cell carcinoma (H score 245) and 1 metaplastic carcinoma with mesenchymal differentiation (cartilaginous sarcomatoid type) (H score 17). Three breast carcinomas were negative for Trop2 (H score 0). All three cases are metaplastic carcinomas, including two spindle cell carcinomas and one with mesenchymal differentiation, which are TNBC. Only two of 5 (40%) metaplastic carcinomas tested expressed Trop2 (p = 0.0034). One breast sarcoma was tested and had no TROP2 expression. Conclusion: Trop2 is commonly expressed in breast cancer. However, metaplastic carcinoma of breast has shown a trend of Trop2 protein loss. Further validation on Trop2 loss in metaplastic carcinoma might help with identifying breast cancer patients less likely to benefit from Trop2-targeted therapy.

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# Immune cell populations in peripheral blood of metastatic breast cancer patients under CDK4/6 inhibitors

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**BackgroundCyclin-dependent kinase 4/6 inhibitors (CDK4/6i) have changed the paradigm of Estrogen-receptor positive (ER+) / human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC) treatment and represent a new standard of care in metastatic setting. Neutropenia is a well-established adverse event associated with CDK4/6i treatment, but the impact of these agents in BC patients' immune profile is unknown. This study aimed to characterize changes in host circulating immune cell subsets in BC patients undergoing CDK4/6i therapy and investigate how these changes associate with clinical benefit, by assessing progression-free survival (PFS).**
**MethodsA prospective cohort of metastatic ER+/HER2- BC patients treated with CDK4/6i (palbociclib or ribociclib) was included. Baseline and every 12−14-week peripheral blood samples were collected and objective tumor status evaluated by RECIST criteria at the same time points. Cohort was categorized in CDK4/6i therapy non-responders (CDK4/6i NResp, progression < 6.0 months) and responders (CDK4/6i Resp, PFS ≥6.0 months) using primary resistance to endocrine therapy definition of metastatic BC. A total of 66 different immune populations were assessed by flow cytometry, mainly: B cells, natural killer T (NKT), natural killer (NK), effector (Eff; CD4+, CD8+ and γδ T), effector memory (EM; CD4+, CD8+ and γδ T), central memory (CM; CD4+, CD8+ and γδ T) and naive (CD4+, CD8+ and γδ T), and regulatory T (Treg subtypes I, II and III) cells. Statistical analysis of longitudinal data was performed using Linear Mixed Effects models (LME) and Generalized estimation equations models (GEE) in R (version 3.6.1) and RStudio (version 1.2.5019). Models allowed to estimate and compare variation rates of each cell population in time.**
**ResultsA total of 26 patients were included, with a median age of 58 years (min-max, 27−79). All patients received letrozole or fulvestrant, together with LHRH agonist if premenopausal. Fifteen patients received palbociclib and 11 ribociclib, with 17 (65.4%) and 9 (34.6%) patients treated in 1st and 2nd line, respectively.With a median follow-up of 17.18 months (CI 95% 12.84 - 21.52), 6 (23.1%) patients were CDK4/6i NResp, with a median PFS (mPFS) of 3.61 months (IQR 2.28 - 4.42); only two patients in 1st line setting had PFS <6.0 months. Twenty (76.9%) patients were CDK4/6i Resp, with mPFS of 11.97 months (IQR 8.86 - 19.15), 16 (61.5%) of which treated in 1st line.In CDK4/6i NResp subgroup, an increase was identified in CD4/CD8 ratio (1.01%/month, *p*=0.001), Treg subtype III (2.74%/month, *p*=0.0008), CD8EM T cells (5.23%/month, *p*=0.029), and γδ1Eff subset of γδ T cells (6.30%/month, *p*=0.007). Interestingly, in CDK4/6i Resp subgroup no significant changes were observed in the same cell populations. Additionally, a decrease in total T (-2.38%/month, *p*=0.002), Treg subtype II (-2.52%/month, *p*=0.0076), CD8CM T (-3.30%/month, *p*=0.006), CD4CM T (-3.97%/month, *p*=0.002), γδ1CM subset of γδ T (-2.73%/month, *p*=0.047), NK (-0.99%/month, *p*=0.011), and CD8Eff T (-1.72%/month, *p*<0.001) cells was observed in CDK4/6i NResp subgroup, with no significant changes in Resp subgroup. Conclusions Results suggest that significant immune profile changes occur in metastatic ER+/HER2- BC patients with early progression to CDK4/6i and endocrine therapy.**

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# A breast cancer risk self-assessment model for Japanese women

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Introduction No fully validated breast cancer risk prediction model exists for Japanese women. We produce a collection of BC risk models and a means of selecting the most clinically interpretable and thus to a model that women can use directly for primary prevention. Methods A dataset of 2494 Japanese women were collected in 2014 - 2015 and was divided into six groups by parity (Parity and Nulliparity) and thereafter segmented into age as an estimate of menopausal status: premenopausal (PRE; 20 ≤ age < 45), perimenopausal (PERI; 45 ≤ age ≤ 55) and postmenopausal (POST; 55 < age ≤ 80). Some “history” status included multiple variables; breastfeeding history: breastfeeding experience (yes or no), number of children breastfed, breastfeeding duration (months); family history: BC cases within the 1$^{st}$, 2$^{nd}$, 3$^{rd}$ and 4$^{th}$ degree relatives (yes or no), number of BC cases in within the 1$^{st}$, 2$^{nd}$, 3$^{rd}$ and 4$^{th}$ degree relatives; smoking history: smoking experience (yes or no), Brinkman index dichotomized at 50 (less or more) and optimal value respectively; alcohol consumption history: regular consumption (yes or no), amount of monthly consumption (g), monthly consumption at optimal value (less or more). Thereafter, a logistic regression model was tested against all variables including age, BMI, parity, breastfeeding history, family history, smoking history, and alcohol history. Optimal fits were derived from adjusting thresholds and best variable representing the ‘history’ to optimize the ROC curves. All resulting optimally fit models were evaluated with AIC, and the top 10% of models (as calculated by AIC) were selected and further evaluated by AUC within the six groups. Internal validation was conducted by stratified five-fold cross validation (CV) (1000 times). Results A total of 2494 patient records were grouped by; Parity: PRE (149 cases and 184 controls): PERI (326, 415): and POST (439, 465); Nulliparity: PRE (73 cases and 148 controls): PERI (78, 122) and POST (28, 67). Based on criteria described in Methods, 480 (Parity) and 96 (Nulliparity) models were fit for use in the optimization. The mean AUC of the top 10% models after CV for Pre, PERI, and POST were (.635, .647, and .635) for Parity and (.625, .658, and .653) for Nulliparity respectively. The range of AUC for the “10% models” in each group was less than 0.02 thus there was no significant evidence that any given group 10% model was optimal. Therefore, we deferred to clinical domain knowledge in the form of which model contained the most clinically interpretable variables to select the model with the most translatable interpretation. The resulting “translatable” models include age and BMI; for Parity the additional variables included were number of childbirths, breastfeeding duration, number of BC cases within the 4$^{th}$ degree relatives, smoking experience and dichotomized monthly alcohol consumption for PRE and PERI (mean AUC after CV was .645 and .656 respectively) and breastfeeding experience, BC case within the 4$^{th}$ degree relatives, smoking experience, regular alcohol consumption for POST (.638); for Nulliparity, BC cases within the 2$^{nd}$ degree relatives, Brinkman index dichotomized at the optimal value, and dichotomized monthly alcohol consumption for PRE and POST (.626 and .648 respectively); BC case within the 2$^{th}$ degree relatives, smoking experience, and dichotomized monthly alcohol consumption at the optimal value for PERI (.657) Conclusion In this study, optimal clinically interpretable risk prediction models were derived for Japanese women. Our approach produced equally accurate models and the most clinically translatable was selected based on deep clinical knowledge. Future study will expand and re-execute the approach to produce higher accuracy while maintaining clinical interpretation and therefore use in clinical practice.

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**Real-world experience of patients treated for HER2-positive metastatic breast cancer at the centre hospitalier universitaire de Quebec: A retrospective cohort study**

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**Introduction: Multiple HER2-targeted therapies are now available and have significantly altered the natural course of HER2-positive metastatic breast cancer (mBC), with overall survival (OS) now exceeding 4 years. However, patients with HER2-positive mBC represent a heterogeneous population with some patients presenting with a history of a localized cancer and some with *de novo* metastatic disease. Our aim was to study the outcomes of HER-positive mBC in a real-life setting and compare the evolution between patients with "recurrent" breast cancer compared to those with "*de novo*" disease. Methods: In this single-center, retrospective study, we included patients with HER2-positive mBC treated at the Centre hospitalier universitaire (CHU) de Quebec using the local cancer registry and patients' medical charts. We included all female patients ≥ 18 years of age who received one or more anti-HER2 therapy for mBC. Patients whose follow-up at our center was incomplete were excluded. We identified patients who developed mBC after the occurrence of a localised disease ("Recurrent" group) and patients diagnosed with metastatic disease upon first presentation ("*De novo*" group). Primary outcome was OS. Secondary outcomes were progression-free survival (PFS) for each line of treatment and for each type of treatment (trastuzumab [T], pertuzumab [P], lapatinib [L] and trastuzumab emtansine [T-DM1]). We performed survival analysis using the Kaplan-Meier method and the log rank test. Results: A total of 106 patients in the Recurrent group and 58 patients in the *De novo* group were identified between May 2002 and December 2018 and data were collected between March and June 2019, by which time 97 (59.1%) had died. There were differences in baseline characteristics between the Recurrent and the *De novo* groups regarding age at first metastasis (50.7 vs 57.4 years, p=0.001). A total of 44.3 % vs 32.8 % of patients developed brain metastasis respectively (p=0.15). There was no statistical difference between the two groups regarding OS (3.8 years for Recurrent vs 4.2 years for *De novo*, p=0.17). PFS were also similar between the 2 groups for every anti-HER2 treatment available during the study period (Table 1). Median PFS could not be established for P in the *De novo* group since 80 % of patients were censured at the time of data collection. In the Recurrent group, P, L and T-DM1 had median PFS at least as long as those reported in landmark clinical trials. PFS were also similar between groups when comparing treatment lines (Table 2). Conclusion: In this retrospective study of patients from a real-world setting, anti-HER2 therapies offered similar OS between HER2-positive mBC patients with recurrent disease and with *de novo* metastatic disease. Median PFS are also equivalent between groups, with durations in the range of the PFS reported in major RCTs.**

Table 1

| Treatment | Recurrent group | Recurrent group | *De novo* group | *De novo* group | P value |
|---|---|---|---|---|---|
| | n | Median PFS (years) | n | Median PFS (years) | |
| Trastuzumab | 74 | 1.7 | 44 | 1.9 | 0.14 |
| Pertuzumab | 33 | 3.1 | 15 | - | 0.15 |
| Lapatinib | 29 | 0.7 | 11 | 0.6 | 0.17 |
| T-DM1 | 31 | 0.7 | 12 | 0.7 | 0.52 |

**Table 2**

| **Line** | **Recurrent group** | **Recurrent group** | ***De novo* group** | ***De novo* group** | **P value** |
|---|---|---|---|---|---|
| | **n** | **Median PFS (years)** | **n** | **Median PFS (years)** | |
| **1sd** | **106** | **1.6** | **58** | **2.0** | **0.14** |
| **2nd** | **49** | **0.7** | **20** | **0.6** | **0.27** |
| **3rd** | **23** | **0.9** | **9** | **0.7** | **0.79** |
| **4th** | **10** | **0.4** | **3** | **0.8** | **0.53** |

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**Publication Number: PS2-41**

# Supplemental contrast enhanced mammography screening of women with elevated risk of breast cancer

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**Objective and Rationale: To investigate the utility of screening Contrast Enhanced Mammography (CEM) imaging as a supplemental screening tool in women at elevated risk for breast cancer. Materials and Methods: This prospective, single institution, IRB approved observational study was conducted in asymptomatic women 35 years of age or older who were deemed at elevated risk of breast cancer, defined as IBIS v.8.0 lifetime risk of breast cancer score >15% or a prior personal history of breast cancer. Enrollment started in January 2019 and is on-going. An interim data analysis was performed. Women were invited to undergo supplemental CEM screening within 180 days of negative (BI-RADS 1 or 2) conventional 2D/3D screening mammography (MG). Patients with prior screening MBI, ultrasound or MR imaging within 12 months were excluded from study participation. Outcome measures were supplemental cancer detection rates, sensitivity, specificity, positive predictive value, and negative predictive value of CEM, along with their 95% confidence intervals, as well as the biologic profiles of MG-occult, CEM detected cancers. Results: A total of 351 women were enrolled in this prospective study over a 20-month period. To date, we have 1 year follow up on 106 cases with negative follow-up MG. Average age of the participants was 56 years ± 9.44 (standard deviation); 11 patients had screening 2D MG, 333 had combined 3-D and 2-D screening MG; 309 dense and 37 non-dense breasts based on ACR BI-RADS categories.**

**CEM depicted 8 additional breast cancers (table 1), which were otherwise MG occult, for an overall supplemental cancer detection rate of 22.7 per 1000 patients, 95% CI (9.9, 44.3). 1 false negative cancer on CEM imaging which was further detected on MR imaging only. Biopsy revealed 16 benign changes (16/28=57%), 4 high-risk lesions (4/28=14%), and 8 breast cancers (8/28=29%) (table 2). CEM imaging screening offered high specificity (0.942, 95% CI (0.917, 0.967), high NPV 0.997, 95% CI (0.991, 1.000) and moderate PPV (0.286, 95% CI (0.118, 0.453) and sensitivity (0.889, 95% CI (0.684, 1.000)). Size of CEM detected cancers ranged from 7 to 57 mm. Conclusion: This pilot trial demonstrates a supplemental cancer detection rate of 22.7 per 1000 during prevalence round of CEM screening in women at an elevated risk for breast cancer. These initial results are comparable to results reported for high-risk surveillance MR imaging. Larger, multi-institutional high-risk CEM trials are needed for those patients who are not otherwise undergoing regular supplemental surveillance MR imaging.**

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# A pro-tumorigenic mechanism of M2 tumor-associated macrophages (TAM) in triple-negative breast cancer

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Introduction:Triple-Negative Breast Cancer (TNBC) comprises approximately 30% of all breast cancers in Indian women. Given their aggressive nature, TNBCs have high rates of systemic metastasis and mortality with only chemotherapy available for treatment. The success of immunotherapy in solid tumors has raised the hope for their utility in TNBCs as well. But only a subset of patients have a clinical response to check-point inhibitors. The cellular and molecular mechanisms that mediate the immunological response or tolerance are just beginning to be understood. Compared to ER/PR+ breast cancer, TNBC features a unique tumor microenvironment (TME) characterized by a large number of tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs). The density of TILs in and of themselves do not accurately predict response to neoadjuvant chemotherapy or survival. M2 tumor-associated macrophages (M2-TAMs) have been reported to associate with solid tumors to facilitate epithelial to mesenchymal transition (EMT), tumor invasiveness, metastasis, and resistance to therapy. In this study, we have characterized presence of M2-TAM in the TNBC immune environment by examining expression of several biomarkers. Methods:Surgically excised tumor specimens from 88 Indian women with TNBC were accessed from the longitudinal observational series of SJNAHS tissue bank under IERB approved protocols and assayed on nCounter® PanCancer Immune Profiling Panel which comprised of 740 genes and characterises 14 different immune cell types. Transcriptome analysis using Non-negative Matrix factorization (NMF) based unsupervised clustering was done to arrive at stable subtypes characterized by different tumour microenvironments within TNBC. CIEBERSORT tool was used to analyse for distribution of cell types. Identification of macrophages was done by Immunohistochemistry (IHC) for CD68 and CD163 markers in TNBCs and a control group of ER+HER2-.Results:NMF analysis with an enriched immune gene signature of 111 genes, yielded 3 subtypes (ST) (37%, 27% and 36% with relative proportions of ST1, ST2 and ST3) within the TNBC. The three subtypes had distinct survival patterns with ST1 having the best prognosis with enriched TH1 gene signature and ST3 had poorest (log rank p=0.5). On application of this gene signature to TNBC groups in METABRIC and TCGA data, similar pattern emerged with a significant survival pattern of ST 3 having the poorest outcome (p=0.005). A closer examination of ST 3 revealed a signature enriched for M2 macrophages also known as TAM. Immunohistochemistry for Pan macrophage marker CD68 and an M2 specific marker CD163 between TNBC and ER/PR+ revealed difference in the two groups was significantly different (Mann Whitney p=0.03), with TNBC exhibiting 2.4 fold higher expression of CD163. CD 68, was enriched in ST2 and ST3. CD163 which is an M2 specific marker was highest in ST3 as compared to ST 1& 2 (p=0.04). This group also correlated with signal molecules secreted by macrophages containing growth factors, cytokines and chemokines, such as TGF-β, VEGF, IL-10 and CXCL and interleukins like IL4 and IL6 suggestive of TAM recruitment and polarization. It is likely that the TAM enriched subgroup is likely to be unresponsive to PD1/PDL1 inhibitors but could be targeted by novel therapeutic strategies to directly target M2-TAM. In vitro and In vivo analysis to target M2-TAM to evaluate the response to these therapeutic compounds in cell lines as well as a mouse syngeneic model is underway.Conclusions and future directions: As a cell type within the tumor microenvironment, that promotes invasion, M2-TAMs makes an ideal therapeutic target in TNBC. In addition, this sub-type lends itself to easy identification by a simple IHC assay.

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# Clinical stage is the only predictor of survival in breast cancer patients with a complete pathological response

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INTRODUCTION In breast cancer (BC) patients, achieving a complete pathological response (pCR) after neoadjuvant chemotherapy (NCT) is associated with better prognosis. Despite this, some of these patients will experience recurrences of the disease and will eventually die of BC. We identified clinical factors that can affect recurrence and survival in BC patients who achieve pCR.METHODSRetrospective analysis of a Chilean BC database including patients treated in public and private hospitals in Santiago, Chile from 2010 to 2019. pCR was defined as the absence of residual invasive disease in the breast and in the axillary lymph nodes (ypT0/is N0) at the completion of the NCT. Invasive Disease-Free Survival (IDFS), Distant Disease-Free Survival (DDFS) and BC-specific survival (BCS) was measured from the time of diagnosis to the event or lost to follow-up. We performed Cox regression analysis to identify factors associated with prognosis.RESULTSFrom 855 patients who received NCT, 195 (22.8%) achieved pCR and were included in this study. Clinical characteristics are shown in table 1. 76 (37.9%) patients had hormone receptor positive (HR+) and 113 (57.4%) had Human epidermal growth factor 2 (HER2) positive tumors. 88.7% were treated with a regimen that included anthracyclines and taxanes. With a median follow-up of 36 months, three-year IDFS, DDFS and BCS and their 95% confidence intervals were 90.9% (84.7 - 94.6), 91.8% (86.0 - 95.3) and 93.8% (87.8 - 97.5); respectively. The stage at diagnosis was the only predictor associated with IDFS (Hazard ratio (HR) = 5.6; p = 0.02), DDFS (HR = 4.1, p = 0.07), and BCS (HR = 8.3, p = 0.04). Body mass index (BMI), age, hospital, HR or HER2 status, lymph node involvement, or the presence of an in-situ component, were not associated with prognosis in the multivariate analysis.CONCLUSIONThe clinical stage at diagnosis was the only predictor of survival in patients who achieved pCR after NCT. Short follow-up and few events may have affected these results. This data is consistent with previously published work.

Table 1. Tumor and patient characteristics

| | |
|---|---|
| Median age | 49 (24 - 78) |
| Hospital | |
| Public | 57.4% |
| Private | 43.6% |
| BMI | |
| Median | 27.2 (18.5 - 44.7) |
| Overweight | 38.0% |
| Obese | 31.9% |
| Receptor Status | |
| RH+/HER2- | 16.4% |
| RH+/HER2+ | 21.5% |
| RH-/HER2+ | 35.9% |
| RH-/HER2- | 26.2% |
| Clinical Stage | |
| I | 2.1% |
| II | 47.4% |
| III | 50.5% |
| Lymph Node + | 69.7% |
| ypT0/N0 | 78.1% |
| Chemotherapy | |
| Anthracycline | 5.1% |
| Taxane | 6.2% |
| Anthracycline-Taxane | 88.7% |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: OT-13-02**

# Bracelet-1 (pre0113): A study to assess overall response rate by inducing an inflammatory phenotype in metastatic breast cancer with the oncolytic reovirus pelareorep in combination with anti-PD-L1 avelumab and paclitaxel

**Kathy Miller[1], Fengmin Zhao[2], Amy Clark[3], Grey Wilkinson[4], Rita Laeufle[5] and Antonio Wolff[6]. [1]Indiana University, Indianapolis, IN;[2]Dana-Farber Cancer Institute, Boston, MA;[3]University of Pennsylvania, Philadelphia, PA;[4]Oncolytics Biotech Inc., Calgary, AB, Canada[5]Oncolytics Biotech Inc., San Diego, CA;[6]Johns Hopkins University, Baltimore, MD**

**Background: A randomized phase 2 study with the intravenously delivered oncolytic virus, pelareorep, in combination with paclitaxel (PTX) demonstrated a statistically significant improvement in overall survival (OS) from 10.4 months with PTX alone to 17.4 months with pelareorep + PTX (HR 0.65, 80% CI 0.46-0.91, P = 0.1) in metastatic breast cancer (mBC) patients. The greatest benefit in OS was seen in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) disease (Bernstein et al, 2018). However, pelareorep + PTX did not improve progression-free survival or objective response relative to PTX alone, suggesting a late-onset adaptive immune response. A subsequent window of opportunity study in early breast cancer has shown that pelareorep can indeed promote an adaptive immune response in breast cancer tissue, enhancing CD8+ T cell infiltration and upregulating PD-L1 expression, correlating with high levels of viral replication in HR+/HER2- tumor tissue (Manso et al, 2020). Moreover, high levels of peripheral T cell clonality (PTCC) have been identified as a candidate blood-based on-treatment biomarker for pelareorep therapy, further highlighting the role of an adaptive immune response in driving pelareorep mediated efficacy (Mahalingam et al, 2020; Manso et al, 2020). Thus, BRACELET-1 will test the hypothesis that pelareorep mediated priming of an adaptive immune response will be synergistic with checkpoint blockade therapy in HR+/HER2- mBC. Moreover, BRACELET-1 will further assess PTCC as an on-treatment biomarker. The overall goal of this study is to expand the number of mBC patients who can benefit from better immunotherapy.**

**Study Design: This is an open-label randomized phase 2, three-cohort study in HR+/HER2- mBC. Patients must be refractory to endocrine therapy and have received prior treatment with a CDK4/6 inhibitor. Study cohorts include: Cohort 1, a control group receiving PTX (n = 15); Cohort 2, treatment with pelareorep added to PTX (n = 15); Cohort 3, treatment with pelareorep, PTX, and avelumab (n = 18). The study includes a three patient safety run-in for Cohort 3.**

**Specific aims: (1) Evaluation of efficacy in terms of overall response rate (ORR) at week 16, according to RECIST v1.1; (2) Examination of the safety of the study treatments; and (3) Assessment of key biomarkers, such as PTCC which will be correlated to treatment efficacy.**

**Present accrual and target accrual: The study is currently enrolling and is registered on clinicaltrials.gov: NCT04215146. Current enrollment = 2; Target enrollment = 48. This study is conducted through PrECOG, LLC and Oncolytics Biotech, Inc. Study contact information: PrE0113@precogllc.org.**

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# Role of MR spectroscopy in evaluation of axilla in breast cancer

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**The role of surgery for women with breast cancer presenting with clinically negative axilla is being questioned. Trials are underway to evaluate axillary ultrasound (AUS) for non-invasive evaluation of axilla instead of sentinel node biopsy. However, AUS has a sensitivity of 50-59%. Thus, there is a need for non-invasive test to complement AUS. MR Spectoroscopy (MRS) identifies metabolites, viz. glycerophosphocholine (GPC), phosphocholine (PC), threonine (Thr), lactate (Lac), Choline (Cho) etc that are associated with presence of metastasis in axillary lymph nodes (LN) . Biochemical changes in tumor infiltrated LNs occur earlier than morphological changes and MRS can detect these chemical changes, it can be a useful investigation in evaluation of axilla. Aim: To evaluate the role of MR Spectroscopy (MRS) in identifying biochemical changes in axillary lymph nodes in breast cancer and correlate the findings with Histopathology (HP) to predict presence of metastasis.Methods: Axillary lymph nodes were obtained from 59 patients with early breast cancer with clinically negative axilla who underwent surgery. Each LN was bisected into two equal halves. One half of LN was snap frozen in liquid nitrogen (-196°C) and then stored at −80°C until perchloric acid extraction was carried out. Other half of LN was subjected to HP evaluation with standard Eosin and Hematoxylin staining . METHOD OF MR Spectroscopy: Water-soluble metabolites from the tissue samples were extracted using PCA extraction procedure (Seenu et al Magn Reson Imaging 2005 doi: 10.1016/j.mri.2005.10.004). Proton (1H) NMR spectroscopy of specimen was performed. Concentrations of GPC, PC, Thr, Lac, Cho and other metabolites were determined by comparing the integrated intensity of isolated resonances of the compounds of interest with that of the TSP signal, correcting for the number of contributing protons and with the tissue weight . Intensity ratio for metabolites, GPC, PC and Thr (GPC+PC/Thr) was also determined.Statistical Analyses: Levels of concentrations of various metabolites were compared between involved and non-involved lymph nodes using Wilcoxon rank sum test. Diagnostic indices of MRS were assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios and overall accuracy taking final histopathology as 'gold standard' with 95% confidence intervals.Results: Mean concentrations of GPC, PC and Thr were significantly increased in involved as compared to non-involved node (table 1). Cho and Lac were not significantly increased. A cut-off value of 0.80 for the GPC-PC/Thr ratio was chosen to obtain a maximum accuracy of 89% based on previous study. MRS accurately predicted metastasis in 21 of the 24 patients who had LN metastasis on HP. Out of 35 patients with no LN metastasis, MRS correlated accurately with HP in 30 of them. Sensitivity, specificity, PPV, NPV and overall accuracy for MRS in detecting LN metastasis were 87.5%; 88%; 80.7%; 90.9%; and 86.4% respectively. Likelihood ratio for positive test and negative test for MRS to detect LN metastasis were 6.1 and 0.14 respectively.Conclusion: MRS can accurately predict presence of metastasis in axillary lymph nodes *in vitro*. *In vivo* studies are essential to corroborate these findings.**

**Mean concentrations of metabolites in axillary lymph nodes**

| | Involved | Non involved | P value |
|---|---|---|---|
| GPC | 0.5923(SD=0.5726) | 0.3648(SD=0.6774) | 0.02 |
| PC | 0.7347(SD=0.9466) | 0.5286(SD=1.1111) | 0.03 |
| Cho | 0.6930(SD=0.6756) | 0.8435(SD=0.5030) | 0.21 |
| Thr | 2.9656(SD=2.2397) | 1.1674(SD=1.2274) | 0.02 |
| Lac | 4.5515(SD=2.3271) | 3.2907(SD=1.3296) | 0.31 |

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**Veru-111 as an orally available tubulin inhibitor suppressing both taxane-sensitive and taxane-resistant triple-negative breast cancer**

**Wei Li, Shanshan Deng, Raya Krutilina, Duane Miller and Tiffany Seagroves. University of Tennessee HSC, Memphis, TN**

**In the United States, breast cancer is the second leading cause of cancer-related deaths. About 15% of all breast cancer cases are classified as a triple negative breast cancer (TNBC) subtype, which is defined by the lack of estrogen receptor, progesterone receptor and HER2. TNBC is highly aggressive, characterized by a poorer prognosis, a quicker relapse after chemotherapy and a higher rate of visceral metastasis. Cytotoxic chemotherapy is still a primary treatment regimen for patients with TNBC due to the lack of targets. FDA-approved drugs, such as paclitaxel, are effective in treating neoadjuvant, adjuvant, or metastatic TNBC, but intrinsic or acquired resistance to taxanes is commonly observed. VERU-111 is a novel, potent and orally bioavailable tubulin inhibitor that targets the colchicine-binding site with potent cytotoxicity, have improved aqueous solubility and overcome multidrug resistance, including P-gp overexpression. We evaluated the efficacy of VERU-111 in treating TNBC. VERU-111 showed significant cytotoxicity to TNBC cells *in vitro*. In addition, orally administered VERU-111 suppressed the growth of MDA-MB-231 xenografts in a dose-dependent manner with efficacies similar to paclitaxel, but without acute toxicity. VERU-111 significantly reduced metastases originating from the mammary fat pad and visceral metastasis in a separate experimental metastasis model. To better understand the effect of VERU-111 on taxane-resistant TNBC, we developed taxane-resistant TNBC cell sublines, namely MDA-MB-231/TxR, MDA-MB-468/TxR, SUM159/TxR, with acquired resistance by exposing paclitaxel continually. MTS assay confirmed that VERU-111 maintained the potency against all taxane-resistant sublines. We also found that VERU-111 arrested both MDA-MB-231 and MDA-MB-231/TxR cells at the G2-M checkpoint in a concentration-dependent manner and induced ultimate cell death. In addition, relative to paclitaxel, orally administered VERU-111 effectively inhibited the tumor growth in two aggressive taxane-resistant TNBC xenograft models, including a taxane-resistant PDX model. VERU-111, but not paclitaxel, significantly repressed the growth of preestablished axillary lymph node metastases and endpoint metastasis in mice bearing HCI-10-Luc2 xenografts, suggesting VERU-111 is a promising drug candidate for the treatment of taxane-resistant TNBC. Taken together, our data demonstrate that VERU-111 is a new generation of oral tubulin inhibitor that potently inhibits the growth of taxane-sensitive and taxane-resistant TNBC.**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS9-37**

**Hereditary breast and ovarian cancer syndrome (HBOC) diagnosis impacts more the life quality of women than men: A case-control report**

**Francisca Fernanda Barbosa Oliveira, Paulo Goberlanio de Barros Silva, Isabelle JoyceLima Silva-Fernandes, Clarissa Gondim Picanco-Albuquerque, Maria Claudia dos Santos Luciano, Maria Julia Barbosa Bezerra, Rosane Oliveira Sant?anna, Flavio Silveira Bitencourt and Marcos Venicio Alves Lima. Haroldo Juacaba Hospital, Fortaleza, Brazil**

**INTRODUCTION: HBOC syndrome is directly associated with a variant in *BRCA*1/2 genes and the diagnosis may increase anxiety and depression levels because of the need for preventive measures. Psychic impacts on women with mutations have been further explored in the literature, although the emotional aspects linked to the diagnosis in male breast cancer is poorly known. AIM: This work aimed to compare the anxiety, depression, and quality of life levels in male and female cancer patients HBOC-suspected, immediately after the result of the genetic test. METHODOLOGY: A retrospective case-control study was carried out with five men matched for age with 39 women, both with *National Comprehensive Cancer Network* (NCCN) criteria for HBOC. The Hospital Anxiety and Depression (HAD) scale and the WHOQOL-bref quality of life inventory were used. Sociodemographic, clinical, molecular, and psychological data were analyzed using χ2/Fisher's exact and Mann-Whitney, Friedman/Dunn, and Wilcoxon tests (SPSS, 20.0; p <0.05). RESULTS: All patients were >45 years old, all recruited women had breast cancer as the primary tumor and eight of them (20.5%) had ovary cancer. We had two male breast cancer and three prostate cancer Gleason>7. Sociodemographic characteristics did not differ between the genders (p> 0.05). Men had a higher prevalence of pathogenic mutation (p=0,031). Women had a higher prevalence of *BRCA*1 mutations (p=0,014) while men had of *BRCA*2 mutation (p=0,001). There was no difference in the anxiety and depression levels immediately after receiving the result, but it was observed that only women had lower quality of life in the physical domain (p=0,048). This domain showed the lowest scores in female patients (p<0,001). Although men have a higher prevalence of the pathogenic mutation in *BRCA*1/2, the emotional impact is greater in women whose impact on the physical domain may be directly associated with cancer treatment, which may have physical and psychological consequences, negatively affecting the quality of life of these women. CONCLUSION: These results reinforce the need to address the psycho-emotional aspects of women with HBOC, to promote better treatment coping, providing a better quality of life. Research Sponsor: Ministerio da Saude, Brasil (PRONON)**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS5-37**

# The feasibility of obtaining oncotype DX breast recurrence score® results from metastatic sites of patients with hormone receptor positive metastatic breast cancer

**Julie Anne L Gemmill[1], Patricia Thompson[1], Rebecca Batiste[1], Caterina Vacchi-Suzzi[1], Christina Preece[1], Jules Cohen[1], Lea Baer[1], Carolyn Mies[2], Michelle Turner[2], Christy A Russell[2] and Alison Stopeck[1]. [1]Stony Brook University Medical Center, Stony Brook, NY;[2]Genomic Health Inc., Redwood City, CA**

**Background: Identifying when to start CDK4/6 inhibitors or use chemotherapy in hormone receptor positive (HR+) metastatic breast cancer (MBC) remains challenging. The 21-gene Oncotype DX Breast Recurrence Score® test is validated to predict chemotherapy benefit in early stage HR+ breast cancer but has not been studied for use in the MBC setting.Objective: To assess the feasibility of obtaining Recurrence Scores from metastatic sites after standard of care biopsy in HR+, HER2 negative patients and correlate Recurrence Score results from matched primary breast cancer when available. Methods: A total of 48 metastatic biopsies were retrieved retrospectively from the residual tissue of patients with primary HR+, HER2 negative breast cancer. This included 36 from bone and 12 from other sites [liver (7), lung (1), rectum (1), brain (1), skin (2)]. Slides were sent to Genomic Health Inc. for RNA isolation and Recurrence Score result determination using standardized protocols. Recurrence Score results were available for 18 matched primary and metastatic biopsy samples. The percent success rate for Recurrence Score result was determined for the various metastatic sites and results compared between matched primary and metastatic site. Results: Recurrence Score results were obtained in 48% of metastatic biopsies (23 of 48 samples) including bone (17), liver (4), lung (1), and skin (1). Reasons for Recurrence Score failure included insufficient RNA (17), poor quality RNA (1), failed QC (4), and other (3). The mean Recurrence Score from the 23 metastatic sites was 35 (range: 1–66). Notably, 70% (16/23) of successful metastatic biopsies yielded Recurrence Scores in the high-risk range (≥25). None of the 23 metastatic biopsies gained HER2 by RT-PCR. Among the 18 paired samples, higher recurrence score results were observed in all but three of the metastatic biopsy samples with mean Recurrence Score results of 20 (range 7 to 41) for the primary and 35 (range 1-66) for the metastatic site. For paired samples, 72% of metastatic biopsies yielded Recurrence Scores ≥25 compared to 17% of primary sample. Primary Recurrence Scores were not predictive of metastatic scores ($r^2$=0.052). Estrogen receptor (ER) expression status was conserved in 87% whereas progesterone receptor (PR) was lost in 69% of the metastatic lesion. Among the pairs, 5 had *de novo* metastatic disease. In these, the Recurrence Score was higher in the metastatic biopsy in each case compared to the matched primary (mean 36 versus 23, respectively). Among *de novo* cases, there was 100% concordance in ER positive and HER2 negative expression and only 60% concordance in PR expression between primary and metastatic sites.**

**Conclusion: Using standard of care metastatic biopsy samples, a Recurrence Score result was successfully generated in 48% of samples including bone. This small series demonstrates wide variability in Recurrence Score results in metastatic disease with overall higher scores, common loss of PR, and minimal correlation to matched primary disease. Further examination of the potential significance of the Recurrence Score for treatment decisions in the metastatic setting requires additional tissue sampling during biopsy as insufficient RNA was the primary reason for failure.**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS7-37**

# Learning from breast cancer clinical trials how to capture recurrence estimates for North American cancer registries: A systematic review

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**Background: There are currently approximately 3.5 million breast cancer survivors in the U.S. This number will continue to rise due to the medical and scientific advances that have improved diagnostic tools and standards of care for women treated for breast cancer. The increasing number of breast cancer survivors also means that the population at risk for cancer recurrence will increase. Cancer recurrence is defined as a cancer that was treated, reduced to undetectable levels, and later returned either locally, regionally, or distantly. After a recurrence diagnosis, patients' experience reduced health outcomes and quality of life as well as the financial burden of additional treatments. Post-treatment surveillance strategies are critical for the early detection of recurrences so that interventions can be more effective at ensuring long term survival and quality of life. Currently, risk factors for breast cancer recurrence are not well understood in part due to limited population level data in cancer registries world-wide. The clinical endpoints that provide recurrence estimates are disease free survival (DFS), relapse free survival (RFS), and time to recurrence (TTR). Studies that provide recurrence estimates are limited to clinical trials (which lack diversity and represent less than 5% of cancer patients) and prospective cohorts that follow patients for a defined number of years. Currently, population-based cancer registries in North America do not collect recurrence data from patients that would allow the calculation of DFS, RFS, and TTR. The absence of population level data has limited the understanding of cancer patients' individual risks and evidence-based recommendations for recurrence prevention strategies. Moreover, recurrence data on cancers with long term latency (greater than 5-10 years) such as estrogen receptor positive breast cancer are limited.Purpose: We seek to identify which data elements and surveillance strategies are collected for recurrence data in breast cancer clinical trials. Our long-term goal is to implement these data elements into the Surveillance, Epidemiology, and End Results (SEER) program to facilitate the calculation of breast cancer recurrence estimates at the U.S. population level.Methods: We performed a systematic literature review evaluating phase II-IV clinical trials, their reported clinical outcomes, surveillance strategies, and their diagnostic tests that confirm recurrence. We used PubMed, clinicaltrials.gov, EMBASE, and the Cochrane Library for search terms "recurrence", "relapse", "recurrence free survival", "surgery", "adjuvant therapy" in breast cancer for our literature search. Inclusion criteria included clinical trials with published results, trials that compared outcomes of surgical resections, surgery with adjuvant treatments, or multiple adjuvant treatments. We included trials that provided DFS, RFS, TTR, recurrence rate, recurrence free interval, progression free survival, and time to progression. We excluded trials that did not provide recurrence estimates and those that performed recurrence modeling.Conclusion: From our review, we identified data elements and recurrence estimates for breast cancer that are collected in clinical trials but are not included in North American registries. New data elements need to be included in North American cancer registries to calculate population-based estimates for recurrence.**

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# Effectiveness of eribulin in poor prognosis subgroups of metastatic breast cancer (mBC) patients (elderly, African Americans, and patients with liver metastases) in the United States

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**Background: Eribulin mesylate was approved in the United States (US) in 2010 as third-line or later treatment (after an anthracycline and a taxane) of mBC. Multiple patient demographic and clinical characteristics have been reported to impact clinical outcomes in mBC patients. The objective of these analyses was to assess real-world clinical outcomes of eribulin therapy in three subgroups that generally have poorer prognoses: elderly (≥65 years), African American, and those with liver metastases in clinical practice in the US. Methods: A retrospective chart review study was conducted across community oncology practices in the US. Adult female patients with mBC who initiated treatment with eribulin as per US prescribing information between 2011 and 2017 were included. Data were extracted by prescribing physicians from individual patient's electronic health records and captured via an electronic case report form. All patient data were de-identified prior to analyses. Clinical outcomes including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were assessed in patients who were elderly, African American, or who had liver metastases. Results: Current analyses were based on data from 278 patients including 175 (63%) patients with liver metastases, 98 (35%) elderly patients, and 73 (26%) African American patients. Mean age at initiation of eribulin in each group was: liver metastases, 59; elderly, 71; and African American, 58. Proportion of patients with ECOG-PS ≥2 at initiation of eribulin was: liver metastases, 46%; elderly, 52%; and African American, 47%. The majority of patients received eribulin in 3rd line: liver metastases, 80%; elderly, 87%; and African American, 85%. ORR to eribulin was 34% in patients with liver metastases, 35% in elderly, and 48% in African Americans. Median PFS from initiation of eribulin was 5.2 months in patients with liver metastases, 5.8 months in elderly, and 7.6 months in African Americans. Landmark OS from initiation of eribulin at 6, 12 and 24 months were 71%, 36% and 18%, respectively, in patients with liver metastases, 72%, 35% and 23% in elderly, and 78%, 46%, and 28% in African Americans. Conclusion: Effectiveness of eribulin in clinical practice in patients with liver metastases, elderly, and African Americans was confirmed within this real-world study in the US.**

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# Real Would Evidence (RWE) of neoadjuvant docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) in patients with HER2 positive early or locally advanced breast cancer treated Single institutional experience

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**Introduction Adding pertuzumab(P) on trastuzumab(H) with cytotoxic chemotherapy increased pathologic complete response (pCR) of early or locally advanced HER2 positive breast cancer (EBC) with neoadjuvant chemotherapy. Since 63.6% of pCR rate has been reported from TRYPHAENA trial, TCHP regimen has been used as a standard of neoadjuvant treatment regimen for patients with HER2 positive EBC. However, this regimen has profound toxicities in terms of myelosuppression, neurotoxicity, and etc. Furthermore we still need more information on clinical outcomes and toxicities with this regimen. Therefore, we report real world experience of EBC patients treated with neoadjuvant TCHP followed by curative surgery. Methods We retrospectively reviewed electronic medical record of EBC patients who received neoadjuvant TCHP. Information which we gathered included patients' and tumor characteristics at the time of diagnosis, details of neoadjuvant chemotherapy, pathologic assessment of tumor response to neoadjuvant TCHP and recurrence free survival after curative surgery. pCR was defined as absence of residual invasive cancer on pathologic evaluation of the resected breast specimen and all sampled regional lymph nodes (ypT0/isN0). Results Between February 2016 and August 2019, 447 patients were treated with neoadjuvant TCHP followed by curative surgery. Median age at BC diagnosis was 56. In clinical stage, stage II was 54.6% and 45.4% of stage III and hormone receptor (HR) positive BC was 48.3%. Most commonly reported adverse event(AE) was mucositis (84%) followed by diarrhea (77%). In terms of Grade 3 AE, anorexia(6%), diarrhea(2%) were frequently observed and 9(2%) of febrile neutropenia occurred despite of prophylactic use of peg-filgrastim. Forty percent of patients experienced dose reduction due to AEs. Of 447 patients, 29% of patients underwent total mastectomy and 71% of breast conserving surgery. In terms of clinical outcome, pCR rate was 64%; 77% of HR negative BCs and 50% of HR positive BCs. Among baseline characteristics, high nuclear grade, high histologic grade, HR stats affected to pCR status (Ps<.005, respectively). Survival analysis presented that median follow up duration was 21months and invasive BC recurrences were observed in 23 patients. Estimated 3year recurrence free survival of patients with pCR was 95% and 87% of whom without pCR (P=.022). Conclusion Our clinical experience with neoadjuvant TCHP was compatible with the efficacy and safety data from TRYPHAENA trial. To concrete the result of BC recurrence after neoadjuvant TCHP, further survival analysis would be warranted.**
**Key words: neoadjuvant chemotherapy, HER2+ breast cancer, pertuzumab, pathologic complete response**

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# Comprehensive association analysis of 21-gene recurrence score and overweight in breast cancer patients

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**Background: The association between 21-gene recurrence score (RS) and host factors such as overweight remains unclear for breast cancer patients. The objectives of the current study are to comprehensively analyze the distribution, single gene expression, and prognostic predictive value of RS between overweight or non-overweight patients.Patients and methods: Luminal-like patients receiving surgery between January 2009 and December 2018 in the Comprehensive Breast Health Center, Shanghai Ruijin Hospital, with 21-gene RS results were retrospectively retrieved. Association and subgroup analysis between BMI and 21-gene RS were conducted. Single-gene expression in 21-gene RS panel was compared between overweight and non-overweight groups. Recurrence-free survival (RFS) and overall survival (OS) were calculated according to RS category and BMI status.Results: Among 1876 patients included, 442 (23.56%), 995 (53.04%) and 439 (23.40%) were classified into low, intermediate and high risk groups. RS category was significantly differently distributed between overweight and non-overweight patients (P=0.035). Overweight patients had a trend of lower RS score than patients with normal weight (25.13 vs 26.17, P=0.080). The effect of BMI on RS significantly varied according to age (P=0.012) and menstruation status (P<0.001). Compared to non-overweight patients, overweight ones presented with higher ER (P<0.001), PR (P<0.001), CEGP1 (P=0.017), Ki67 (P=0.020) and STMY3 (P=0.026) mRNA expression levels. Regarding menstrual status, postmenopausal women with BMI≥24 kg/m$^2$ were associated with higher ER group score (P<0.001), with higher ER (P=0.041), PR (P<0.001), CEGP1 (P=0.005), as well as GRB7 (P=0.015) expression, which was not significant in premenopausal women. After a median follow-up of 39.40 months (range 1.67-119.53), overweight patients had similar RFS (P=0.670) and OS (P=0.077) to non-overweight ones. Moreover, RS category could significantly predict RFS in the whole population (P<0.001), in either those overweight (P=0.003) or non-overweight (P=0.019).Conclusion: 21-gene RS was differently distributed between overweight and non-overweight patients, which interacted with age and menopausal status. ER, PR, CEGP1, Ki67 and STMY3 genes were more expressed in overweight patients. RS category could predict RFS regardless of BMI status, which warranted further validation.**

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# Development of random forest classifier method to predict breast cancer mortality among early stage breast cancer patients

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**Background: Among women diagnosed with early stage breast cancer, breast cancer mortality was conditional on the onset of distant recurrence. Gene expression profiling (GEP) tests (e.g., Oncotype Dx) have been commonly used to determine the risk level of distant recurrence, but its predictive ability is often questioned. The objective of this study aims to explore the potential of random forest machine learning to predict the risk of breast cancer mortality.Method: 63,104 patients with node-negative early stage breast cancer in the SEER-GHI dataset were randomly sampled into two groups, for the purpose of training and testing the model where each group consisted of 67% and 33% of all patients, respectively. The patient characteristics and tumor features in the study included age, tumor size, grade, chemotherapy use, Oncotype DX test recurrence score, and more. Further feature selection in the construction of the predictive model was conducted via the Boruta algorithm. As the dataset is highly imbalanced with only a very small percentage of samples being fatal, Synthetic Minority Over-Sampling Technique (SMOTE) was employed to address this issue. A cross-validated grid search finds the best combination of hyper-parameters to improve the model's performance.Results: The mean and standard deviation of follow-up duration in the cohort of patients were 32.4 and 14.3 months, respectively. Of 37,043 patients, there were 158 breast cancer deaths. Within up to a 59-month follow-up period, the breast cancer specific mortality rate was 0.43%. Based on the limited available data, the outcome of the random forest classifier method in predicting breast cancer mortality shows sensitivity 0.712, specificity 0.773, overall accuracy 0.773, and AUC (area under ROC curve) 0.742.**

**Conclusion: The use of the random forest ML algorithm to predict breast cancer mortality is promising when the hyper-parameters are fine-tuned. However, the model's positive predictive value is highly associated with sufficient data sources.**

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**Pathologic characteristics of African American women with breast cancer treated at the DoD's Murtha Cancer Center: Understanding why survival cancer is not disparate to European American women when treated within the US Military Healthcare System**

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**Background: In the United States, breast cancer mortality rates in African American women (AAW) are significantly higher than in European American women (EAW). In contrast, within the Department of Defense Military Healthcare System (DoD MHS) healthcare system, overall survival did not differ significantly between AAW and EAW with early-stage breast cancer. In this study, we evaluated pathological factors of AAW treated within the Murtha Cancer Center at Walter Reed National Military Medical Center to identify factors associated with this lack of disparate outcomes within the DoD MHS. Methods: Between 2001-2018, 345 AAW and 759 EAW treated at MCC/WRNMMC enrolled in the Clinical Breast Care Project (CBCP). Extracted demographic data included BMI, Charlson comorbidity index (CCI), education level and marital and smoking status. All diagnoses were performed by a single breast pathologist and included stage, grade, size, lymph node, hormone receptor and HER2 status. Statistical analyses included odds ratio (OR) and log-rank analyses. Results: Within this cohort, AAW were not at increased risk for having higher CCI scores, cigarette use or a college education, however, AAW were significantly more likely to be obese (OR 2.07, 95% CI 1.5, 2.9) and unmarried (OR 2.4, 95% CI 1.8, 3.2). The average age at diagnosis was 56.1 years in AAW and 57.5 years in EAW with 11% of AAW and 8% of EAW diagnosed <40 years of age. AAW were more likely to have higher stage (OR 1.6, 95% CI 1.3, 2.1), high-grade (OR 2.6, 95% CI 1.9, 3.6), larger (OR 1.6, 95% CI 1.2, 2.1) tumors. AAW were at increased risk for having triple negative tumors (OR 2.1, 95% CI 1.5, 2.9). Neither 5-year nor 10-year survival differed significantly between populations. Conclusion: While a previous study found no overall survival difference in early-stage AAW and EAW treated within the DoD MHS, this study found that across all stages of breast cancer breast cancer-specific survival was not inferior for AAW treated at MCC/WRNMMC. Critically, AAW did not have disparate survival despite having tumors with less favorable pathological characteristics, similar to those seen in the US general population. Evaluation of pre- and post-diagnostic care within DoD MHS should be performed to determine how breast care is provided to AAW within an equal-access healthcare setting and the results used as a model of care template to reduce breast cancer disparities within the US general population.** **The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions or policies of Uniformed Services University of the Health Sciences (USUHS), The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense (DoD) or the Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.**

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# Improving adherence to hormone therapy among breast cancer patients through a mobile app and patient navigation: App development and testing

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**Background: The successful use of hormone therapy (HT) has contributed to improved 5-year cause-specific breast cancer survival rates and evidence shows that long-term use produces a larger reduction in recurrence and mortality, with nearly 50% reduction in breast cancer mortality during the second decade after diagnosis. Despite the proven benefits, hormone therapy adherence is suboptimal (less than 80% of daily doses taken) and about 33% of women who are prescribed HT do not take their medication as prescribed and are at increased risk of disease recurrence and increased mortality. Smartphone ownership has increased substantially over the past decade, providing an extraordinary opportunity for innovation in the delivery of tailored interventions to improve patients' adherence to hormonal therapy. Purpose: We present the design and development process of a theory-based, culturally tailored, interactive mobile app to improve adherence to HT among breast cancer patients to be used in combination with patient navigation in a two-group randomized clinical trial study at the Mays Cancer Center. The intervention group (n= 60) will receive the phone app + patient navigation and the control or usual care group (n=60) will receive the information oncologists provide to patients prescribed HT. Methods: Four focus groups (n=21) were conducted with breast cancer patients and personal semi-structured interviews (n=8) with oncologists, nurses, and patient navigators from the Mays Cancer Center, to assess barriers and facilitators to hormone therapy adherence, key symptoms, app content, and features. Qualitative data informed the initial design and development of app mock-ups; these were assessed with two additional focus groups (n=10). Based on formative research, a functional phone app prototype was developed and beta-tested with five breast cancer patients, minor refinements were made, and the app is ready for recruitment. Results: Inputs from patients and healthcare team members helped to identify specific app content and features. Key themes included the importance of increasing patient education, enhancing self-efficacy, facilitating communication with the medical team and helping patients develop self-care skills to promote optimal adherence to hormone therapy. Specific app features included notification pop-ups, reminders, motivational messages, symptom tracking and management tips, educational content, social networking among patients, communication with a patient navigator, local resources and support groups, and technical support. In addition to colors, background and icon preferences, patients emphasize the need for a user-friendly app that is easy to navigate with clear educational content. Beta-testers found the app easy to use, credible and trustworthy, and their reactions were very positive about app appearance, content, purpose, and usability. Minor technical issues were fixed, and the study app was refined and finalized. Conclusions: An iterative and patient-centered design process was followed to develop a bilingual and interactive mobile app prototype to be used in a randomized control trial. The anticipated outcome is a scalable, evidence-based and easily disseminated intervention with potentially broad use to patients using HT and other oral anticancer agents.**

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# Association of tumor infiltrating lymphocytes (TILs) density and PD-L1 expression with pembrolizumab (P) plus gemcitabine (Gem) efficacy in patients with HER2-negative advanced breast cancer (ABC) from the GEICAM/2015-04 (PANGEA-Breast) study

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**Background Immune cells (ICs) infiltration and immune checkpoints have been shown to be important for BC patients' (pts) prognosis and response to immunotherapy. We aimed to analyze the relation between TILs prevalence and PD-L1 expression with efficacy to an immunostimulatory combination with P and Gem in ABC HER2-negative pts previously treated with ≤4 chemotherapy and/or ≥2 hormone therapy lines from the PANGEA-Breast trial (NCT03025880). Methods Pre-treatment (ttm) metastatic BC samples were assessed for TILs density [% of occupied stromal area upon H&E staining] and for PD-L1 immunohistochemistry expression using monoclonal anti-PD-L1 antibody clone 22C3 (Merck) by calculating ICs score (% of positive infiltrated ICs) and combined positive score [CPS; PD-L1 stained cells (tumor cells, lymphocytes, macrophages) divided by total viable tumor cells, multiplied by 100]. Cut-offs ≥5%, ≥10%, ≥30% were explored for TILs. PD-L1 scores were considered positive if ≥1%. Cut-offs (≥5%, ≥20%, ≥50%) were additionally assessed for PD-L1 as CPS. Logistic regression models were used to evaluate association between TILs density and PD-L1 expression with ttm efficacy in terms of Objective Response Rate [ORR; Complete + Partial Response (CR + PR)], Clinical Benefit Rate [CBR; CR + PR + Stable Disease ≥24 weeks] and Progression Free Survival (PFS), according to RECIST v1.1. Results Thirty-six pts were included, 58% had triple negative BC and 98% ECOG score ≤1. Median number of prior ttm lines was 4. ORR and CBR were 15.2% and 17%, respectively; median PFS was 3.1 months. TILs and PD-L1 were evaluated in 30 and 29 pts, respectively. No association was found between TILs density and ttm efficacy in terms of ORR, CBR and PFS. Analysis of PD-L1 ICs score did not reveal any significant association with ORR, CBR or PFS. However, pts with negative PD-L1 expression by CPS (<1%) had a significantly prolonged PFS [p-value=0.031; HR 0.39 (95%CI 0.16; 0.95)], not maintained at CPS <20% cut-off [p-value=0.062; HR 0.42 (95%CI 0.17; 1.08)]. Conclusions Our findings support that: 1) P plus Gem ttm in heavily pre-treated HER2-negative ABC pts obtains a modest ORR of 15.2%; 2) TILs density and PD-L1 expression in ICs does not predict its benefit; 3) PD-L1 in tumor cells scored as CPS impacts in worse outcome (PFS) but not in ORR, suggesting an eventual prognostic role in this population; 4) no long-term responders were observed with P plus Gem in this trial.**

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# Cardiotoxicity among patients with breast cancer treated with doxorubicin: A real-world database study

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**Background While novel targeted agents are increasingly used to care for patients with breast cancer, doxorubicin (DOX) continues to play a role in management of patients, particularly those with aggressive disease. Dose-dependent cardiomyopathy is a challenge in its use. Strategies have been proposed to mitigate this, including administration by continuous intravenous (CIV) infusion as an alternative to bolus (BOL) administration. This study used real world data to explore the impact of DOX administration mode on cardiotoxicity, duration of DOX and time to treatment failure (TTF). Methods IBM MarketScan claims were used to identify patients age ≥ 18 who received at least 2 DOX administrations (excluding liposomal DOX) after cancer diagnosis. Patients with history of cardiac events were excluded. Cardiac events based on a range of International Classification of Disease (ICD) codes were compared for BOL versus CIV overall, by tumor site and by regimen during three follow-up periods, early (within 1 year), middle (>1 to 5 years) and late (>5 years), from DOX initiation using Fisher's exact test. Duration of DOX and TTF, defined as time from initiation of DOX to subsequent systemic therapy, hospice or death, were evaluated using Kaplan-Meier method and unadjusted Cox proportional hazards models. Results: A total of 38,924 patients with breast cancer met eligibility criteria (13,186 with confirmed metastatic disease). The most common regimen used was DOX plus cyclophosphamide (n=31,815, 81.7%). Most patients had codes for both modes on the same claim date and could not be definitely assigned to BOL or CIV infusion groups; however, 917 and 5,433 patients had exclusive BOL and CIV codes, respectively. Among patients receiving DOX monotherapy (n=687), 361 and 100 had exclusive BOL and CIV codes, respectively. For patients with exclusive infusion type codes, the mean duration of DOX treatment was not significantly different for BOL vs CIV (58.9 vs 56.2 days, p=0.33 overall; 74.4 vs 74.8 days for monotherapy, p=0.97). Overall, cardiac events for BOL vs CIV were 5.1% vs 4.7% (p=0.55) during the early period, 3.1% vs 5.0%, (p=0.01) during the middle period, and 0.4% vs 1.0% (p=0.10) in the late period. There were no differences in cardiac events for BOL vs CIV among those treated with DOX monotherapy (p=0.90, 0.56 and 0.52 for the early, middle, and late period, respectively). TTF was shorter for BOL vs CIV (262.3 vs 366.0 days, p<0.001). However, when evaluating TTF, there was a significant relationship between cardiotoxicities and longer TTF (hazard ratio, HR=0.85, 95% confidence interval, CI: 0.81-0.88, p<0.001). This relationship was statistically significant for the early, middle and late periods, respectively (all p<0.001). Conclusions: These data suggest that cardiac events may occur at a similar rate for BOL and CIV. This study is limited by the retrospective nature of this study and the ability to determine causality; the use of strict coding rules to correctly assign patients to BOL vs CIV groups maintained scientific integrity and a large sample size but did result in the loss of eligible patients. Future research, including adjusted analyses, are needed to further investigate the relationship between mode of infusion and clinical outcomes.**

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# Comparative analysis of differentially abundant proteins quantified by LC-MS/MS between flash frozen and laser microdissected OCT-embedded breast tumor samples

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Background: Proteomic studies are typically conducted using flash-frozen (FF) samples utilizing tandem mass spectrometry. However, FF samples are comprised of multiple cell types, making it difficult to ascertain the proteomic profiles of specific cells. Conversely, OCT-embedded (Optimal Cutting Temperature compound) specimens can undergo laser microdissection (LMD) to capture and study specific cell types separately from the cell mixture. In the current study, we compared proteomic data obtained from FF and OCT samples to determine if samples that are stored and processed differently produce comparable results. Methods: Proteins were extracted from FF and OCT-embedded invasive breast tumors from 5 female patients. FF samples were lysed via homogenization (FF/HOM) while OCT-embedded specimens underwent LMD to collect only tumor cells (OCT/LMD-T) or both tumor and stromal cells (OCT/LMD-TS) followed by incubation at 37°C. Proteins were extracted using the illustra triplePrep kit and then trypsin-digested, TMT-labeled, and processed by two-dimensional liquid chromatography-tandem mass spectrometry (2D LC-MS/MS). Proteins were identified and quantified with Proteome Discoverer v1.4 and comparative analyses performed to identify proteins that were significantly differentially expressed amongst the different processing methods. Results: Among 4,950 proteins consistently quantified across all samples, 216 and 171 proteins were significantly differentially expressed (adjusted p-value < 0.05; $|\log_2 FC| > 1$) between FF/HOM vs. OCT/LMD-T and FF/HOM vs. OCT/LMD-TS, respectively, with most proteins being more highly abundant in the FF/HOM samples. PCA and unsupervised hierarchical clustering analysis with these 216 and 171 proteins were able to distinguish FF/HOM from OCT/LMD-T and OCT/LMD-TS samples, respectively. Likewise, PCA analysis and unsupervised clustering analysis using the 402 and 60 significantly differentially enriched GO terms (adjusted p-value (BH) < 0.2) in the FF/HOM vs. OCT/LMD-T and FF/HOM vs OCT/LMD-TS comparisons, respectively, not only distinguished OCT/LMD from FF/HOM samples but also separated LA and LB1 breast cancer subtypes within each storage/preparation method from one another. Although FF/HOM appears to be more similar to OCT/LMD-TS than OCT/LMD-T based on the number of differentially enriched proteins (216 vs. 171; p=0.022) and GO terms (402 vs. 60; $p < 2.2 \times 10^{-16}$), FF/HOM shows no greater similarity to OCT/LMD-TS than OCT/LMD-T based on PCA analysis with either proteins or GO terms ( based on weighted distance for pairwise samples, p = 0.97 from paired t-test). No significantly differentially enriched proteins or GO terms were detected between the OCT/LMD-T and OCT/LMD-TS samples but trended differences were detected. Conclusions: The proteomic profiles of the OCT/LMD-TS samples were more similar to those from OCT/LMD-T samples than FF/HOM samples, suggesting a strong influence from the sample processing methods. These results indicate that in LC-MS/MS proteomic studies, FF/HOM samples exhibit different protein profiles from OCT/LMD samples and thus, results from these two different methods cannot be directly compared. Our study also provides preliminary data for designing new studies to explore why OCT/LMD-TS samples are more similar to OCT/LMD-T than to FF/HOM samples, and to separate LA from LB1 samples. Disclaimer: The contents of this publication are the sole responsibility of the author(s) and do not necessarily reflect the views, opinions or policies of USUHS, HJF, the DOD or the Departments of the Army, Navy or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

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# A comparison of oncotype DX and NHS predict to assess the benefit of adjuvant chemotherapy in patients with early breast cancer

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## INTRODUCTION

Early breast cancer (EBC) which is hormone receptor positive, HER2 negative and 0-3 Lymph node positive, defines a Luminal subtype with an excellent outcome and the benefit of adjuvant chemotherapy in this subgroup of patients is increasingly questioned. Gene-expression profile tests have evolved to help stratify risk and to individualise treatment decisions. The 21-gene recurrence-score assay, “Oncotype DX” (ODX) is a genomic test used to quantify the likelihood of distant recurrence (Recurrence Score i.e. RS) and predict chemotherapy benefit. Although it is included in international guidelines as a tool to identify patients who could safely avoid adjuvant chemotherapy, its utility is restricted due to cost in countries with limited resources where it is not covered by insurance. The “NHS Predict” (NHSP) is a freely available online prognostic and predictive test based on cancer registry data. It utilises an algorithm based on clinical parameters and biomarker status to provide an estimate of survival as well as the potential benefit of third generation chemotherapy, hormonal and targeted therapy. The NHSP is based on “Clinical Risk (CR)” while the ODX is based on “Genomic Risk (GR)” assessment. The present study was undertaken to compare the results obtained by ODX with those obtained by NHSP so as to determine the concordance of the two tests and establish the utility of the NHSP in resource-constrained countries.

## PATIENTS AND METHODS

Patients with early ER positive, HER2 negative, 0-3 nodes positive breast cancer, who underwent the ODX assay from January 2010 to March 2020 at a tertiary referral centre were entered into this study. Patients were stratified as per the ODX RS into Low (RS= 0-20 for ≤ 50 years, 0-25 for >50 years) and High (RS= >21 for ≤ 50 years and 26-100 for >50 years) risk for recurrence with absolute chemotherapy benefit (ACB) estimated to be ≤7% and >7% respectively at 9 years.Subsequently, the NHS Predict 2.2 tool (https://breast.predict.nhs.uk/tool ) was used to compute the absolute benefit of third generation chemotherapy for each of these patients. Relevant clinical data i.e. age, menopausal status, tumour size, grade, Ki-67, ER/PR/HER2 status, nodal status and method of detection was entered into the algorithm. The ACB at 10 years, as determined by NHSP, was stratified into Low risk≤ 7% and High risk >7% so as to correspond to the ACB derived from ODX. The results obtained by NHSP were compared to those of the ODX to determine the concordance between the two tests.

## RESULTS

104 patients were entered into the study. The mean age was 53 years (range 31-76 years), 39.4% were premenopausal and 60.5% post-menopausal. The average tumour size was 19.4mm (range 8-55mm) with 61.53% T1, 36.53% T2 and 1.92% with T3 disease.14.4% were grade 1, 66.3% grade 2, and 19.2% grade 3. 74% were lymph node negative and 14.4%, 9.6% and 0.96% had 1, 2 and 3 positive nodes respectively. On ODX evaluation, low RS was seen in 87 (83.65%), and high RS in 17(16.34%) patients. As per NHSP, 99 (95.19%) patients were classified into low CR and 5 (4.8%) into high CR. There was 82.7% (86/104) concordance between NHSP and ODX with discordance in 18 patients. Of the concordant group, 84 had low CR and GR and 2 had high CR and GR. In the discordant group 15 patients had low CR on NHSP but high GR on ODX and while 3 patients had a high CR on NHSP but ODX showed low GR.

## CONCLUSIONS

In a group of patients with low clinical risk EBC there is high concordance between the NHSP and ODX tests. There is a subgroup of patients with discordant results in whom the ODX may identify patients who could potentially benefit with adjuvant chemotherapy. NHSP can aid decision making regarding adjuvant chemotherapy and identify patients who could potentially avoid chemotherapy in low risk early breast cancer.

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# Evaluation of novel diagnostic kits using the semi-dry dot-blot method combined with an automatic reader for detecting metastases in lymph nodes of patients with breast cancer : A single-center prospective study

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**Background: The semi-dry dot-blot (SDB) method, a diagnostic procedure for detecting lymph node (LN) metastases using anti-cytokeratin (CK) antibody, is based on the theory that epithelial components such as CK are not found in normal LNs. Thus, metastases are diagnosed on basis of the presence of CK in lavage fluid of sectioned LNs. We prospectively evaluated novel SDB kits that use a newly developed anti-CK19 antibody and an automatic reader for diagnosing LN metastases in patients with breast cancer. Methods: We obtained 117 LNs dissected from 58 patients with breast cancer between January 2020 and June 2020 at Nagasaki University Hospital. These were sliced at 2-mm intervals and washed with phosphate-buffered saline. Cells suspended in the lavage fluid of sliced LNs were centrifuged and lysed to extract protein. The extracted protein was applied to the SDB kit to diagnose LN metastasis using an automatic reader that evaluates absorbance. Hematoxylin and eosin (H&E) stained washed LNs were blindly examined by pathologists. Diagnoses based on SDB kit and automatic reader findings were compared with diagnoses made by histological examination of paraffin-embedded H&E stained sections of the LNs. Results: Six of the 117 LNs were assessed as positive and 111 as negative by histological examination. With a borderline CK19 absorbance of 50 milli-absorbance (mAbs) for detecting LN metastases excluding isolated tumor cells, the sensitivity, specificity, and overall agreement of the SDB kit were 66.7%, 99.1%, and 97.4%, respectively. Two patients with false-negatives had micrometastases of 0.6 and 0.5 mm in diameter. There was contamination by breast epithelial tissue in one false-positive case. With a borderline CK19 absorbance of 100 mAbs for distinguishing macrometastases from micrometastases, the sensitivity, specificity, and overall agreement of the SDB kit were 100%, 100%, and 100%, respectively. Furthermore, the kits and the automatic reader yielded diagnoses in approximately 20 min at a cost of less than 30 USD. Conclusions: The kits with an automatic reader used in our study were accurate, quick, and cost-effective in diagnosing LN metastases without loss of LN tissue, and were especially useful for detecting distinguish macrometastases. We plan to start a prospective multi-center study to evaluate clinical performance soon.**

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# Short course of preoperative tamoxifen in premenopausal breast cancer patients: Biomarker changes and survival

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Background: Luminal HER2 negative breast cancer is a highly heterogeneous disease, which complicates the choice of optimal systemic treatment in early stage disease. It is known that in postmenopausal patients (pts) Ki67 level after short course of preoperative endocrine therapy (PET) correlates with survival in contrast to baseline level. We performed the trial of PET in premenopausal early stage breast cancer pts.Patients and methods: This is a non-randomized, open-label, single-arm, phase II study of short course of preoperative tamoxifen in premenopausal pts. Primary objective was a decline in Ki67 level below 10%, secondary objectives were biomarker changes and disease free survival. Between 2011 and 2017 74 pts with T1-2N0-1M0 ER+ HER2 negative breast cancer were included in the study, median age was 45 (range, 32-55), median baseline Ki67 30% (range, 5-96), median stromal TILs 5% (range, 0-40). All pts were treated with tamoxifen for 2-3 weeks before surgery. Median follow-up was 56 months (range, 29.6-124.3).Results: There was a statistically significant decline in Ki67 during the short course of endocrine therapy (p<0,001), median Ki67 level after PET was 20% (range 3-75). Also we noticed significant decline in estrogen receptor (ER) expression level (p=0,001), but not in progesterone receptor (PR) expression. There was an increase in the level of stromal TILs (p=0.09). Baseline level of Ki67 and tumor grade had significant impact on decline in Ki67 below 10%. None of 28 pts with baseline Ki67>30% had post-PET Ki67<10% in comparison with 20,5% (9/44) with baseline Ki67 10-30%. No pts with baseline TILs≥20% had decline in Ki67 below 10%. Baseline level of Ki67 did not correlate with survival, 3-year DFS with baseline Ki67≤30 was 94,4%, Ki67>30% - 92,6% (p=0.54). Also there was no difference in survival according to Ki67 level after the course of endocrine therapy: with post-PET Ki67<10% 3-year DFS was 100% (none of pts was treated with chemotherapy), 10-30 – 92,4%, >30 – 94,4% (p=0.61). We explain this with the changes in adjuvant treatment in pts with high (>30%) level of Ki67 after endocrine therapy – all pts were receiving adjuvant chemotherapy and, what is more important, they also had ovarian suppression and tamoxifen has been changed to aromatase inhibitors (AI). Conclusion: to our knowledge this is the first study of the short course of PET in premenopausal pts. We demonstrated that post-PET Ki67 level can be used for individualization of adjuvant therapy (intensification with chemotherapy, ovarian suppression, AI in poor responders and avoiding of chemotherapy in good responders). Further prospective randomized trials are warranted.

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# Ginsenoside rg3 enantiomers in a defined ratio as a novel treatment for metastatic triple negative breast cancer

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**Background and Aims: Chemotherapy is the main treatment for metastatic triple negative breast cancer (mTNBC) but many patients develop resistance and progress to metastatic disease, with a 5-year survival rate of 11%. Therefore, more effective and less toxic treatments are required. 20(S)-ginsenoside Rg3 (SRg3) and 20(R)-ginsenoside Rg3 (RRg3) are two pharmacologically active enantiomers extracted from *Panax ginseng*. In our studies, we have shown that these two enantiomers have stereoselective activities in inhibition of proliferation, migration and invasion of triple-negative breast cancer (TNBC) cells, and hence, could be considered as two separate drugs that can be combined in a synergistic dose (S+R). Based on the inhibitory effects of single enantiomers on loop formation of human umbilical vein endothelial cells (HUVEC), we have optimized the concentrations of Rg3 enantiomers to be combined that have shown time- and dose-dependent inhibition of loop formation and migration of human and mouse endothelial cell lines. The aim of the current study was to show the mechanisms of S+R in inhibition of angiogenesis *in vitro* and its efficacy in inhibiting metastasis *in vivo*.**

**Methodology: Molecular docking was used to study the Rg3- vascular endothelial growth factor receptor (VEGFR) 2 interaction, and the VEGF bioassay kit (Promega) was used to show this interaction *in vitro*. ELISA, quantitative-PCR and western blot (WB) were used to study the expression of transcript and protein levels of signalling molecules. Two TNBC cell lines (MDA-MB-231 and HCC1143) were cultured as mammospheres and the effects of S+R on formation of mammospheres, viability (trypan blue assay and flow cytometric analysis of apoptosis or cell cycle arrest) and expression of CD44+ cells (flow cytometry) were studied. Expression microarrays were used to determine the effect of the treatment on the PI3K signalling pathway in MDA-MB-231. Nod *Scid* gamma mice were used to develop a murine model of metastatic breast cancer model. Luciferase-tagged MDA-MB-231 cells were injected into the 4th mammary fat pad of the mice and upon primary tumour establishment, treatment started. Tumour growth and metastasis was monitored using IVIS Spectrum. Statistical analysis was performed using ANOVA (Prism v8).**

**Results: According to molecular docking, binding score of Rg3-VEGFR2 was -9.0 cal/mol. The VEGF bioassay showed that Rg3 is an allosteric modulator of VEGFR2 receptor. In HUVEC, S+R treatment decreased the expression of VEGF (ELISA) and its receptor VEGFR2. It also decreased the expression of pAKT:AKT, aquaporin 1 (AQP1) and pFAK:FAK (WB). These proteins are involved in cell survival, migration, invasion and proliferation. In breast cancer cell lines, S+R decreased the expression of AQP1 and decreased mammosphere formation efficiency, not by decreasing cell viability but by decreasing the expression of CD44+ stem cell marker. In expression arrays, the treatment decreased the expression of BTK, a tyrosine kinase promoting cell death escape; increased the expression of both CASP9, promoting apoptosis, and INPPD5, favouring inhibition of metastasis. *In vivo* experiments showed that S+R lead to tumour shrinkage ($p < .0001$), decreased body burden of tumour ($p < .0001$) and decreased number of metastases ($p = .002$).**

**Conclusion: These results support the anti-cancer effects of the combination of S+R for the treatment of mTNBC.**

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# Identify breast cancer patients with pathologic complete response in the breast after neoadjuvant systemic treatment - an international, multicenter analysis

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Purpose: Neoadjuvant systemic treatment elicits a pathologic complete response (pCR) in an average of 35% of women with breast cancer. In such cases, breast surgery may be considered overtreatment. However, imaging and vacuum-assisted biopsy (VAB) alone showed high rates of missed cancer compared to standard breast surgery. We therefore evaluated multivariate algorithms using patient, tumor, and VAB variables to accurately identify patients with breast pCR.
Methods: We developed and tested three multivariate approaches: elastic net regression, Support Vector Machines (SVM), and a deep neural network. We analyzed 452 patients, randomly partitioned into training and test samples (2:1 ratio), who participated in three prospective studies assessing the feasibility of VAB to accurately detect residual disease after neoadjuvant systemic treatment (NST). The studies were conducted at 23 sites in the United States, Germany, and South Korea. The trials enrolled women who presented with clinical stage I-III breast cancer of any biological subtype and a partial or complete response to NST confirmed by ultrasonography, mammography, or magnetic resonance imaging; all patients underwent guideline-adherent surgery. We compared the performance of the multivariate algorithms to the histopathologic evaluation of disease response in the surgical specimen (reference standard) - false-negative rate (FNR, missed residual cancer) and specificity (identification of breast pCR) were the main outcome measures. The best performing algorithm on the test set with respect to sensitivity and specificity was validated using data of an independent fourth trial. We compared the performance of the multivariate approaches to the performance of imaging and/or VAB.
Results: In the test set (n=152), elastic net regression, SVM and the neural network revealed an FNR of 1.2% (1 of 85 patients with missed residual disease). Specificity of the elastic net regression was 46.3% (31 of 67 women with surgically confirmed breast pCR identified), of the SVM 62.7% (42 of 67) and of the neural network 67.2% (45 of 67). All multivariate algorithms performed better than imaging or VAB: FNR 25.9% (22 of 85) and 16.5% (14 of 85), respectively. Subsequent external validation (n=50) of the neural network algorithm showed a false-negative rate of 0% (0 of 27) and a specificity of 65.2% (15 of 23). The area under the ROC curve for the deep neural network was 0.97 (95% CI, 0.94 to 1.00). Analyzing the coefficients of the elastic net regression (regularized beta; ß) showed that the lesion diameter on imaging after NST (ß = 0.31) and VAB results (ß = 0.49) were the most important variables in the prediction of residual tumor. Other variables were also important: age (ß = 0.18), in-situ in the initial diagnostic (not VAB) biopsy (ß = 0.11), difficulties during the pathologic evaluation of the VAB specimen (ß = 0.11); needle size 7G (ß = -0.06, as opposed to 8G, 9G, 10G), multicentricity on imaging after NST (ß = 0.06), hormone-receptor positivity (ß = 0.01), and a clip marker positioned within the (former) lesion (ß = -0.01, as opposed to a clip marker positioned <5mm or >5mm from the lesion
Conclusion: A multivariate algorithm can accurately select breast cancer patients without residual disease after neoadjuvant treatment. This finding may pave the way to study omission of breast surgery in these patients in the future.

Performance of multivariate algorithms compared to imaging and vacuum-assisted biopsy

| | False-negative rate - value (95% CI) | Specificity - value (95% CI) | Negative predictive value - value (95% CI) | Positive predictive value - value (95% CI) |
|---|---|---|---|---|
| Test set (n=152) | | | | |
| Imaging | 25.9% (17.0-36.5%) | 61.2% (48.5-72.9%) | 65.1% (52.0-76.7%) | 70.8% (60.2-79.9%) |
| VAB | 16.5% (9.3-26.1%) | 89.6% (79.7-95.7%) | 81.1% (70.3-89.3%) | 91.0% (82.4-96.3%) |
| Imaging + VAB | 5.9% (1.9-13.2%) | 52.2% (39.7-64.6) | 87.5% (73.2-95.8%) | 71.4% (62.1-79.6%) |
| Elastic net regression | 1.2% (0.0-6.4%) | 46.3% (34.0-58.9%) | 96.9% (83.8-99.9%) | 70.0% (61.0%-78.0%) |
| Support Vector Machine | 1.2% (0.0-6.4%) | 62.7% (50.0 - 74.2%) | 97.7% (87.7-99.9%) | 77.1% (68.0-84.6%) |
| Deep Neural Network | 1.2% (0.0-6.4%) | 67.2% (54.6-78.2%) | 97.8% (88.5-99.9%) | 79.3% (70.3-86.5%) |
| Validation set (n=50) | | | | |
| Deep Neural Network | 0.0% (0.0-12.8%) | 65.2% (42.7-83.6%) | 100% (78.2-100%) | 77.1% (59.9-89.6%) |

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# A prospective, randomized, multicenter, double-blinded, placebo-controlled phase III trial of the HER2/neupeptide GP2 + GM-CSF versus bacteriostatic saline/WFI placebo as adjuvant therapy after any trastuzumab-based therapy in HER2-positive women with operable breast cancer

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**Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with an FDA-approved immunoadjuvant Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF, Sargramostim, Leukine) that stimulates an immune response targeting HER2/neu expressing cancers. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb clinical trial completed in 2018, no recurrences were observed in the HER2/neu positive adjuvant setting after median 5 years of follow-up, if the HLA 2+ patient received the 6 primary intradermal injections over the first 6 months (*p = 0.0338*) in a pre-specified subgroup analysis. Furthermore, the GP2 immunotherapy elicited a potent immune response measured by local skin tests and immunological assays. Of the 138 patients that have been treated with GP2 to date over 4 clinical trials, GP2 treatment was well tolerated and no serious adverse events were observed related to the GP2 immunotherapy. This Phase III trial aims to reproduce the Phase IIb study and will explore the use of GP2 + GM-CSF as adjuvant therapy to prevent the recurrence of breast cancer in HER2/neu positive and HLA 2+ patients, post-surgery and following the first year treatment with any trastuzumab-based therapy.**

**Trial Design: This Phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy or an approved biosimilar, treatment with GP2 + GM-CSF or placebo (Bacteriostatic Saline/WFI ) will be administered intradermally for the 6 primary immunization series over the first 6 months and 5 subsequent boosters over the next 2.5 years for a total of 11 injections over 3 years of treatment. The participant duration of the trial will be 3 years treatment plus 2 years follow-up for a total of 5 years following the first year treatment with trastuzumab-based therapy or approved biosimilar. An interim analysis is planned and patients will be stratified based on prior and current treatments, among other factors.**

**Eligibility Criteria: The majority of breast cancer patients will be HER2/*neu* positive and HLA 2+, disease-free, conventionally treated node-positive, post breast tumor removal surgery and following the first year treatment with trastuzumab-based therapy.**

**Trial Objectives:**

**1. To determine if GP2 therapy reduces recurrence in HER2/*neu* positive breast cancer patients.**

**2. To monitor the in vitro and in vivo immunologic responses to GP2 therapy and correlate these responses with the clinical outcomes.**

**3. To monitor for any unexpected adverse events and toxicities related to GP2 therapy.**

**Accrual: The target enrollment is up to approximately 500 patients.**

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**Funding: This trial is supported by Greenwich LifeSciences.**

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# The day after - a comprehensive rehabilitation program for breast cancer survivors

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"The Day After" a comprehensive rehabilitation program for breast cancer survivors Ora Solange Rosengarten, Naama Constantini, Milka Bertisch, Shaare Zedek Medical Center, Jerusalem Background: The most intensive part of the breast cancer (BC) treatment includes operation, radiation and chemotherapy. After completion of this stage women often are presented with a major deception: prolonged side effects of treatments and added symptoms of endocrine therapies create a physical, psychological and social burden – not allowing them to resume normal life and activities. The lack of supportive system at this point may lead them into deep crisis. Another aspect is the abundant information showing that physical activity is very efficient in controlling treatment side effects. Many studies have also shown benefit in terms of recurrence freedom of disease (HR 0.65-0.79) and overall survival for cancer patients (HR 0.52-0.61), specifically for BC – by adopting lifestyle that includes routine physical activity and healthy nutrition. Methods: The survivorship program for BC patients was designed to help coping with these challenges. The program includes a twice weekly exercise training, consulting and guidance (general and personal) by a dietician, psychologist, menopause symptom expert, sexuality expert, lymphedema physiotherapist and a series of lectures regarding breast cancer. The training is performed in 15 women group each time. Evaluation of the program was made by physical parameters- including 6 minute walk capacity, pressing power using Dynamometer, body fat composition. The results were also compared to the average values in the general population. The total impact on quality of life was evaluated by the FACT-ES (version 4) questionnaire – specifically designed and validated for BC survivors.Results: 3 groups have completed the 6 months program so far. (COVID-19 caused major interference of 3$^{rd}$ group activity). 6 min walking capacity – increased by 13.5%- from 511 m to 579 m (value pre-program in the 3$^{rd}$ quartile, post – 4$^{th}$ quartile). Pressing power increased by 10.5% from 53 kg to 59.2 kg (all values in the intermediate population range). Fat percentage decreased by 3.4% - from 43.52% to 41.8% (all in the obesity range). Quality of life: mild changes (0.5-1.0 point) were noted in 14 parameters – such as energy level, sadness, treatment side effect influence, general condition. Major changes (>1 point each) were detected in weight, arthralgia, hot flashes and vaginal discharge.QoL scores: Total GACT-G – increased from 73.1 to 79.5 (normal range 0-108); Endocrine symptom scores – increased from 49.4 to 51.9 (range 0-76);Total FACT-ES – increased from 120.8 to 131.4 (range 0-180)Conclusion: many reports show the benefit of physical activity in survivors. To our knowledge – this is the first comprehensive rehabilitation program offered to BC survivors – with regard to all aspects of post treatment distress. Both the physical measures and the questionnaires showed significant improvement (though still low). All patients expressed high level of satisfaction and stated that the program allowed faster and better recovery both physical,
emotional and functional. Further evaluation can establish the exact needs of the patients. We consider that such a program should be offered to all breast (and other) cancer survivors.

References:1.Endocrine related QoL in a randomized trial of exercise on Aromatase Inhibitor induced arthralgia in breast cancer survivors. Baglia M , Cancer 2019 2.Effect of nutrition and physical activity intervention on health behaviors of cancer survivors and carers. James EL , BMC Cancer 2015 3.The risk of metabolic syndrome in postmenopausal breast cancer survivors. Bottros DA, Menopause 2013 4.The impact of exercise on cancer mortality, recurrence and treatment related adverse events, Cormie P, Epidemiologic Reviews 2017

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**Inhibition of acetate metabolism enhances host anti-tumor immunity**

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**Acquired resistance to anti-cancer therapy is an enormous challenge. One of the main factors contributing to therapy resistance is tumor hypoxia. The stress imposed by tumor hypoxia forces cancer cells to adapt in order to survive. These metabolically adapted cancer cells are often more invasive, more malignant, and more drug resistant. As a result, the cancer cells that emerge from hypoxic tumor regions are more likely to cause patient relapse. There is therefore a critical need to understand the mechanisms that promote the survival of cancer cells in stressful tumor microenvironments. We previously showed that the enzyme acetyl-CoA synthetase 2 (ACSS2) supports cancer cell metabolism in hypoxic and nutrient-depleted environments. ACSS2 endows cancer cells with the ability to use acetate as an alternative nutrient source to drive acetyl-CoA biosynthesis during stress and genetic silencing of ACSS2 inhibits human breast tumor growth in xenograft models. Given the important role of acetate metabolism in breast cancer we expanded upon our studies by using immunocompetent hosts and syngeneic mouse tumor models. Our results revealed a previously unknown role of ACSS2 in modulating host anti-tumor immunity. We found that ACSS2 deficient tumors are unable to grow when host immunity is intact. Depletion of host immunity (T cells) using genetic or pharmacological models rescues the growth of ACSS2 deficient tumors. Pharmacological inhibition of ACSS2 in tumors in vivo displayed gene signatures associated immune infiltration and activation within the tumor microenvironment. Moreover, ACSS2 deficient breast cancer cell lines show a marked susceptibility to T cell killing in vitro. Our current research demonstrates a novel role for acetate metabolism in supporting tumor extrinsic modulation of host anti-tumor immunity. Since activation of acetate metabolism via ACSS2 is a near universal hallmark of metabolically stressed cancer cells, targeting acetate metabolism represents an unrealized opportunity with significant upside for improving current therapeutic modalities in breast cancer.**

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# Solti-1716. Targeting non-Luminal disease by PAM50 with pembrolizumab + paclitaxel in Hormone Receptor-positive/HER2-negative advanced/metastatic breast cancer patients who have progressed on or after CDK 4/6 inhibitor treatment (TATEN trial)

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Background. Patients with metastatic Hormone Receptor-positive/HER2-negative (HR+/HER2-) breast cancer (BC) are usually treated with CDK4/6 inhibitors combined with endocrine therapy (ET) as first line treatment. The addition of CDK4/6 inhibitors to endocrine therapy has demonstrated improved progression free survival (PFS), overall response rate (ORR) and more recently overall survival (OS). However, there is a 20% of patients who do not benefit from these drugs and those who respond eventually progress to the treatment. Notably, there is no standard treatment for patients progressing to CDK4/6 inhibitors. The information provided by the intrinsic subtypes (PAM50) highlight the potential value of BC molecular classification as a prognosis and predictive marker. Within HR+/HER2- disease, patients with non-luminal subtypes (HER2-enriched and Basal-like) present poorer prognosis than those with luminal subtypes, may be more sensitive to chemotherapy, and have higher expression of immune-related genes and tumor infiltrating lymphocytes (TILs). Recently, immunotherapy has been approved for treating metastatic triple negative breast cancer and several trials evaluating the action of immune checkpoint inhibitors are ongoing, including HR+/HER2- BC patients. TATEN study aims to evaluate the combination of pembrolizumab and chemotherapy in metastatic HR+/HER2-, PAM50 non-luminal BC.

Study design. TATEN is an open-label, single arm, multicenter phase II study evaluating treatment with pembrolizumab in combination with paclitaxel in patients with locally advanced or metastatic non-luminal HR+/HER2- BC who had recurrence or progression while receiving previous therapy with a CDK4/6 inhibitor plus endocrine therapy in the adjuvant and/or metastatic setting. Tumor samples collected during advanced/metastatic disease are mandatory. No prior chemotherapy for inoperable locally advanced or metastatic BC is permitted. Eligible patients will receive pembrolizumab 200 mg every 3 weeks (on day 1 of each 21-day cycle, beginning in Cycle 1) in combination with paclitaxel 80 mg/m$^2$ administered at days 1, 8, 15 of each 21-day cycle beginning at cycle 2. The primary endpoint of the study is to evaluate ORR according to RECIST V1.1. The study will use a Simon's 2-stage design and will include up to 46 patients. If 6 or more responses are observed in up to 15 patients in the first stage, the trial will continue to the second stage and 31 additional patients may be evaluated for a maximum total of 46 evaluable patients. The null hypothesis will be rejected if 19 or more responses are observed. Tumor assessments will be performed every 9 weeks. Secondary endpoints include clinical benefit rate (CBR), PFS, duration of response (DoR), time to response (TtR), OS, as well as to assess the correlation of clinical benefit (ORR, PFS) with PD1 mRNA expression and early dynamic changes in ctDNA after 1 cycle of pembrolizumab (collection of blood samples at Cycle 1 Day 1, Cycle 2 Day 1 and end of treatment are mandatory). Safety and tolerability of the combination will also be assessed. Exploratory objectives include to determine ORR, PFS, DoR and TtR based on iRECIST and to identify predictive biomarkers of response to pembrolizumab plus paclitaxel.

Patients will be enrolled in 7 sites in Spain. Recruitment started in July 2020. This study is financially supported by MSD. NCT04251169.

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# Efficacy and tolerability of neoadjuvant Pertuzumab, Trastuzumab, and weekly Paclitaxel in Locally advanced Her-2 positive Breast cancer

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**Background:Administration of neoadjuvant Pertuzumab (P), trastuzumab (T) along with chemotherapy is the standard of care for the management of locally advanced/inflammatory Her-2 positive breast cancer. Neutropenia and diarrhea are often the significant side-effects observed with the commonly used chemotherapy regimens. We evaluated the efficacy and safety of neo-adjuvant regimen consisting of P and T with weekly paclitaxel (Pac) in locally- advanced Her-2 +ve patients.Methods: Patients with newly diagnosed Her-2 positive tumor were treated in a neo-adjuvant fashion. The schedule of the treatment regimen was; P on D-1 at a loading dose of 840 mg, followed by 420 mg every 3 weeks , T on D-1 at a dose of 8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks, and Pac on D-1/8 at a dose of 80 mg/m2. Cycles were repeated every three weeks. A total of six cycles were given prior to the surgery. Herceptin was continued for a total of one year. NCCN guidelines were followed for adjuvant radiation and hormonal treatments. LVEF was measured at baseline and every 6 weeks during neo-adjuvant treatments.Results: A total of 64 women were treated between Mar 2014 - Mar 2019. Median age was 56 years (30-81). Twelve pts had T-1 disease, 43 had T-2, 7 had T-3 and, 2 pts. had inflammatory breast ca. Twenty five pts. (39%) had lymph node involvement at diagnosis. The receptor profile was: ER/PR +ve: 43 pts., ER+/PR-ve: 5 pts., ER/PR -ve: 16 pts. All patients completed the planned six cycles. Twenty seven pts. achieved a pCR (42.8%). Nine out of 16 ER/PR-ve patients (56.2%) had a pCR. Grade-3/4 neutropenia was seen in 7 patients (10.9%) but febrile neutropenia was not observed in any pt. (0%). Grade-3/4 diarrhea was seen only in 2 pt. (3.1%).Grade-3/4 neuropathy was seen in 4 pts. (6.2%). LVEF drop of more than 10% from baseline to less than 50% was seen in two patient (3.1%). No recurrence has been observed with a median follow-up of 31 months.Conclusions: A combination of Pertuzumab, Trastuzumab and weekly Paclitaxel (PTPac) delivers impressive pCR rates with an acceptable side-effects as compared to other commonly used chemotherapy regimens given along with anti-Her-2 therapy. This combination should be explored in larger studies.**

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# A novel prognostic nomogram for 2-year survival in HER2-positive patients

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**Background: Targeted therapies have largely improved prognosis of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. Yet, disease can still progress rapidly for some patients in the first two years after diagnosis. Our study aimed to establish a nomogram model to predict 2-year breast cancer-specific survival (BCSS) in early HER2-positive breast cancer patients. Patients and Methods: A total of 32,481 HER2-positive patients derived from Surveillance, Epidemiology, and End Results (SEER) database were included in the construction of nomogram. Concordance index (C-index) and calibration curve were used to evaluate the discrimination ability and predictive accuracy. We also tested the model in 804 patients from Shanghai Jiao Tong University Breast Cancer Data Base (SJTU-BCDB).Results: Age, estrogen receptor (ER) status, progesterone receptor (PR) status, histologic type, T stage and N stage were selected to construct the nomogram according to multivariable analysis. The 2-year BCSS rate was 95% and 60% for patients at low risk (<8 points) and high risk (>13 scores) respectively. The C-index of model derived from SEER database is 0.81 (95%CI 0.79-0.83). Sensitivity analysis was performed in patients undergoing breast surgeries with the C-index of 0.81 (95%CI 0.79-0.83). Validation in 804 patients from SJTU-BCDB showed respective C-index of 0.77 (95%CI, 0.62-0.92) in total population, 0.67 (95%CI 0.44-0.90) in patients receiving anti-HER2 therapy and 0.90 (95%CI 0.81-0.90) in those without targeted therapy.Conclusions: The novel nomogram can predict 2-year survival outcome in HER2-positive patients independent of receiving anti-HER2 therapy or not and help clinicians to adjust therapeutic strategies for those patients with higher risk.**

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# Phase II pilot study of trastuzumab biosimilar (herzuma®) plus gedatolisib in patients with HER-2 positive metastatic breast cancer who progressed after 2 or more HER-2 directed chemotherapy [KM-10A/KCSG18-13 interim analysis]

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Background: Prognosis of patients with HER-2 positive metastatic breast cancer (MBC) has been revolutionized with the development of dual antibodies targeting HER-2 and antibody-drug conjugate, but resistance to anti-HER-2 therapy is inevitable ultimately. PI3K-AKT-mTOR pathway aberration is known to be one of the resistance mechanisms. This randomized phase 2 pilot study evaluated safety and efficacy of Herzuma® (trastuzumab biosimilar) plus Gedatolisib (dual PI3K/mTORC inhibitor) in patients with HER-2 positive MBC who progressed after multiple lines of therapy. Methods: Patients with HER-2 positive MBC with known PIK3CA pathologic mutation or amplification whose disease progressed after more than two HER-2 directed therapy were enrolled in the study. They received Herzuma® (8mg/kg IV for 1$^{st}$ cycle loading dose, and then 6mg/kg IV every 3 weeks) plus Gedatolisib (180mg on D1, 8, 15 of every 21 days). We evaluated efficacy of the combination treatment as interim analysis. The data cutoff of this interim analysis was Aug 4, 2020. Results: As a pilot study, 15 patients were enrolled and followed for a median of 2.3 months. At data cutoff, 11 patients were eligible for response assessment. All patients were confirmed to have pathologic PIK3CA aberrations: H1047R, H1047L, E542Q, E542K, E453K, N345K, and PIK3CA amplification. Five patients reached partial response (PR) as their best response, three were stable disease (SD), and three had progressive disease (PD). All patients who have reached PR remain on investigational treatment at the data cutoff point, and the longest one is on treatment for 7.8 months. One of the SD patients ended treatment due to disease progression, and the other two have been undergoing treatment. Overall, response rate was 45.5% and disease control rate was 72.7%. No fatal adverse events related to trial medication were reported. Conclusion: In this phase 2 pilot study, Trastuzumab biosimilar plus Gedatolisib presented 45.5% of response rate with manageable toxicity in patients with HER-2 positive MBC with PIK3CA aberration. Clinical trial information: NCT03698383 Acknowledgement: this research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health &Welfare, Republic of Korea (Grant number: HI17C2206).

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# Tumour cellularity size as a biomarker to predict response after *neoadjuvant endocrine therapy*: Correlation analysis between Ki67 expression and PEPI score

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Background: Neoadjuvant endocrine therapy (NET) is an approach that allows real-time evaluation of drug efficacy as well as investigation of the biological and molecular changes that occur after estrogenic deprivation. This evaluation is mainly performed in surgical specimens after NET and it has been used as a research tool to obtain prognostic and predictive information using tumour response to decide adjuvant treatment. In this setting, there are not many validated biomarkers to predict response beyond Ki67 expression and Preoperative Prognostic Index (PEPI score) in NET. The aim of this study is to determine if the tumour cellularity size (TCS) in surgical specimen after NET correlates with PEPI score and Ki67 expression. Methods: Retrospective study of postmenopausal patients with estrogen receptor (ER) positive/HER2 negative resectable breast cancer, treated with an aromatase inhibitor for at least 4 months prior to surgery. Pathological characterization of tumour specimens: Evaluation of the percentage of residual tumour cellularity of formalin fixed paraffin embedded surgical specimens and immunohistochemistry characterization of ER and Ki67. Tumour cellularity size: calculated by combining the percentage of residual tumour cellularity and tumour pathological size. Results: N=104. Tumour characteristics at surgery and breakdown for the calculated PEPI score: table 1. Correlation between the percentage of Ki67 positive cells at surgery and TCS: (r=0.2503) p=0.04 (95% CI, 0.0014 to 0.4700). Correlation between TCS and PEPI score: (r=0.2582) p=0.05 (95% CI, -0.0131 to 0.4940).
Conclusions: Tumour cellularity size is a promising biomarker to determine response and prognosis after NET. There is a need to find other biomarkers to predict response after NET.

| Table 1 | | |
|---|---|---|
| Pathology/Biomarker status | PEPI score RFS points | No. of patients |
| pT | | |
| Not available (NA) | | 1 |
| pT1/T2 | 0 | 102 |
| pT3/T4 | 3 | 1 |
| pN | | |
| NA | | 7 |
| Negative | 0 | 75 |
| Positive | 3 | 22 |
| KI67 level | | |
| NA | | 1 |
| 0%-2.7% | 0 | 39 |
| >2.7%-7.3% | 1 | 31 |
| >7.3%-19.7% | 1 | 19 |
| >19.7%-53.1% | 2 | 13 |
| >53.1% | 3 | 1 |
| ER-status Allred score | | |
| NA | | 12 |
| 0-2 | 3 | 0 |
| 3-8 | 0 | 92 |
| PEPI score | | |
| NA | | 19 |
| 0 | | 28 |
| 1 | | 34 |
| 2 | | 5 |
| 3 | | 3 |
| 4 | | 9 |
| 5 | | 5 |
| 6 | | 1 |
| PEPI group | | |
| Not calculated | | 19 |
| I (0 score) | | 28 |
| II (1-3 score) | | 42 |
| III (≥4 score) | | 15 |

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# Risk factors for all-cause death and breast cancer-specific death in patients with HER2-positive and lymph node negative breast cancer : A retrospective analysis based on SEER database (2010 to 2017)

**Ju Wang[1], Yi Zhang[2], Jun Jiang[2] and Xiaowei Qi[2]. [1]Chongqing Center for Disease Control and Prevention, Chongqing, China[2]Army Medical University, Chongqing, China**

**Purpose: Trastuzumab combined with pertuzumab (HP) is currently the standard treatment for HER2-positive (HER2+) and lymph node-positive (LN+) breast cancer, but it is not clear which subgroup of patients with HER2+ and LN- breast cancer are suitable for HP dual-targeted therapy. By collecting the clinicopathological and prognostic information of HER2+ and LN- breast cancer patients in the SEER database from 2010 to 2017, we explored the risk factors of recurrence in these populations, aiming to identify subgroup who may need HP dual-targeted therapy among HER2+ and LN- breast cancer patients. Methods: From the SEER database, the clinicopathological and prognostic information of pathologically confirmed HER2+ and LN- breast cancer from 2010 to 2017 were extracted, and the risk factors of breast cancer-specific survival and overall survival were analyzed by multivariate Cox risk proportional model and competitive risk model.Results: After data cleaning, a total of 5163 patients were included in the current analysis. The median survival time was 49 months (IQR: 34 to 70 months). A total of 209 patients had breast cancer-specific deaths, and 325 patients died due to all causes. Multivariate Cox analysis showed that compared with patients of 20-34 years old, the 70-74 age group (HR=2.683, 95%CI=[1.221,5.895], P=0.014), 75-79 age group (HR=5.303, 95% CI=[2.437,11.543], P<0.001), 80-84 age group (HR=7.971, 95%CI=[3.655,17.386], P<0.001) and 85+ age group (HR=13.591, 95%CI =[6.327,29.192], P<0.001) had significantly higher risk of all-cause death, respectively; compared with T1 patients, the T2 patients (HR=1.784, 95%CI=[1.481,2.148], P<0.001), Patients with T3 (HR=2.413, 95%CI=[1.649,3.532], P<0.001), patients with T4 (HR=2.943, 95%CI=[1.968,4.401], P<0.001) are at significantly higher risk of total cause of death, respectively. Compared with patients of 20-34 years old, the 85+ age group (HR=2.923, 95%CI=[1.299,6.583], P=0.010) had significantly higher risk of breast cancer-specific death; compared with T1 patients, the T2 patients (HR=2.316, 95%CI=[1.709,3.139], P<0.001), T3 patients (HR=2.421, 95%CI=[1.298,4.514], P=0.005), and T4 patients (HR=8.906, 95%CI=[5.394,14.713], P<0.001) are at significantly higher risk of breast cancer-specific death, respectively; compared with patients with histological Grade I, the risk of breast cancer-specific death is significantly increased in patients with Grade III (HR=2.424, 95%CI=[1.021,5.751], P=0.045); compared with PR-positive patients, the risk of breast cancer specific death was significantly increased for PR-negative patients (HR=1.665, 95%CI=[1.141 , 2.431], P=0.008).Conclusion: Tumor size, histological grade, and hormone receptor status are independent prognostic factors for breast cancer-specific death in patients with HER2+ and LN- breast cancer. In clinical practice, patients can be recommended for single-targeted (H) or double-targeted (HP) therapy according to the individualized factor.**

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# Estrogen receptor beta agonists for triple negative breast cancer

**Jharna Datta, Natalie Willingham, Jasmine Manouchehri, Joel David, Mirisha Sheth, Bhuvaneswari Ramaswamy, Ramesh Ganju and Mathew A Cherian. The Ohio State University, Columbus, OH**

**Background:Triple negative breast cancer (TNBC) represents about 10-15% of all breast cancers. Given the lack of targeted therapies, chemotherapy and immunotherapy are the only treatment options. The five-year survival rate of TNBC patients is approximately 15% less than other forms of breast cancer. Therefore, there is an urgent need to develop novel effective therapeutics for TNBC.Material and Methods:RNA isolated from human immortalized mammary epithelial MCF10A, and various TNBC cell lines was DNase treated and quantitative RT-PCR (qRT-PCR) performed using gene-specific primers spanning exon-exon junctions that include introns in the corresponding genomic sequence to avoid genomic DNA amplification. Gene expression was calculated by ΔΔCt method using GAPDH as an internal control. Immuno-blot analyses were performed on lysates prepared from cells in log phase of growth. Proteins were detected by Enhanced Chemi-Luminescence (ECL) method. Viability of cells treated with ERβ specific agonists was determined by using CellTiter-Glo® 2.0 assay. MB231 cells were treated with ERβ agonists following transfection with pcDNA3 (vector) or Flag-tagged ESR2 plasmids. Western blot analyses using specific antibodies and qRT-PCR were performed with the protein extracts and RNA isolated from the cells, respectively. Results:Our experiments demonstrate that ESR2 (ERβ) is differentially expressed and its level of expression is about 3 to 22-fold higher in TNBC cell lines tested than MCF10A. We have shown that viability of estrogen receptor (ER) positive breast cancer cell lines can be significantly inhibited by selective activation of ERβ. A highly selective ERβ agonist has been invented in the Drug Development Institute at the Ohio State University. Treatment of TNBC lines with these ERβ agonists exhibited a dramatic reduction of cell viability. While comparable IC50 values were observed with our in house and commercially available compounds, TNBC had 2-3-fold lesser IC50 values than ER-positive cell lines. Increased expression of FOXO3 and c-Myc1 and decreased expression of c-Myc2 isoform was noted in ERβ overexpressing MB231 cells upon treatment with ERβ agonists.Conclusion:Our results demonstrate that treatment with highly selective ERβ agonists could be an effective therapeutic strategy for TNBC patients. To improve and develop novel therapeutics for TNBC understanding the mechanism of action of these compounds will be crucial.**

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# Efficacy of combined CDK4/6 inhibitor and PARP inhibitor in the treatment of BRCA1 mutant triple negative breast cancer

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Background: PARP inhibitors (PARPi) benefit only a fraction of breast cancer with BRCA mutation, and are even more limited in triple negative breast cancer (TNBC), due to clinical primary and acquired resistance. Here we found that the efficacy of PARPi in TNBC can be expanded with CDK4/6 inhibitors (CDK4/6i). Methods: We screened sensitive and resistant PARPi cell lines from existing TNBC cell lines and cultured PARPi-resistant strains by gradient concentration increase method. The effects of PARP inhibitor Olaparib and CDK4/6 inhibitor Palbociclib on TNBC cells lines were examined in vitro and in vivo. Combination index (CI) was used to evaluate the synergistic effects of drug combination. Results: We screened out the cell line MDA-MB-436, which was the most sensitive to PARPi, and the cell lines HCC1937 and SUM149, which were relatively resistant to PARPi, all of which were BRCA1 mutants. We demonstrated for the first time that the combination of PARPi and CDK4/6i has synergistic effects against some TNBCs both in vitro and in vivo, and was verified by CI<0.9. Further experiments confirmed that PARPi combined with CDK4/6i inhibited cell proliferation and migration, and increased apoptosis and DNA damage. In the PARPi sensitive BRCA-/TNBC cell (MDA-MB-436), the inhibitory effect of monotherapy PARPi was obvious; In the PARPi resistant BRCA-/TNBC cells (HCC1937 and SUM149), CDK4/6i was added to achieve significant growth inhibition. In the timing of medication, PARPi followed by CDK4/6i had better inhibitory effect.Conclusions: In some BRCA-/ TNBCs, PARPi combined with CDK4/6i had a synergistic effect. Even in PARPi-resistant cells, combined treatment could enhance the efficacy and might reverse the drug resistance to some extent.

The combination index index of HCC1937 at different drug concentrations (uM)

| The combination index index of HCC1937 at different drug concentrations (uM) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| OlaparibPalbociclib | 25.00 | 16.67 | 11.11 | 7.41 | 4.94 | 3.29 | 2.19 | 1.46 | 0.98 | 0.65 |
| P-25.00 | 0.45911 | 0.66832 | 0.86654 | 0.86964 | 0.99345 | 0.98989 | 0.9784 | 1.00322 | 1.07374 | 1.00809 |
| P-20.00 | 0.53709 | 0.85113 | 1.02265 | 1.14956 | 1.23156 | 1.27027 | 1.18907 | 1.14502 | 1.1481 | 1.25795 |
| P-15.00 | 0.59412 | 1.01814 | 1.13448 | 1.05696 | 0.92814 | 0.95567 | 0.88976 | 0.84204 | 0.8106 | 0.81348 |
| P-10.00 | 0.47554 | 0.86058 | 0.7719 | 0.71748 | 0.6233 | 0.61588 | 0.56139 | 0.5296 | 0.51025 | 0.49752 |
| P-5.00 | 0.50945 | 0.76223 | 0.74656 | 0.68334 | 0.5603 | 0.49941 | 0.46739 | 0.4149 | 0.39067 | 0.37502 |
| P-2.50 | 0.57313 | 0.70641 | 0.71475 | 0.66123 | 0.51927 | 0.45596 | 0.35098 | 0.2934 | 0.31931 | 0.2756 |

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# Survival differences in chinese versus white women with breast cancer in the United States: A SEER-based analysis

**David Wai Lim, Vasily Giannakeas and Steven A Narod. Women's College Hospital, Toronto, ON, Canada**

**Purpose: Several studies have reported lower breast cancer survival rates among Black women compared to White women, but less is known regarding outcomes in Chinese women. We compared survival rates for Chinese and White women with breast cancer in the Surveillance, Epidemiology, and End Results (SEER) database diagnosed between 2004 and 2015.**

**Methods: We conducted a cohort study of Chinese and White women with breast cancer diagnosed between 2004 to 2015 in the SEER18 registries database. We abstracted information on age and year of diagnosis, marital status, median household income, tumour size and grade, lymph node status, clinical stage, receptor status (estrogen, progesterone, and HER-2/neu receptor), surgical treatment (lumpectomy versus mastectomy), receipt of radiotherapy and chemotherapy, and death. Chinese and White women were compared for demographic, pathologic and treatment variables and differences were assessed using standardized differences. Our primary outcome was death from breast cancer. We compared crude breast cancer-specific mortality rates between the two ethnic groups. We also calculated adjusted hazard ratios (HR) in a propensity-matched design using the Cox proportional hazards model. Women were matched on the year of diagnosis and age at diagnosis (both within 2 years), tumour grade, nodal status, clinical stage, estrogen receptor status, HER2/neu status and propensity score. The propensity score accounted for marital status, household income, tumour size, progesterone receptor status and surgical procedure. A log-rank test was used to compare differences between groups using the Kaplan-Meier method. *P* values < .05 were considered statistically significant.**

**Results: There were 7,553 Chinese women (1.8%) and 414,618 White women (98.2%) with stage I-IV breast cancer registered in the SEER database. There were only small differences in tumour size, stage at presentation, node-positivity, the proportion of HER2-positive cancers, and the treatments received. Among women with stage I-IIIC breast cancer, 10-year breast cancer-specific survival was 88.8% for Chinese women, compared with 85.6% for White women. The cumulative mortality from breast cancer after 11 years of follow-up was 12.9% for Chinese women and 16.4% for White women; crude HR 0.73 (95% CI 0.67 - 0.80; *P* < .0001). In the first nine years after diagnosis, annual mortality rates are higher in White women than for Chinese women. Following the first nine years after diagnosis, the annual mortality rate for Chinese women then exceeds that of White women. In a propensity-matched analysis, the cumulative mortality from breast cancer after 11 years of follow-up was 8.9% for Chinese women and 11.9% for White women (*P* = .0002). The adjusted hazard ratio was 0.71 (95% CI 0.62 - 0.81) and was similar to the crude hazard ratio of 0.73 (95% CI 0.67 - 0.90). The adjusted hazard ratios demonstrate that Chinese women had better survival than White women in subgroups defined by age of diagnosis, tumour size and grade, clinical stage, nodal status and estrogen receptor status. The largest effects were observed for stage I cancers (HR 0.57, 95% CI 0.36-0.90) and for node-negative cancers (HR 0.61, 95% CI 0.46-0.82).**

**Conclusion: Chinese women diagnosed with breast cancer in the SEER database between 2004 to 2015 had significantly better survival rates than White women with breast cancer. Over a 10-year follow-up period, Chinese women with stage I-IIIC breast cancer experienced a 30% lower risk of death than a comparable group of White women with breast cancer. The observed difference cannot be accounted for by clinical presentation or by differences in treatment and suggests that there are intrinsic biological differences in breast cancer between Chinese and White women.**

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# Innovating a magnetic experience on wirral peninsula in the United Kingdom- our experience with magseed localisation of impalpable breast tumours and axillary node for therapeutic surgery and staging

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**INTRODUCTION Magseed is a novel localization technology in which a tiny seed is inserted to accurately mark the site of breast tumour. These can be detected intra-operatively by sentimag localization system. These can be implanted days prior to surgery and do not require use of radioactive material. It aids localization of impalpable breast lesions improving margin clearance rates. METHODS A study was undertaken of 50 patients undergoing Magseed localization of non-palpable breast lesions in rural and urban areas of Wirral Peninsula in the UK. Data including age, mode of localization (Stereo-guided/ Ultrasound guided), presentation (Symptomatic/Screen detected), and time to surgery after localization, size and weight of specimen, histology and re-excision rates was collected between June 2019 and November 2019. RESULTS A total of 50 patients had 52 Magseed inserted. n=14 were symptomatic, n=35 were screen detected and n=1 was an incidental finding on surveillance mammogram for a B3 lesion. All 50 patients had therapeutic surgery. 30 seeds were inserted on the right and 22 were inserted on the left (two were bilateral). 44 seeds were inserted under Ultrasound guidance and the rest were targeted under stereo guidance (n=8).Deployment of 2 Magseed resulted in malposition requiring wire localization. Mean age of subjects was 59.76 (range 31-81) years. Mean time to surgery after Magseed insertion was 8.04 (range 1-27) days. Mean weight of the specimen was 48.57(range 10-264) gm. Mean size of the lesions was 20.32 (range 8-65) mm. Redo surgery for margin clearance was performed bringing the re-excision rate to 15.38% (n=8). CONCLUSION We conclude that Magseed localization of breast tumours is a safe and reliable technique in terms of accuracy, localization and clearance of margins without any radiation concerns. Our re-excision rate for margin clearance is comparable to the national average. The only caveat we observed was localization of impalpable lesions prior to surgery in bulky breasts where we had to utilize wire guided localization on the day of surgery. Large scale data are lacking to compare Magseed localization with other localization techniques for non-palpable breast lesions.**

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# Can sentinel lymph node biopsy be avoided in patients of breast cancer with normal preoperative ultrasound of axilla

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**Introduction: Need for any form of surgery for axillary lymph nodes in breast cancer with clinical and radiologically negative axilla is being increasingly questioned. Randomized controlled trials are underway to answer this question. This study was undertaken to evaluate the results of sentinel node lymph biopsy (SLNB) in patients with normal preoperative axillary ultrasound (AUS) after obtaining institution ethics committee approval. Materials and Methods: All patients of operable breast cancer seen in the Breast Cancer Clinic at Sultan Qaboos University Hospital, underwent routine preoperative AUS as part of staging work up. In patients with suspicious lymph nodes, fine needle aspiration cytology (FNAC) was performed. Patients with clinical and radiologically normal axilla underwent BCS/ mastectomy with SLNB (Group 1), while patients with positive lymph nodes underwent neoadjuvant chemotherapy (NACT) and repeat AUS after completion of chemotherapy. Patients who were reported to have normal AUS post NACT underwent SLNB (Group 2). Negative Predictive Value (NPV) and probability of positive SLN when AUS was normal were calculated for the entire cohort, group 1 and group 2. A comparison of NPV between two groups was performed at a 5% level of significance (MedCalc 12.7, 2013). Results: Between 2016-2018, 165 patients with normal AUS underwent SLNB. One hundred and thirteen of these patients underwent 'upfront' SLNB, while 52 patients had received NACT and then underwent SLNB. Mean age of patients was 49.33 years (range: 32-74 years ) and was similar in both groups. Mean number of lymph nodes obtained was 4.7 (range 2-8) in group 1 and 4.69 (range 2-6) in group 2. Mean number of positive lymph nodes was 1.69 in group 1 and 2.4 in group 2. Out of 165 patients with normal AUS, 51 patients had metastasis in SLNs. Twenty nine of 113 patients in group 1 showed metastasis in SLNs while 22 out 52 patients in group 2 showed metastasis. NPV for AUS for the whole group was 69.1% (95% CI=62.0%-76.2%), and for group 1 & 2 were 74.3% (95%CI=66.2%-82.4%) and 57.6% (95% CI=44.2%-71.0%), respectively. A significant higher NPV was found in group 1 than in group 2 ($\chi^2$=3.873, p=0.049). Thus, the probability of positive SLN even when AUS was normal was 0.31 for whole group, 0.25 for group 1 and 0.42 for group 2. Conclusion: Probability of metastasis in SLN when AUS with or without FNAC is normal is more than 20%. Thus there is need for better preoperative imaging of axilla in patients of breast cancer with clinically and radiologically negative axilla before abandoning SLNB altogether.**

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# Evidence for reproductive control of liver size with implications for risk of liver metastases in postpartum breast cancer patients

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**Women diagnosed with breast cancer within 10 years of a completed pregnancy are 2~3x more likely to develop liver metastases than never-pregnant (nulliparous) patients, even after controlling for prognostic variables (Goddard 2017). This finding suggests a unique biology in the postpartum liver, a putative pre-metastatic niche, which makes postpartum patients more susceptible to liver metastases. In rodent models, we previously reported increased liver size, hepatocyte proliferation, and anabolic metabolism during pregnancy and lactation. Within one week post-weaning, the rodent liver returned to its pre-pregnant size via a coordinated cell death and tissue remodeling process we call liver involution (Goddard 2017). We find that this process of involution supports overt liver metastasis using two different mammary tumor cell lines. In women, a liver-breast interaction during pregnancy and weaning, as occurs in rodents, has not been described. To investigate the human liver with pregnancy and weaning, we conducted a prospective, non-interventional clinical trial in healthy pregnant women. 47/77 women completed the pregnancy study visits and 17/47 completed post-wean visits. Participants underwent magnetic resonance imaging (MRI) of their livers, provided blood samples, and completed body metric analyses at each study time point. The majority of women (~70%) had increased liver size and evidence of increased liver function at third trimester compared to first trimester, with liver size returning to pre-pregnancy levels with weaning. In this cohort, the increase in liver size exceeded levels expected if the metabolic demands associated with increased body weight during pregnancy were the primary mediator. Intriguingly, primary bile acid and bile acid synthetic enzyme concentrations correlated with liver size increase during pregnancy. Women whose liver growth did not follow the most often observed pattern of increase with pregnancy and decrease postpartum had unchanged bile acid levels, were more likely to have gestational hypertension, and did not have expected increases in liver glucose production during pregnancy. Combined, this study provides the first description of human liver size increase with pregnancy, and return to pre-pregnant baseline size after weaning, with evidence that women who do not experience these liver changes may be metabolically distinct. Furthermore, these data are consistent with the hypothesis that reproductive alterations to the liver, in particular weaning-induced involution, contributes to the increased risk for liver metastases in women diagnosed with breast cancer postpartum.**

**Reference: Goddard, E. T., Hill, R. C., Nemkov, T., D'Alessandro, A., Hansen, K. C., Maller, O., Mongoue-Tchokote, S., Mori, M., Partridge, A. H., Borges, V. F., & Schedin, P. (2017, Feb). The Rodent Liver Undergoes Weaning-Induced Involution and Supports Breast Cancer Metastasis. *Cancer Discov, 7*(2), 177-187. https://doi.org/10.1158/2159-8290.CD-16-0822**

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# Her2 low status and response to neoadjuvant chemotherapy in Her2 negative early breast cancer

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Background: HER2-positive status has for 20 years defined a subgroup of breast cancer (BC) patients who benefit from anti-HER2 therapies. Studies testing trastuzumab in HER2-low patients – defined as IHC 1+ or 2+/ISH non-amplified have not shown an improvement in outcomes. Recently, the results of Phase I studies with novel antibody drug conjugates targeting HER2 (Trastuzumab-deruxtecan and trastuzumab-duocarmazine) have suggested a benefit in HER2-low patients with advanced breast cancer. Little is known about HER2-low BC and data on early stage disease and the prognostic value of HER2-low is scarce. More data on this population is urgently needed in order to prepare the integration of these new drugs into treatment guidelines. Most large Phase 3 trials conducted in the past in luminal or triple negative (TNBC) disease did not collect detailed HER2 status data, rendering retrospective cohorts of particular value Patients and Methods: This is a retrospective cohort of all early breast cancer patients treated with neoadjuvant chemotherapy (2007 – 2018) in a single cancer center. HER2 positive (IHC +3 or IHC +2 FISH/SISH amplified) patients were excluded. HER2-low status was defined as HER2 IHC 1+ or 2+/ISH non-amplified. Other patients were classified as HER2-0. Our primary objective was to investigate whether HER2-low status impacts on efficacy outcomes, including pathologic complete response (pCR), relapse free survival (RFS) for patients undergoing neoadjuvant chemotherapy. Secondary objectives include describing this novel population from a demographical and pathological perspective. Categorial variables were compared by Fisher's exact test. Survival was estimated by the Kaplan-Maier method. Prognostic factors were adjusted by Cox regression model and logistic regression.
Results: 478 non-HER2-positive patients were eligible, with a median follow-up of 59 months. 315 pts had luminal (65.9%) and 163 TNBC subtypes (34.1%). HER2-0 in 330 pts (69%), +1 in 87 (18.2%) and +2/ISH non-amplified in 61 (12.8%). Among luminal tumors, 70 patients had HER2 IHC +1 (22.2%) and 56 IHC +2/ISH non-amplified (17.8%). This proportion was lower in TNBC, with only 17 HER2 IHC +1 (10.4%) and 5 IHC +2 (3.1%). The baseline characteristics and outcomes of this population stratified by the presence/absence of the her2 low status is described in Table 1. Most pts had T3/4 , node positive, grade II/III and stage III tumors, irrespectively of her2-low status or subtype. pCR was achieved in 10.7% of the luminal pts and in 49.4% of TNBC, with no impact of HER2-low status. Five-year relapse-free survival (RFS) was also not affected by this factor. HER2-low was not associated with pCR or RFS in univariate and multivariate analysis. Conclusion: In this cohort, 31% of patients were HER2-low. There were no substantial differences in demographic/pathologic terms between HER2-low and HER2-0 patients. HER2-low status did not impact pCR rates or RFS of luminal and triple negative tumors treated with neoadjuvant chemotherapy. Larger studies are urgently needed to better characterize this subpopulation and determine whether focused phase 3 trials will be warranted.

Table 1: Baseline characteristics stratified by Her2-low status

| Characteristics | TNBC | | Luminal | |
|---|---|---|---|---|
| | HER2-0 | HER2-Low | HER2-0 | HER2-Low |
| | N 141 | N 22 | N 189 | N 126 |
| Mean age (range) | 45 (27-90) | 44 (26-65) | 46 (27-72) | 48 (27-77) |
| cT | | | | |
| T1 | 9 (6.5%) | 3 (13.6%) | 8 (4.3%) | 7 (5.5%) |
| T2 | 61 (43.9%) | 6 (27.3%) | 54 (28.7%) | 38 (30.2%) |
| T3 | 37 (26.6%) | 3 (13.6%) | 61 (32.4%) | 34 (27%) |
| T4 | 31 (22.3%) | 10 (45.5%) | 64 (34%) | 47 (37.3%) |
| missing | 3 (0.7%) | | 2 (0.6%) | |
| cN | | | | |
| N positive | 92 (65.2%) | 17 (77.3%) | 119 (62.9%) | 86 (68.3%) |
| N negative | 47 (33.3%) | 5 (34.7%) | 69 (36.5%) | 40 (31.7%) |
| missing | 2 (0.5%) | | 1 (0.6%) | |
| Stage | | | | |
| I-II | 64 (47.0%) | 6 (27.3%) | 70 (38.0%) | 41 (32.5%) |
| III | 72 (52.9%) | 16 (72.7%) | 114 (62.0%) | 85 (67.5%) |
| Histologic grade | | | | |
| I | 1 (0.7%) | 0 | 13 (6.9%) | 17 (13.5%) |
| II | 31 (22.0%) | 4 (18.2%) | 114 (60.6%) | 69 (54.8%) |
| III | 94 (66.7%) | 16 (72.7%) | 51 (27.1%) | 36 (28.6%) |
| Missing | 15 (10.6%) | 2 (9.1%) | 11 (5.3%) | 4 (3.2%) |
| pCR | 68 (48.6%) | 12 (54.5%) | 19 (10.1%) | 15 (11.9%) |
| | | *p 0.65* | | *p 0.71* |
| 5y RFS (%) | 74.6% | 75.3% | 75.4% | 75.4% |

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# Does complete surgical removal of metastases in oligometastatic breast cancer improve survival? A matched-pair analysis of the AGMT_MBC-registry

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**Background: Metastatic breast cancer (MBC) is generally thought to be a systemic and incurable disease requiring systemic therapy. However, surgical resection of oligometastatic disease might be of benefit similar to other malignant diseases. Here, we present the results from a matched analysis of patients undergoing radical surgery of metastases.**
**Methods: The MBC registry of the Austrian Study Group for Medical Tumor Therapy (AGMT) is an ongoing multicenter registry for MBC patients in Austria. Patients undergoing surgical removal of all metastatic sites (+/- primary tumor and lymph node dissection) were identified and matched 1:1 according to disease-free survival (*de novo* metastatic vs. < 24 vs. ≥ 24 months), location of metastases, subtype (HR+/HER2- vs. HR+/HER2+ vs. HR-/HER2+ vs. triple-negative) and age (≥ 60 vs. < 60). OS was defined as time from diagnosis of metastatic disease until death. Only patients with available matching parameters and sufficient outcome data were included in this analysis.**
**Results: As of 24/06/2020, 1904 patients were enrolled into the AGMT_MBC-Registry; 24 of them received surgery of metastases and 23 had a complete match with patients without surgery. In the surgery group, five patients (21.7%) received immediate postperative chemotherapy and 80.0% received further chemotherapy after surgery. Out of patients with HR+ disease (n=15), 86.7% received endocrine therapy prior and/or after surgery. We found a numerically but not statistically significant longer overall OS in patients undergoing surgery (47.4 vs. 29.6 months, HR 0.61; 95%CI 0.30-1.24; P=0.171). Two, five and ten year survival estimates were 82.6% (95%CI 68.5-99.6), 31.3% (95%CI 15.7-62.5) and 31.3% (95%CI 15.7-62.5) in the surgery group and 59.1% (95%CI 41.7-83.7), 24.8% (95%CI 11.7-52.6) and 13.2% (95%CI 4.0-43.1) in the non-surgery group, respectively. The largest benefit for surgery was found in the luminal and HER2-positive subtypes, while no benefit was observed in the triple-negative subgroup.**
**Conclusion: Radical surgery of all metastases seems to improve survival, especially in luminal and HER2-positive subtypes, however, the analysis did not reach statistical significance, most probably due to the low patient number. Furthermore, because of the retrospective and non-randomized design, a systematic bias cannot be totally excluded.**

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# Clinical risk criteria and recurrence index for distant recurrence for patients with early stage luminal breast cancer

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**Background:**Clinical risk criteria (CRC) has been used in two well-known gene-expression trials (TAILORX and MINDACT) to predict the risk of distant recurrence (DR). The definition of clinical low-risk patients was (1) node-negative associated with (grade 1 with tumor ≤3cm, grade 2 with tumor≤2cm, or grade 3 with tumor ≤1cm) and N1 with grade 1 and tumor ≤2cm. Recurrence Index for distant recurrence (RI-DR) is a clinical-genomic model, based on genomic profiling derived from Asian women. The primary purpose of this study is to access the clinical utility of RI-DR and CRC in Asian breast cancer patients.
**Methods:**A total of 208 patients (N0 70.2%, N1 29.8%) with luminal-like breast cancer were enrolled in a retrospective study across Taiwan medical centers. Kaplan-Meier method was used to calculate the survival rates and the log rank test was applied for the survival difference between two or more independent groups. The primary endpoint was the recurrence-free interval (RFI).
**Results:**With a median follow-up of 49.05 [IQR 29.72-71.96], the 5-year RFI was significantly poorer in the high-risk group than the low-risk group (87.2% [95% CI, 80.0-95.0] versus 95.2% [89.75-100] by the RI-DR, p = 0.011; and 86.9% [79.8-94.6] versus 97.0% [92.9-100] by the clinical risk, p = 0.03). Combined the CRC and RI-DR together, clinical high (CH) and RI-DR high (RH)had the poorest 5-year RFI (85.2%, [76.6-94.8]); clinical low (CL) and RI-DR low (RL) had the best 5-year RFI (98.0% [94.08, 100]). Among CL-risk patients, RL group has a trend towards less recurrence than RH group (1/66□[1.51%] versus 2/19□[10.52%], p= 0.15). Similar trend was observed in CH-risk patients (RL: 2/41 (4.88%) versus RH: 12/82□[14.63%], p = 0.17) (Table 1).
**Conclusions:**The present study provides robust evidences that clinical-risk criteria and RI-DR testing could partition patients into good and poor prognosis in early-stage luminal breast cancer. RI-DR has a trend to identify low- and high-risk patients if clinical risk criteria have been applied in clinical practice.

Analyses of Clinical Risk Criteria and Recurrence Index Together

| | No. of Patients | No. of Events | 5-year RFI % (95% CI) | Log rank, P valueClinical- |
|---|---|---|---|---|
| Clinical-High | | | | |
| RI-DR high | 82 | 12 | 85.20 [76.55, 94.81] | 0.17 |
| RI-DR low | 41 | 2 | 91.30 [80.15, 100] | |
| Clinical-Low | | | | |
| RI-DR high | 19 | 2 | 94.12 [83.57, 100] | 0.15 |
| RI-DR low | 66 | 1 | 97.96 [94.08, 100] | |

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# Real life efficacy of palbociclib and endocrine therapy in HR positive, HER2 negative advanced breast cancer

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**Background** Palbociclib, a highly selective inhibitor of CDK4/6, is indicated for the treatment of hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC), in combination with an aromatase inhibitor or with fulvestrant for patients who have progressed with an aromatase inhibitor, and in premenopausal women with a luteinising-hormone-releasing-hormone (LH-RH) agonist. Emerging real world data suggest that the efficacy of a palbociclib-based therapy is highly conserved. We report here the Institut Curie (IC) experience.

**Patients and methods** We retrospectively reviewed all patients with HR+ HER2- ABC treated with a palbociclib-based therapy as 1st or 2nd line of therapy for ABC, from November 2016 to December 2018. Clinical, biological and imaging data were retrieved from IC electronic health record system. Data lock was December 31st 2020. Descriptive analyses, univariate and multivariate Cox regression analyses were performed.

**Results** We included 310 consecutive premenopausal (24.5%) and menopausal (75.5%) women. Median age was 61.8 years-old [23.5-92.1]. Among them, Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 59.7%, 1 in 32.1%, and 2 in 8.2% of patients (pts). The ABC diagnosis was *de novo* for 26.8%. There was at least one visceral lesion in 51.0% of pts, only bone lesions in 30.3%, 28.1% had three metastatic sites or more, and none of them have brain lesions. Previous treatments were chemotherapy (49.4%) and endocrine therapy (60.7%). Among pts pretreated by at least one endocrine therapy, 51.1% had shown prior sensibility, as defined by an absence of recurrence during adjuvant endocrine therapy or during 24 months after its completion, or an absence of progression during 6 months after the beginning of an endocrine therapy for a metastatic disease. Palbociclib was prescribed in the 1st line setting for 72.6% of pts and in the 2nd line setting for 27.4% of pts. The initial dose was 125 mg daily (95.2%). It was associated with an aromatase inhibitor (66.8%) or with fulvestrant (33.2%). LH-RH agonist was prescribed in 19.7% of pts. Denosumab was prescribed in 68.5% of pts with bone lesions. Median follow-up was 20.7 months (m). At 12 m from the initiation of palbociclib, 94.5% of the pts were alive. Median progression free survival was 23.4 m (95%CI: 21.6-NR) for pts without previous endocrine therapy, 22.7 m (95%CI: 14.7-NR) for pts who have shown endocrine sensibility, HR=1.2 (95%CI: 0.81-1.77), p=0.0027 and 13.4 m (95%CI: 10.7-20.8) for pts who have not shown endocrine sensibility, HR=1.88 (95%CI: 1.29-2.73), p=0.003. Although sensibility to previous endocrine therapy was a prognostic factor for progression free survival with the univariate analyse, it was not with the multivariate analysis. Three independent poor prognostic factors for progression free survival were identified: previous chemotherapy, HR=1.6 (95%CI: 1.12-2.29), p<0.001; initial ECOG performance status 2, HR=2.72 (95%CI: 1.55-4.79), p<0.001; and three or more metastatic sites, HR=1.61 (95%CI: 1.152.26), p<0.001. Hematologic grade 3-4 adverse events were neutropenia (72.3%), leukopenia (43.9%), anemia (3.2%) and thrombocytopenia (2.9%). Other adverse events observed (all grades) were infections (16.5%), stomatitis (13.9%) or alopecia (13.9%). At least one dose reduction occurred in 29.4% of pts and permanent discontinuation because of treatment toxicity was observed in 5.7% of pts.

**Conclusion** In a non-selected population of patients with HR+ HER2- ABC, the efficacy and safety data are strikingly similar to those previously reported. Palbociclib, in combination with hormone therapy, is a cornerstone treatment of HR+ HER2- metastatic breast cancer.

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# A novel and highly selective CDK9 inhibitor (D11) suppresses proliferation of triple negative breast cancer cells

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**Targeted treatment for triple-negative breast cancer (TNBC) remains an elusive clinical challenge. Cyclin-dependent kinase 9 (CDK9) is a transcriptional regulator shown to promote growth of multiple cancers, including TNBC, and represents a potential new therapeutic target. CDK9 increases RNA Polymerase II (RNAPII) activity, which facilitates sustained expression of normally short-lived oncogenic and anti-apoptotic proteins. However, preclinical evaluation of CDK9 as a therapeutic target has been hampered by the poor selectivity of existing CDK9 inhibitors (CDK9i). Herein, we evaluated the preclinical efficacy of a newly developed, highly selective CDK9i (D-11) across a panel of TNBC cell lines: MDA-MB-453, MDA-MB-468, MDA-MB-231 and MFM-223. Cells were treated with increasing concentrations of D-11 and effects on proliferation, apoptosis, cell cycle and expression of known CDK9 substrates were examined. Treatment with D-11 significantly reduced cell proliferation, induced G2/M cell cycle arrest and increased apoptosis in MDA-MB-453 and MDA-MB-468 cell lines (IC50s of 160 and 258 nM, respectively). Cell proliferation was also inhibited by D-11 in MDA-MB-231 and MFM-223 cells, but with IC50s of 400 and 468 nM, respectively, but without inducing apoptosis. Protein expression of known CDK9 targets, including phosphorylated-RNAPII, the proto-oncogene C-MYC, and the anti-apoptotic marker MCL-1, were examined by Western blot using the optimal D-11 dose determined for each cell line. As expected, D-11 suppressed phosphorylation of RNAPII (Ser2) without affecting total RNAPII expression in all cell lines, indicative of targeted CDK9 inhibition. C-MYC and MCL-1, which highly expressed in the TNBC models, were significantly decreased by treatment with D-11. To determine whether**
**D-11 influenced normal breast epithelial cells, breast tissues were collected from women undergoing reduction mammoplasty and cultured *ex vivo* as explants treated with or without different doses of D-11 for 48h. A high dose of D-11 (2.7μM) elicited a 20% decrease in the proliferative index (Ki67 positivity) of epithelial cells within normal tissue explants but had no effect on their histology. Collectively, these data demonstrate that D-11 effectively inhibits CDK9 in TNBC cell lines, resulting in growth inhibition with non-toxic effects on histologically normal breast tissues.**

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# CDKN2A loss can be a predictive marker of palbociclib in breast and gastric cancer

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**Background: Abnormal cell cycle progression is a characteristic of cancer, and targeting the cell cycle is a strategy for cancer treatment. TCGA reported that 7% and 12% of gastric cancers exhibit CCND1 or CCNE1 alterations, respectively. Besides, Cyclin D1 is overexpressed in 25% to 60% of invasive breast carcinomas, and gene amplification is observed in 10% to 30% of breast cancer cases. Furthermore, CDK4/6 and CDNK2A/B aberrations are frequently observed in gastric (39.6%) and breast (7.6%) cancers. The presence of such abnormalities in cell cycle-related molecules suggests that gastric and breast cancers are good candidates for treatment with cell cycle inhibitors. Palbociclib is a specific inhibitor of CDK4/6, a vital regulator of the G1 checkpoint, and has been approved by the FDA because it provided a significant benefit by extending PFS in a phase III trial for hormone-positive advanced breast cancer. However, the predictive marker of palbociclib is not determined. Even though CDKN2A loss has been considered as a sensitive marker of palbociclib, there is no preclinical evidence to support whether CDKN2A deficient cancer shows sensitivity to palbociclib, especially in gastric and breast cancer. Therefore, we investigated the effects of palbociclib on CDKN2A loss gastric and breast cancer cell lines as well as patient derived-xenograft (PDX) models. Methods: The cytotoxic assay, cell cycle analysis, and western blotting were conducted to determine the anti-tumor effect and action mechanisms of palbociclib on gastric and breast cancer cell lines. Moreover, modulation of CDKN2A expression was conducted by siRNA and plasmid overexpression. These in vitro data were validated in vivo model and gastric cancer PDX models which have CDKN2A loss as well. Results: There is a meaningful correlation between CDKN2A loss and palbociclib sensitivity among gastric and breast cancer cell lines. CDKN2A loss cells showed G1 cell cycle arrest by blocking Rb phosphorylation and inhibited proliferative cell signaling. Moreover, palbociclib promoted senescence rather than apoptosis. The depletion of CDKN2A expression using siRNA increased palbociclib sensitivity with G1 cell cycle arrest accompanied by senescence. In contrast, CDKN2A overexpression in sensitive cells showed insensitivity to palbociclib. The anti-tumor effects of palbociclib on CDKN2A loss breast cancer cells were validated in the xenograft model, and the two different gastric cancer PDX models have CDKN2A loss also showed a significant response to palbociclib as well. Conclusions: CDK4/6 inhibitor palbociclib showed an anti-tumor effect in vitro and in vivo xenograft model of CDKN2A loss gastric and breast cancer. Our results suggest that palbociclib has therapeutic potential for the treatment of not only breast cancer but also gastric cancer, not limited to a hormone-positive breast cancer type. Our results provide a rationale for the future clinical trials of palbociclib in the treatment of breast cancers.**

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# The genomic landscape of Chinese breast cancer

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**The Genomic Landscape of Chinese Breast CancerBackground : The comprehensive genomic profiling (CGP) through next-generation sequencing (NGS) brought a new understanding of breast cancer and provided more information about further clinical treatment . However, the genomic features in Chinese breast cancer group are limited to date, which might offer both prognostic and predictive values.**
**Patients and Methods: Hybrid capture-based CGP was performed on 126 primary and 38 relapsed/metastatic breast cancer patients using a 324-gene panel assay (FoundationOne CDx) to identify all classes of genomic alterations, including base substitutions, insertions and deletions, rearrangement and copy number changes. Tissue samples were obtained by surgery or biopsy.**
**Results:There was no sample with unstable microsatellite status both in primary and relapsed/metastatic breast cancer patients. The tumor mutational burden was higher in Relapsed/metastatic breast cancer than in primary breast cancer (2.91±0.29 for primary, 5.10±0.50 for relapsed/metastatic breast cancer, respectively, $p<0.001$). There were 11 genes detected more than 10% incidence across all samples, including TP53(63.69%), PIK3CA(38.85%), ERBB2(22.29%), RAD21(17.20%), CCND1(15.29%), FGF3(14.01%), FGF19(14.01%), MYC(13.38%), NSD3(WHSC1L1)(11.36%), ZNF703(10.83%), among which RAD21, NSD3(WHSC1L1) were novel significantly mutated genes in Chinese breast cancer patients other than the previous genes identified in other ethnic groups and might be related to poor prognosis. The 10 top genes with greater difference mutational incidence between primary and relapsed/metastatic breast cancer were mostly identified in relapsed/metastatic group frequently (TP53, MYC, RAD21, PTEN, MLL2, CCND1, RB1), only 3 gene occurred more often in primary group (PIK3CA, FGFR1, MDM2). Relapsed/metastatic breast cancer patients were probably to get instruction in targeted therapies than primary group from CGP, the proportion of relapsed/metastatic breast cancer patients getting instruction in one or more targeted therapies was 94.74%, whereas the proportion of primary group was 76.98%($p=0.014$).**
**Conclusions:There was significant molecular heterogeneity between primary and relapsed/metastatic breast cancer in Chinese patients and between Chinese and other ethic group.**
**Fig The mutational landscape of top 21 most frequently mutated genes (mutational incidence >5%) in Chinese breast cancers (n=184). The upper histogram showed the total number of mutations in every patient. The bottom bars indicated the clinical characteristics, samples were grouped by primary breast cancers (n=141) and relapsed/metastatic breast cancers (n=43). Sidebar on the left summarized the mutational incidence of each gene and listed the separate frequencies of primary and R/M patients. Sidebar on the right classified different mutation types.**

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# Fatty acid metabolism at the connection of histone methylation and mammary cell plasticity

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INTRODUCTION:Metabolic switching has been linked with cancer progression. We initially reported increased expression of lipids metabolism genes in the contralateral breasts of women with unilateral estrogen receptor negative (ER-) breast cancer. We then demonstrated chromatin remodeling in normal mammary epithelial cells following exposure to lipids. Metabolites from intermediate metabolism are substrates that generate chromatin modifications, connecting metabolism to epigenetics. Key to this crosstalk is the fact that the kinetic and thermodynamic properties of chromatin modification reactions are in line with the dynamic range of the physiological concentrations of the corresponding intermediates in metabolism. Since substrates for histone methylation and acetylation reactions often have cellular concentrations that are commensurate with enzyme Km values, and are sensitive and responsive to changes in metabolism, we now present evidence regarding changes in metabolic flux and cellular plasticity connecting lipid metabolism to ER- cancer progression.
Methods:MCF-10A cells were grown in the presence of medium chain fatty acid- octanoic acid (5mM) for 24 hours. RNA sequencing was performed on the treated and control cells using Illumina Next Seq 500 for 75bp single-read sequencing. Differential expression and gene set enrichment analyses were utilized to identify significantly enriched biological processes and molecular functions upon fatty acid treatment. Differential metabolic flux was determined using flux balance analysis. For proteomic analysis of post-translational histone modifications, histones were acid extracted from nuclei and LC-MS based mass spectrometry was used to quantitate the modifications and data is represented as the relative abundance in %.
Results:Transcriptome data from RNA sequencing, incorporated into the human metabolic network reconstruction, revealed a significant increase in methylation flux in octanoate treated MCF10-A cells. The treated cells showed an increase in the flux in fatty acid oxidation and one-carbon metabolism reactions. The proteomic histone modification profile showed an increase in histone methylation specifically at H3K9, H3K4, H3K27 and H3K36, which corroborates with the GSEA analysis showing a significant correlation of H3K27 methylation (NES = 2.47, q-value = 0.05), a marker of constitutive heterochromatin, in the octanoate treated phenotype. Further, RNA-Seq of octanoate treated MCF-10A cells revealed prominent upregulation of cell-fate commitment and
cell differentiation pathways, specifically neural differentiation, and adenylate cyclase-activating adrenergic receptor signaling.
Conclusion:Lipids are a source of acetyl-CoA which serves as a donor for histone acetylation; our data shows that resultant increased flux through metabolic reactions produces s-adenosine methionine (SAM), an important methylating agent. These post-translational modifications have profound effects on chromatin structure, effecting changes that range from the expression of a single gene to a complete conversion of phenotype. We observe both an alteration of the molecular phenotype, as well as adenylate cyclase-activating adrenergic receptor signaling, which may be a clue to the development of ER- disease as GWAS have revealed that the adenylate cyclase-activating pathway is enriched in susceptibility to ER-negative disease.

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# Multiple activities improve oncologists' knowledge and competence with CDK4/6 inhibitors in HR+ breast cancer over time

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**Background:Recently, CDK4/6 inhibitors have revolutionized the care of patients with hormone receptor (HR)-positive, HER2-negative breast cancer, improving survival outcomes. Already, there are multiple CDK4/6 inhibitors available that differ in their pharmacologic features, reported outcomes, therapeutic indications, and adverse event profiles. As data from clinical trials or subgroup analyses become available, landmark trials are published, and guideline recommendations or clinical utility of these therapies change, continuing medical education (CME) for oncologists is necessary to facilitate timely and accurate translation of evidence to their clinical practice. Methods: A series of 5 CME-certified activities were launched to educate oncologists on CDK4/6 therapies in HR-positive advanced breast cancer following data releases from ESMO 2019 through SABCS 2019. Education followed adult learning principles starting with a goal of increasing awareness on novel data and then integrating these agents into clinical practice, including adverse event management. Panel discussions were utilized to provide multiple faculty perspectives and clinical anecdotes. Effectiveness was analyzed using 3 multiple-choice and 1 self-efficacy question measuring knowledge, competence, and confidence, presented as pre-/post-CME repeated pairs for each of the activities. Oncologists who completed both the pre- and post-CME questions were included in analysis and MeNemar's tests were conducted to assess statistical significance of the results with *p* < .05 being considered significant. The 5 CME activities launched from September 2019 through December 2019.Results: As of 6/9/2020, 6,037 global physicians had participated in the activities including 2,511 oncologists. 64% of the oncologists identified themselves as practicing in a community setting and 82% of them intended to modify their treatment plans as a result of education. Analyses from 3 activities using data from n=356-458 oncologists found significant improvements in: •Knowledge of clinical trial safety and efficacy data with CDK4/6 inhibitors (% pre correct 65% vs. % post correct 73%; *p* < .001) •Competence implementing personalized CDK4/6 inhibitor for a patient (% pre correct 74% vs. % post correct 84%; *p* < .001) •Knowledge of adverse events with CDK4/6 inhibitors (% pre correct 63% vs. % post correct 74%; p <.001)•Confidence personalizing and implementing CDK4/6 inhibitor therapy in practice (% pre confident 37% vs. % post confident 50%, *p*< .001)Conclusions: This series of live and online, expert-led, CME-certified educational activities resulted in significant improvements in knowledge, competence, and confidence among oncologists regarding the use of CDK4/6 inhibitor therapies in the management of advanced HR-positive breast cancer. These results also highlight the effectiveness of on-demand education to facilitate information transfer from conferences to clinical practice.**

**Grantors:This educational initiative was supported through educational grants from Lilly.**

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# Correlation of thermalytix - an artificial intelligence based thermal breast screening tool in detecting a breast lesion as benign, malignant or normal

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**Aim: To correlate results of Thermalytix - an artificial intelligence (AI) based breast screening tool with mammography and the final diagnosis as established by histopathology**

**Introduction: Screening and early diagnosis has proved to be useful in improving clinical outcome and survival of breast cancer patients. Mammography, the only breast cancer screening modality approved is not accessible or economically sustainable in low and middle-income countries (LMICs). Thermalytix, an artificial intelligence (AI) based breast cancer screening tool is low cost, portable and radiation free and uses AI-based techniques to analyze and interpret breast thermal images captured using a high-resolution infrared camera. Areas of high thermal activity are identified using relative temperature thresholding while vascular structures are analyzed using a novel image processing technique. These hotspots and vascular patterns are further analyzed to extract a set of features that are input to 3 pre-trained machine learning models to generate quantitative scores. The final scores generated based on these parameters are used to label a breast lesion as malignant, benign or normal at first screening. In this study, we present a comparative analysis of the results of thermalytix and mammography with final diagnosis as established by histopathological diagnosis.**

**Methods:In this retrospective study, 65 patients who had undergone biopsy and histopathological examination of breast for symptoms such as breast lump, pain or discharge were recruited. Each patient had mammography and the non-invasive Thermalytix test done as a preliminary screening modality prior to biopsy. Automated results generated by Thermaytix were then independently compared with the histopathological diagnosis retrospectively. Similarly, the mammography results were also compared with the biopsy findings to compare the coherence of each modalities in detecting breast lesion independently.**

**Results:Out of the 65 symptomatic patients who were followed up by biopsy for any suspicious lesion 48/65 were neoplastic with 37/65 malignant lesions 11/65 benign lesions. Rest 17/65 patients were non-neoplastic comprising of 13/65 inflammatory cases and 4/65 normal cases.**

**1.Thermalytix detected 31/37 malignant cases while mammography detected 35/37 as malignant. 2.Among benign lesions thermalytix came out positive for 6/11 cases while mammography did so in 10/11 cases. 3.For inflammatory cases thermalytix and mammography raised a suspicion for malignancy in 10/13 and 11/13 cases respectively. 4.All 4 cases which were normal on biopsy were all labelled as suspicious by mammography while 3 were labelled as suspicious by thermalytix.**

**Conclusion:This preliminary study shows that thermalytix fared well with radiological findings in detecting breast lesions as benign, malignant or normal. The findings were somewhat skewed in favour of radiological findings as mammography was done as the primary screening test before the patients underwent biopsy and histopathological examination for any suspicious lesion.**

**Thermalytix can act as a low cost, portable and radiation-free test that can be of great help in detecting neoplastic lesions of breast at first screening in in low- and middle-income countries (LMICs) where mammography is not accessible or economically scalable. With its automated scoring and annotations of potential neoplastic lesion Thermalytix is poised to be a promising modality for breast cancer screening in future.**

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# Dolaf- an international multicenter phase 2 trial of durvalumab (medi4736) plus olaparib plus fulvestrant in metastatic or locally advanced er-positive, her2-negative breast cancer patients selected using criteria that predict sensitivity to olaparib (UCBG308)

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Background: Olaparib is a PARP inhibitor that has shown high response rates and clinical activity in patients with advanced HER2-negative breast cancer (BC) and a germline *BRCA1* and *BRCA2 mutation*. There is also evidence of cellular sensitivity to PARP inhibitors associated to defects in other genes involved in homologous recombination DNA repair (HRR) or mismatch repair pathway (microsatellite instability MSI). Moreover, about 15% of patients with ER+/HER2- metastatic BC have at least 100 mutations in their tumor, leading to genomic instability and potential sensitivity to PARP inhibitors. Several preclinical and clinical studies have suggested the benefit of an association of immune checkpoint blockade, like durvalumab, with PARP inhibitor. Indeed, tumors with *BRCA1/2* mutations or other deficiency in HRR have high mutagenic burden and produce a larger number of neoantigens. Most BRCA-associated BC are ER+/HER2-. Although loss of the *BRCA* gene function is a key driver of oncogenesis in these patients, ER-pathway appears to remain a key target for their therapy. Preclinical data indicate that olaparib may enhance endocrine therapy efficacy and circumvent resistance. Therefore, the combination of durvalumab, olaparib and endocrine therapy could be a therapeutic option for patients with *BRCA1/2* mutation or for patients with selected ER+/HER2- advanced BC.
Trial design: DOLAF is an open-label, international, multicentric, phase II trial assessing the combination of olaparib, fulvestrant, and durvalumab. Olaparib will be administered orally twice daily at 300 mg. Fulvestrant will be administered as two intramuscular injections of 250 mg (Cycle 1 Days 1 and 15, and Day 1 of each subsequent 28-
day cycle). Durvalumab will be started 4 weeks after the first dose of olaparib at 1500 mg intravenous every 4 weeks.
Eligibility criteria include: ER+/HER2- metastatic or locally advanced BC with documented germline alteration in *BRCA1* or *BRCA2* or deleterious germline or somatic alterations implicated in the HRR pathway *(ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FAND2, FANCL, MRE11A, NBN, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D and RAD54L)* or in MSI status or other actionable genes *(AKT1, ESR1, FGFR1, FGFR2, FGFR3, and PIK3CA)* all based on central tumor next generation DNA sequencing. Patients could have received 1 line of endocrine therapy and/or 1 line of chemotherapy in the metastatic setting.Specific aims: To evaluate the efficacy of the combination in terms of progression-free survival rate at 24 weeks using RECIST v1.1. Secondary endpoints include: safety (according to the NCI-CTCAE v5.0), overall survival, progression-free survival, objective response rate, duration of response in the overall study population and in the germline *BRCA* mutated population.
Statistical methods: Given the lack of safety data from this association, a safety run-in of 6 patients was planned. With an optimum two-stage Simon design,$\alpha = 2.5\%$, $\beta = 5\%$, p0 (the probability of inefficiency maximum) = 50%, p1 (the probability of minimum efficiency) = 65%, it would be necessary to include 149 evaluable patients. The strategy could be considered sufficiently effective if there are at least 87 successes. According to the established design (including a rate of 5% of patients lost to follow-up or non-evaluable), it will be necessary to include 158 patients. We hypothesized that about 20% of screened patients will have a molecular alteration to allow enrollment. Thus, we need to screen 790 patients.
The study is recruiting. The safety run-in is over. By July 1, 2020, 62 patients have been screened and 8 have been treated (NCT04053322).
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# Triple negative breast cancer in New Orleans, part deux

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**Version 7/7/2020 with edit Triple-Negative Breast Cancer in New Orleans – part deaux Objectives: To update our previously reported findings with more current data from SEER 18 registries to compare race-specific incidence rates of triple-negative breast cancer (TNBC) in New Orleans (NO) and Louisiana (LA) with other SEER metro areas and identify the predictors of TNBC. Background: We previously reported significantly increased incidence rates of TNBC in black women (BW) in NO and LA than other SEER metro areas. Methods: We analyzed tumor characteristics of invasive female breast cancers diagnosed from 2011-2017 from SEER 18 for BW and white women (WW). We compared LA data with SEER 18 and metropolitan areas (Atlanta, Detroit, Los Angeles and San Francisco) as we did with our previous data set. Predictors of TNBC in NO and LA were identified in multivariate logistic regression adjusting for age, BMI, poverty, insurance, tumor size, Bloom-Richardson grade and AJCC stage. Results: The overall incidence rate of TNBC in BW was again significantly higher in NO (29.8 per 100,000) than any metro area and the SEER metro areas combined (23.9 per 100,000). Detroit again had the second highest rate (27.2) followed by San Francisco/Oakland (23.8) Los Angeles (22.3) and Atlanta (22.1). The multivariable analysis showed that younger age, large tumor size, high grade were associated with increased risk of TNBC in BW. Conclusions: The incidence rates of TNBC in BW in NO continue to be consistently higher compared to LA and other SEER 18 metro areas. This data reiterates the importance of ongoing translational research to broaden the understanding and optimize the treatment of this aggressive disease, especially in this vulnerable population.**

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# Real-world outcomes in patients receiving neo-adjuvant chemotherapy for early-stage breast cancer

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**Background: Real-world data on characteristics, outcomes, and toxicity in patients with early breast cancer (EBC) receiving neo-adjuvant chemotherapy (NACT) is lacking. This study characterises experience of NACT in a single UK NHS specialist oncology centre.**
**Methods: Retrospective case note review of sequential patients with EBC treated with NACT between April 2013 and Sept 2019. Treatment regimens, toxicity data, pathological response (PathCR, defined as no residual invasive tumour in the breast and lymph nodes), recurrence-free survival (RFS) and overall survival (OS) were compared between groups according to baseline characteristics and tumour subtype, defined by oestrogen receptor (ER) and HER2 status.**
**Results: 405 patients (median age 52 years (IQR 45–61)) were included with a median follow up of 36.4 months. At diagnosis most (253 (62%)) were symptomatic, 368 (91%) had invasive ductal carcinoma, 19 (5%) invasive lobular carcinoma and 18 (4%) inflammatory, spindle or mixed histology. Most were pre-NACT stage 2 or above (Stage 1 - 12 (3%), Stage 2a - 129 (32%), Stage 2b 148 (37%), Stage 3a - 73 (18%), Stage 3b – 25 (6%), Stage 3c -14 (3%)) with no clear trend in stage by year of diagnosis or disease subtype and overall 244 (60%) were node positive pre-NACT. 99% had grade 2 or grade 3 cancer; 320 patients (79%) had Ki-67 >15% and 72 patients (18%) had Ki-67 <15%. 392 (96.8%) patients received primary prophylaxis with Granulocyte-Colony Stimulating Factor (GCSF) and 327 patients (76.9%) received an anthracycline-taxane (AT) containing schedule. There were few dose delays due to toxicity (no delay 353 (87%) v delay 51 (13%)) however, 187 (46%) had one or more dose reductions which was significantly more common in patients >61 years (Odds Ratio (OR) v patients <45 years 1.32, 95% (CI 1.10-1.58,P=0.003). PathCR rates did not significantly vary by year of treatment, tumour size or nodal stage but did vary by subtype: ER+/HER2- 8/128 (6.25%), ER+/HER2+ 34/111 (30.6%), ER-/HER2+ 42/69 (60.9%), ER-/HER2- 32/97 (33%). PathCR was predictive of RFS: recurrence occurred in ER+/HER2- pathCR 0/8 (0%) v non-pathCR 24/120 (20%), ER+/HER2+ 0/34 (0%) v 7/77 (9.1%), ER-/HER2+ 4/42 (9.5%) v 6/27 (22%) and ER-/HER2- 4/32 (12.5%) v 21/65 (32%). There was a non-significant trend towards improved pathCR with the addition of platinum (P) to AT in ER-/HER2- disease (19/43 (44.2%) v 11/41 (26.8%) respectively, OR 2.16 (95% CI 0.86-5.40, p=0.09). In HER2+ disease, the addition of pertuzumab (P) to trastuzumab (H) with AT chemotherapy did not increase pathCR rates. At time of analysis 10% of patients had died precluding meaningful analysis of OS by response. Ki-67, Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) had no significant associations with pathCR.**
**Conclusions: Real-world outcomes from NACT at a single UK centre are consistent with published randomised data for pathCR rates by tumour subtype. Despite 96.8% of patients receiving GCSF almost half had at least one dose reduction, potentially compromising dose intensity. Whilst this retrospective analysis must be interpreted with caution, as expected there was a trend toward improved response with the addition of platinum in ER-/HER2- disease but an interesting lack of further pathCR when adding pertuzumab in HER2 positive disease. Further analyses will be presented including site of recurrence, type of surgery by response, radiotherapy treatment given and multi-variate analysis.**

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# Penetrance of male breast cancer susceptibility genes: A systematic review

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Background: Family history is one of the strongest predisposing factors for male breast cancer (MBC). Several MBC susceptibility genes have been identified, but the risk of MBC for individuals with a pathogenic variant in these genes (i.e., penetrance) remains unclear. We conducted a systematic review of studies reporting the penetrance of MBC susceptibility genes.
Methods: A search query was developed to identify MBC-related abstracts indexed in PubMed, with the followings structure: "Breast Neoplasms, Male"[Mesh] OR ((("Men"[MESH]) OR (male*[TIAB]) OR (man[TIAB]) OR (men[TIAB])) AND (("Breast Neoplasms"[MESH]) OR (Breast Cancer*[TIAB]) OR (Breast neoplasm*[TIAB]))). A validated natural language processing (NLP) method was applied to retrieve and classify abstracts reporting penetrance estimates. Abstracts labeled as relevant were manually reviewed. The full-text papers of identified penetrance studies were then annotated to extract MBC risk data. These penetrance studies' bibliographies were also reviewed to ensure comprehensiveness.
Results: We identified 17 penetrance studies from 11,799 abstracts, covering five MBC susceptibility genes: *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2* (Table 1). 53% of these studies were case-control studies, while the rest were cohort studies. Odds ratio (OR), cumulative risk (CR), and relative risk (RR) were three commonly reported risk measures. For *BRCA2*, eight out of nine studies reported significantly increased risk of MBC or a lifetime CR of over 6%; only one study reported an increased but not statistically significant risk. For *BRCA1*, one out of six studies reported an elevated lifetime CR of 5.8%, while a second reported a minor increase (OR=1.49) that was statistically significant. The risks reported in the remaining four studies showed no statistically significant increase in risk. Seven studies reported the penetrance of *CHEK2*, but the risks diverge between the variants tested (Table 2). All three *PALB2* studies reported significantly increased risk, while only one *ATM* study reported an increased risk of MBC, which did not reach statistical significance.
Conclusion: To our knowledge, this review provides the first complete set of reported penetrance data for five MBC susceptibility genes. Contradictory MBC risks (significantly increased risk vs. risks that were not statistically significant) were common, which may be due to the studies' different ascertainment criteria resulting in risk estimates for differing populations. Risk across these studies cannot be directly compared unless studies adjust for ascertainment, though this cataloging of risk defines our current understanding.

Table 1: MBC penetrance studies

| Gene | Number of Studies | Study Type | Risk Estimate Reported | MBC Risk |
|---|---|---|---|---|
| *BRCA2* | 9 | 6 Cohort, 3 Case-control | OR, RR, CR | Statistically significant increased risk (or lifetime CR > 6%) in 8/9 studies |
| *CHEK2* | 7 | 7 Case-control | OR, RR | Varying risk by variant |
| *BRCA1* | 6 | 3 Cohort, 3 Case-control | OR, RR, CR, HR | Statistically significant increased risk in 1/6 studies, one study report lifetime CR = 5.8% |
| *PALB2* | 3 | 1 Cohort, 2 Case-control | OR, RR | Statistically significant increased risk in 3/3 studies |
| *ATM* | 1 | 1 Case-control | OR | Statistically significant increased risk in 0/1 study |

OR: odds ratio; RR: relative risk; CR: cumulative risk; HR: hazard ratio

Table 2: As an example: Reported penetrance of *CHEK2* for male breast cancer in studies with varying ascertainment criteria

| First Author, Year of Publication, Patient Population * | Pathogenic Variant | Number of Carriers | Risk Type | Risk Estimate (95% CI) | Statistical Significance |
|---|---|---|---|---|---|
| Meijers-Heijboer H, 2002, Multiple Countries | 1100delC | 57 | RR | 10.28 (3.54-29.87) | Yes |
| Syrjakoski K, 2004, Finland | 1100delC | 28 | OR | 1.27 (0.04-7.92) | No |
| Wasielewski M, 2009, Netherlands | 1100delC | 21 | OR | 4.1 (1.2-14.3) | Yes |
| Pritzlaff M, 2017, USA | All | 441 | OR | 2.4 (1.4-3.9) | Yes |
| | 1100delC | 135 | OR | 3.8 (1.7-7.8) | Yes |
| | I157T | 238 | OR | 1.3 (0.5-3.0) | No |
| Hallamies S, 2017, Finland | 1100delC | 30 | OR | 4.47 (1.51-13.18) | Yes |
| | I157T | 104 | OR | 1.12 (0.4-3.13) | No |
| Lu HM, 2019, USA | Not specified | Not specified | OR | 1.66 (0.04-10.34) | No |
| Kleiblova P, 2019, Czech Republic | Truncations | 3 | OR | 20.21 (3.5-80.0) | Yes |
| | Deleterious missense | 1 | OR | 11.87 (0.25-100.83) | No |
| | Intermediate missense | 2 | OR | 1.3 (0.15-5.07) | No |
| | Neutral missense | 2 | OR | 9.07 (0.98-40.41) | No |

OR: odds ratio; RR: relative risk
* All studies in Table 2 are case-control studies

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# Tailored education prescribed throughout the breast cancer journey via a mobile application

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Background: Improved educational tailoring to a breast cancer patient's specific situation, diagnosis and treatment plan, has been shown to decrease anxiety and improve treatment adherence. We demonstrate that technology can facilitate the provisioning of patient education at the point of need through a prescription model using focused videos to address various aspects of diagnosis and treatment. Methods: We created a patient-clinician bi-directional platform that houses mini-videos that can be prescribed by the clinician according to the details of the patient's diagnosis as well as the stage of the patient's care journey. Videos were created to reflect the American Cancer Society's education web content in an animated and easy to consume format. Each video is 3 to 10 minutes long and contains questions to consolidate and reinforce the learning. Patients retain access to the video content indefinitely and can also share with caregivers with whom they grant access. Results: For breast cancer, we created a diagnosis video that explains the basic information every women needs to understand. This includes an explanation of breast anatomy, how doctors describe the location of the tumor, which cells generally give rise to breast cancer (ductal and lobular) and how it is described (in situ vs. invasive), how breast cancer is staged, and finally what the biomarkers (ER, PR, Her2) are as well as what positive/negative means in terms of treatment options. In addition, specific videos are available to be prescribed based on the patient's treatment plan.

| | Chemotherapy | Radiation | Targeted Therapy |
|---|---|---|---|
| Overview | How different drug classes workHow regimens are scheduled | How different modalities work and are givenHow treatment is scheduled | Main classes of targeted therapy and how they workHow treatment is scheduled |
| Per treatment | Video on each chemo drug | Video on each radiation modality | Video on each drug |
| Per side effect | Video on each type of side effect explaining why it happens, which drugs usually cause it, how to manage, what signs mean you should contact the clinic | Video on each type of side effect explaining why it happens, which drugs usually cause it, how to manage, what signs mean that you should contact the clinic | Video on each type of side effect explaining why it happens, which drugs usually cause it, how to manage, what signs mean you should contact the clinic |

Conclusion: To our knowledge, we are the first to develop a prescription-based approach to breast cancer patient education. In addition, our knowledge consolidation questions added to the prescribed education is also novel in this area. We demonstrate that technology can support patient education in way that supports patients and can alleviate the burden on clinics.

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# Solti-1503 PROMETEO: Talimogene laherparepvec (T-VEC) + atezolizumab combination in early breast cancer

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Background Residual disease (RD) after standard neoadjuvant chemotherapy (NAC) is composed of drug resistant cells and associates with increased risk of relapse, especially in triple negative, HER2-positive, and highly proliferative Luminal tumors. Immunotherapy combinations can induce of specific anti-tumor immune responses, such as those mediated by T-cells, and which might represent an additional strategy for the control or elimination of residual tumor cells. Preliminary results in melanoma showed that the combination of T-VEC with an anti PD-L1 or anti CTLA4 has greater efficacy than either therapy alone, without additional safety concerns beyond those expected for each agent. The presence of RD after neoadjuvant chemotherapy (NAC) in early BC patients remains an unmet medical need. We hypothesize that combining T-VEC with Atezolizumab may offer clinical benefit in the preoperative setting for early breast cancer (BC) patients with intermediate to high risk of recurrence who present RD after standard NAC. Methods SOLTI-1503 PROMETEO is an open-label, multicenter trial of T-VEC + Atezolizumab in patients with RD after completing standard NAC. Thirty patients with triple negative BC (TNBC) or Luminal B-like/HER2- will be included. RD must be confirmed by core-biopsy and have a diameter ≥ 15 mm measured by magnetic resonance imaging. Adequate organ function and ECOG PS 0-1 are required. T-VEC is administered intratumorally in week 1 ($10^6$ plaque-forming units/mL [pfu/mL]), then in week 4 and every 2 weeks thereafter ($10^8$ pfu/mL) for 4 injections. Atezolizumab (840 mg) is administered intravenously every 2 weeks for 4 infusions, beginning in week 4. BC surgery will be carried out 1 to 3 weeks after completion of treatment. A protocol amendment was approved, the steering committee of the study decided to change the primary objective of the trial to a more clinical endpoint that is to evaluate the efficacy by the rate of RCB class 0/1 at surgery. Secondary endpoints include rate of pCR, ORR, safety and the increase of mean expression of a gene signature tracking activated CD8 T-cells. The first safety analysis was performed in October 2019. Independent safety date review board considered the trial safe and supported its continuation. To date, 8 patients have been included at 4 sites in Spain. Second safety and efficacy data analysis is planned after 10 patients have completed treatment. If a rate of PD higher than 50% is observed in the first 10 patients, then the trial will be permanently stopped. We expect to achieve 10 patients in July 2020. We thank AMGEN for their provision of Talimogene Laherparepvec and their financial contribution to this clinical study. We thank ROCHE for their provision of Atezolizumab and their financial contribution to this clinical study. Clinical trial identification: NCT03802604

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# Somatic mutational landscapes of invasive ductal and lobular carcinomas in the GENIE consortium cohort: Real-world gene actionability assessment of 8,756 breast cancer patients

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**Background: Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) of the breast typically present distinct clinicopathological characteristics and responsiveness to systemic therapy. In addition, breast cancer data from The Cancer Genome Atlas (TCGA) have shown these two pathological subtypes also present distinct genomic features when analyzed using DNA copy number arrays and whole exome sequencing platforms. More recently, the AACR Project GENIE Consortium, which is a publicly accessible international cancer registry of real-world data assembled through data sharing among leading cancer centers in the world, have allowed in-depth analyses of clinical actionability using patient-level data from clinical next-generation sequencing (NGS) assays. In this study, we assessed the somatic mutational landscapes of a large cohort (n = 8,756) of invasive breast carcinomas from 19 institutions participating in the GENIE Consortium Cohort (v8.0) and examined clinical actionability of unique mutations identified in each breast cancer subtype. Method: We assessed the eighth data release of the GENIE Consortium Cohort encompassing targeted sequencing data from 7,647 IDC and 1,109 ILC cases. Clinical features and somatic mutations including single-nucleotide variants, small indels, fusions, and copy number alterations (CNAs) were retrieved from cBioportal and SAGE Bionetworks. Gene actionability was examined using both OncoKB and CiVIC publicly available knowledgebases. All patient samples were de-identified and encoded with GENIE sample codes. Results: Patients with IDC tumors were 5 years younger than patients with ILC tumors at the time sequencing data was reported (median 55 *versus* median 60 years old, *Kruskal-Wallis*, *p* < 10e-10). Both IDC and ILC had on average 2 mutations per tested sample. Overall, IDC and ILC tumors had median fractions of 22% and 14% of their genomes altered, respectively (*Kruskal-Wallis*, *p* < 10e-10). An initial gene enrichment analysis including 938 genes with point mutations and small indels identified *CDH1* [Log-ratio (LR) 4.66, *p* < 1e-10], *RHOA* (LR 2.81, *p* = 1.3e-10), *PTK2B* (LR 2.68, *p* = 5.2e-4), *ERBB2* (LR 1.80, *p* < 1e-10), *TBX3* (LR 1.72, *p* < 1e-10), *FOXA1* (LR 1.49, p = 2.5e-10) and *RUNX1* (LR 1.25, *p* = 3.1e-9) as genes significantly enriched in ILC tumors. On the other hand, mutations in *GATA3* (LR = 1.67, *p* < 1e-10) and *TP53* (LR = 1.55, *p* < 1e-10) were significantly enriched in IDC tumors. A further gene enrichment analysis for copy-number alterations in 1139 genes showed amplification in *PARP1* (LR 1.55 *p* = 2.5e-3) and deep deletions in *IKZF1* (LR 2.8, *p* = 2.2e-3) and *CDH1* (LR = 1.88, *p* = 1.7e-4) as the most enriched genes with CNAs in ILC. In parallel, amplifications in *AURKA* (LR 3.2, *p* = 1e-8), *PPM1D* (LR 3.1, *p* <1e-10), *RAD51C* (LR 2.85, *p* = 3.8e-8), *BRIP1* (LR 2.66, *p* < 1e-10), *ERBB2* (LR 1.65, *p* = 1e-10), *MYC* (LR 1.64, *p* = 1e-10), *CDK12* (LR 1.55, *p* = 2.6e-9), and *COL22A1* (LR 1.19, *p* = 1.6e-5), and deep deletion in *CDKN2A* (LR 2.1, *p* = 1.9e-6) were enriched in IDC tumors. Among those enriched alterations for each histological subtype, the knowledgebase CiVIC did not present curated data available for genes *TBX3*, *FOXA1*, *GATA3*, *COL22A1*, *BRIP1*, *PPM1D*, and *RAD51C*. OncoKB only missed genes *PTK2B* and *COL22A1*. Conclusions: Real-world genomic data from the GENIE Consortium Cohort support that breast cancer presents distinct mutational landscapes for IDC and ILC tumors. For each histological subtype, we confirmed there are different levels of enrichments for shared mutations in actionable genes. Despite the fact that publicly available knowledgebases present comprehensive curated information about commonly mutated genes in cancer, we noticed that actionability data of important cancer driver genes were missed.**

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# Breast cancer outcomes among a diverse racial/ethnic south Florida population

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Background: Breast cancer is the most common cancer diagnosed among Hispanic women in the US and is the leading cause of cancer-related death in this population. However, controversy remains as to whether this population has improved, or worse, overall survival (OS) outcomes compared to their non-Hispanic White (NHW) and non-Hispanic Black (NHB) counterparts. Given our location in South Florida, where Hispanics account for approximately 70% of the population we are perfectly poised to analyze breast cancer overall survival (OS) outcomes in a Hispanic population compared to a non-Hispanic population. Furthermore, given the diverse nature of our Hispanic population, this is the first study to also evaluate outcomes in Hispanic Whites (HW) compared to Hispanic Blacks (HB).
Methods: Patients presenting to our medical campus with stage I-IV breast cancer from 2005-2017 were identified from the local tumor registry. Kaplan-Meier survival analysis was performed to identify patient, tumor, and NCCN-guideline based treatment characteristics associated with OS. Factors with a $p < 0.1$ were included in the Cox proportional hazards model.
Results: 5,951 breast cancer patients were evaluated from 2005-2017. Patient demographics, tumor characteristics, and treatments received are presented in Table 1. NHB tended to be more economically disadvantaged, presented with later stage disease, had rates higher triple negative disease, and were less likely to complete NCCN-guideline based treatment. The 5-year OS across all races/ethnicities was 82.5% with a median follow-up of 65 months. The 5-year OS stratified by race and ethnicity is as follows: NHW 85%, HW 84.8%, HB 79.4%, and NHB 72.7%. On Cox proportional hazards model, when adjusting for stage, race/ethnicity, insurance, marital status, income, smoking/alcohol, receptor status, tumor grade, and NCCN-guideline based treatment, NHB had a hazard ratio of 1.25 [(95% CI:1.01-1.52), $p< 0.041$)].
Conclusion: At our institution, located in South Florida, we treat a large number of patients with breast cancer from South Florida, Central and South America, and the Caribbean who self-report as Hispanic. Our study is the first to suggest survival differences amongst HW and HB. Moreover, HB had improved OS compared to NHB, suggesting unaccounted for protective factors associated with Hispanic ethnicity.

Table 1: Patient demographics, tumor, and treatment characteristics

| Factor | NHW N=1647 | Hispanic White N=3127 | NHB N=1070 | Hispanic Black N=107 | All N=5951 | p-value |
|---|---|---|---|---|---|---|
| PATIENT DEMOGRAPHICS | | | | | | |
| Age at diagnosis | | | | | | p<0.001 |
| <50 years | 441 (26.8%) | 990 (31.7%) | 358 (33.5%) | 30 (28.0%) | 1819 (30.6%) | |
| 50-69 years | 898 (54.5%) | 1769 (56.6%) | 607 (56.7%) | 62 (57.98%) | 3336 (56.1%) | |
| 70-79 years | 205 (12.4%) | 279 (8.9%) | 76 (7.1%) | 14 (13.1%) | 574 (9.6%) | |
| 80+ years | 103 (6.3%) | 89 (2.8%) | 29 (2.7%) | 1 (0.9%) | 222 (3.7%) | |
| Birthplace | | | | | | p<0.001 |
| US-born | 778 (47.2%) | 139 (4.4%) | 482 (45.0%) | 4 (3.7%) | 1403 (23.6%) | |
| Foreign-born | 214 (13.0%) | 2307 (73.8%) | 430 (40.2%) | 92 (86.0%) | 3043 (51.1%) | |
| Unknown | 655 (39.8%) | 681 (21.8%) | 158 (14.8%) | 11 (10.3%) | 1505 (25.3%) | |
| Relationship | | | | | | p<0.001 |
| Married | 947 (57.5%) | 1462 (46.8%) | 355 (33.2%) | 34 (31.8%) | 2798 (47.0%) | |
| Single | 295 (17.9%) | 756 (24.2%) | 472 (44.1%) | 42 (39.3%) | 1565 (26.3%) | |
| Divorced/Separated/Widow | 346 (21.0%) | 832 (26.6%) | 218 (20.4%) | 28 (26.2%) | 1424 (23.9%) | |
| Other/Unknown | 59 (3.6%) | 77 (2.5%) | 25 (2.3%) | 3 (2.8%) | 164 (2.8%) | |
| Area Deprivation Index | 35.4 ± 27.2 | 52.8 ± 26.7 | 67.0 ± 23.1 | 66.1 ± 23.8 | 50.9 ±28.3 | p<0.001 |
| Median Income Quartiles | | | | | | p<0.001 |
| <$36,572 | 130 (8.0%) | 909 (29.8%) | 405 (39.6%) | 40 (38.1%) | 1484 (25.6%) | |
| $36,573-48,450 | 317 (19.6%) | 787 (25.8%) | 384 (37.5%) | 32 (30.5%) | 1520 (26.2%) | |
| $48,451-64,599 | 521 (32.3%) | 700 (22.9%) | 143 (14.0%) | 26 (24.8%) | 1390 (24.0%) | |
| >$64,600 | 649 (40.1%) | 658 (21.5%) | 91 (8.9%) | 7 (6.7%) | 1405 (24.2%) | |
| Insurance | | | | | | p<0.001 |
| Private | 1054 (64.0%) | 1111 (35.5%) | 397 (37.1%) | 24 (22.4%) | 2586 (43.5%) | |
| Medicare | 320 (19.4%) | 343 (11.0%) | 117 (10.9%) | 16 (15.0%) | 796 (13.4%) | |
| Medicaid | 94 (5.7%) | 716 (22.9%) | 276 (25.8%) | 34 (31.8%) | 1120 (18.8%) | |
| Uninsured | 72 (4.4%) | 667 (21.3%) | 187 (17.5%) | 28 (26.2%) | 954 (16.0%) | |
| TUMOR AND TREATMENT CHARACTERISTICS | | | | | | |
| Clinical Stage | | | | | | p<0.001 |
| I | 765 (46.4%) | 1137 (36.4%) | 281 (26.3%) | 28 (26.2%) | 2211 (37.2%) | |
| II | 512 (31.1%) | 1120 (35.8%) | 386 (36.1%) | 38 (35.5%) | 2056 (34.5%) | |
| III | 211 (12.8%) | 563 (18.0%) | 221 (20.7%) | 24 (22.4%) | 1019 (17.1%) | |
| IV | 122 (7.4%) | 226 (7.2%) | 141 (13.2%) | 14 (13.1%) | 503 (8.5%) | |
| Unknown | 37 (2.2%) | 81 (2.6%) | 41 (3.8%) | 3 (2.8%) | 162 (2.7%) | |
| Tumor Grade | | | | | | p<0.001 |
| Well diff. | 334 (20.3%) | 531 (17.0%) | 132 (12.3%) | 13 (12.1%) | 1010 (17.0%) | |
| Moderately diff. | 715 (43.4%) | 1341 (42.9%) | 370 (34.6%) | 46 (43.0%) | 2472 (41.5%) | |
| Poorly diff. | 415 (25.2%) | 959 (30.7%) | 450 (42.1%) | 37 (34.6%) | 1861 (31.3%) | |
| Anaplastic/Undifferentiated | 7 (0.4%) | 19 (0.6%) | 20 (1.9%) | 2 (1.9%) | 48 (0.8%) | |
| Unknown | 176 (10.7%) | 277 (8.9%) | 98 (9.2%) | 9 (8.4%) | 560 (9.4%) | |
| Receptor Status | | | | | | p<0.001 |
| ER+/HER2+ | 170 (10.3%) | 336 (10.7%) | 109 (10.2%) | 18 (16.8%) | 633 (10.6%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **ER+/HER2-** | **1078 (65.5%)** | **1983 (63.4%)** | **525 (49.1%)** | **60 (56.1%)** | **3646 (61.3%)** | |
| **ER-/HER2-** | **315 (19.1%)** | **571 (18.3%)** | **335 (31.3%)** | **22 (20.6%)** | **1243 (20.9%)** | |
| **ER-/HER2+** | **84 (5.1%)** | **237 (7.6%)** | **101 (9.4%)** | **7 (6.5%)** | **429 (7.2%)** | |
| **Pathologic Stage** | | | | | | **p<0.001** |
| **0** | **12 (0.7%)** | **20 (0.6%)** | **7 (0.7%)** | **1 (0.9%)** | **40 (0.7%)** | |
| **I** | **759 (46.2%)** | **1086 (34.7%)** | **281 (26.3%)** | **31 (29.2%)** | **2157 (36.3%)** | |
| **II** | **406 (24.7%)** | **859 (27.5%)** | **268 (25.0%)** | **26 (24.5%)** | **1559 (26.2%)** | |
| **III** | **146 (8.9%)** | **340 (10.9%)** | **106 (9.9%)** | **12 (11.3%)** | **604 (10.2%)** | |
| **IV** | **44 (2.7%)** | **81 (2.6%)** | **37 (3.5%)** | **9 (8.5%)** | **171 (2.9%)** | |
| **Unknown** | **277 (16.8%)** | **740 (23.7%)** | **371 (34.7%)** | **27 (25.5%)** | **1415 (23.8%)** | |
| **Treatments** | | | | | | |
| **Surgery** | **1494 (90.7%)** | **2782 (89.0%)** | **856 (80.0%)** | **88 (82.2%)** | **5220 (87.7%)** | **p<0.001** |
| **Chemotherapy** | **854 (51.9%)** | **1891 (60.5%)** | **658 (61.5%)** | **61 (57.0%)** | **3464 (58.2%)** | **p<0.001** |
| **Radiation** | **848 (51.5%)** | **1761 (56.3%)** | **528 (49.3%)** | **56 (52.3%)** | **3193 (53.7%)** | **p<0.001** |
| **Endocrine Therapy** | **1121 (68.1%)** | **1924 (61.5%)** | **482 (45.0%)** | **59 (55.1%)** | **3586 (60.3%)** | **p<0.001** |
| **NCCN Guideline-Based Care (by stage and receptor)** | **1311 (79.6%)** | **2366 (75.7%)** | **745 (69.6%)** | **77 (72.0%)** | **4499 (75.6%)** | **p<0.001** |
| **Treatment at Comprehensive Cancer Center** | **1368 (83.1%)** | **1445 (46.2%)** | **432 (40.4%)** | **37 (34.6%)** | **3282 (55.2%)** | **p<0.001** |

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# Mammaprint and blueprint as prognostic indicators for elderly patients with early stage breast cancer

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Background: Elderly breast cancer (BC) patients are an understudied population, with limited evidence regarding treatment options and outcomes and a lack of research involving prognostic multigene assays for this group. One study in patients 65-89 years old with an Oncotype DX Recurrence Score ≥ 26 concluded that gene expression profiling tests have limited utility in elderly patients, and should only be used for patients aged 65-74 with no/low to moderate comorbidities and not for patients ≥ 75. In this study, the 70-gene risk of distant recurrence signature, MammaPrint (MP), and 80-gene molecular subtyping signature, BluePrint (BP), were evaluated in both the neoadjuvant and adjuvant settings in elderly patients with early stage BC.
Methods: This analysis included 211 BC patients classified as cT2-4N0-3M0 (T2 > 3.5 cm if N0) who received neoadjuvant chemotherapy and enrolled in the Multi-Institutional Neoadjuvant Therapy MammaPrint Project (MINT) study from 2011-2016. Lymph node (LN) involvement was established following neoadjuvant treatment. The second analysis included 517 early stage BC patients with 0-3 positive LNs who enrolled in the community based cohort study (COPPER) from 2009-2016. Patients were given adjuvant treatment following standard of care. Patients from both cohorts were divided into age at diagnosis groups: < 65, 65-74, and > 74. MP stratified patients into either Low Risk (LR) or High Risk (HR) groups. BP classified patient samples into Luminal, HER2, or Basal subtype. Kaplan Meier analysis and log-rank test were used to assess differences in overall survival (OS) and distant metastasis free survival (DMFS). Clinical risk assessment based on the MINDACT trial algorithm was performed.
Results: From MINT, 35 patients were ≥ 65 years old; 80% were HR and 20% were LR. Pathological complete response (pCR) was achieved in 36% (10/28) of elderly HR patients, of whom 70% were HER2 and 30% were Basal by BP. Nodal downstaging occurred in 55% (11/20) of LN positive elderly HR patients, of whom 64% (7/11) achieved pCR. BP classified patients with nodal downstaging as HER2 (55%), Basal (36%), or Luminal (9%). Importantly, pCR and nodal downstaging were more likely to be achieved in HR tumors and correlated with BP subtype in both young and elderly patients. From the COPPER cohort, 77% of HR patients 65-74 years old received chemotherapy (CT), whereas 74% of LR patients omitted CT. Of patients > 74, 49% of HR patients received CT, whereas 75% of LR patients omitted CT. OS and DMFS probabilities indicated good survival outcomes in LR patients that omitted CT and HR patients that received CT, with no significant difference between age groups. A majority of HR patients treated with CT and over 1/3 of LR patients that omitted CT had high clinical risk. Interestingly, among all patients that had a metastasis event, mortality was less likely to occur in patients that received dose dense AC (doxorubicin and cyclophosphamide).
Conclusion: MP and BP may identify HR elderly patients who are likely to achieve nodal downstaging and pCR. Elderly patients were safely spared or assigned adjuvant CT based on MP results independent of clinical risk. Furthermore, these data are in line with previous studies that suggest similar survival benefits between older and younger patients who are candidates for aggressive CT regimens. MP and BP elucidate information about tumor biology and provide prognostic value, which may help inform treatment decisions, independent of patient age.

| | | | | | | |
|---|---|---|---|---|---|---|
| MINT | | | | | | |
| Age group | < 65 | | 65-74 | | > 74 | |
| MP result | HR | LR | HR | LR | HR | |
| # of patients | 152 | 24 | 21 | 7 | 7 | |
| % of patients with pCR | 35% (53/152) | 0 | 33% (7/21) | 0 | 43% (3/7) | |
| # of LN+ patients | 103 | 18 | 14 | 5 | 6 | |
| % of LN+ patients with nodal downstaging | 49.5% (51/103) | 22% (4/18) | 50% (7/14) | 0 | 67% (4/6) | |
| % of LN+ patients with pCR & nodal downstaging | 65% (33/51) | 0 | 71%(5/7) | 0 | 50%(2/4) | |
| COPPER | | | | | | |
| Age group | < 65 | | 65-74 | | > 74 | |
| MP result | HR | LR | HR | LR | HR | LR |
| # of patients | 140 | 99 | 88 | 66 | 55 | 69 |
| # of patients received CT | 121 | 25 | 68 | 13 | 27 | 8 |
| # of patients omitted CT | 11 | 67 | 17 | 49 | 20 | 52 |
| # of patients with unknown treatment | 8 | 7 | 3 | 4 | 8 | 9 |
| Groups treated based on MP | HR treated with CT | | | LR omitted CT | | |
| Age group | < 65 | 65-74 | > 74 | < 65 | 65-74 | > 74 |
| 5-yr DMFS probability (95% CI) | 91% (80.2-96.7) | 87% (60.2-91.4) | 87% (55.2-96.6) | 100% | 98% (84.3-99.7) | 94% (75.9-98.5) |
| 5-yr OS probability (95% CI) | 94% (80.2-98.2) | 96% (83.4-98.9) | 86% (54.7-96.5) | 100% | 98% (84.3-99.7) | 97% (80.4-99.6) |
| % Clinical high risk | 83% (100/121) | 76% (52/68) | 63% (17/27) | 34% (23/67) | 37% (18/49) | 35% (18/52) |

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# PARP inhibitors for treatment of BRCA positive metastatic breast cancer: A systematic review and meta-analysis

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Background: PARP Inhibitors (inh), Olaparib and Talazoparib, are approved for deleterious germline BRCA mutated (gBRCA+) metastatic breast cancer (MBC). This approval was based on a progression-free survival (PFS) benefit seen in two randomized controlled trials (RCTs). Other PARP inh such as Veliparib and Niraparib have also been studied. We conducted this meta-analysis of RCTs aiming to assess PFS and OS of PARP inh in gBRCA+ MBC.
Methods: We performed a systematic search for RCTs using Cochrane Library, PubMed, Embase, and Web of Science up to June 2020. Only phase II and III RCTs evaluating PFS for PARP inh alone or in combination with chemotherapy (CT) to standard CT were eligible for this meta-analysis. The pooled analysis of hazard ratio (HR) was performed with RevMan 5.4 software using random effect model.
Results: A total of 5 RCTs including 1563 patients were included in this meta-analysis. Baseline study characteristics are listed in Table 1. The pooled HR for PFS was 0.77 (95%CI 0.55-1.09) and the pooled HR for OS was 0.96 (95%CI 0.80-1.16). The only statistically significant adverse event more common in PARP inh group was anemia (Odds Ratio, 3.01; CI95%, 1.14-7.93, *P*=0.03). (Table 2)
Conclusion: The results of our meta-analysis confirmed the previously reported PFS benefit of PARP inh either alone or with standard CT when compared to standard CT alone in gBRCA+ MBC. PARP inh when combined with temozolomide did not show PFS benefit. OS benefit is not seen with PARP inh alone or with standard CT. Ongoing trials are evaluating the benefit of PARP inh in early stage gBRCA+ BC.

Table 1: Baseline study characteristics as experimental group vs. control groupVCP: veliparib with carboplatin/paclitaxelVT: veliparib with temozolomidePCP: placebo plus carboplatin/paclitaxelNA: Not available** Subgroup germline BRCA+ pts (n=37, 13 vs 24) is used for PFS and OS analysis in this study.

| Trials | Sample size | Experimental group | Control group | ECOG PS % (0/1/2) | Previous CT no. (%) | Previous platinum no. (%) | Median PFS (mo) | Median OS (mo) |
|---|---|---|---|---|---|---|---|---|
| OlympiAD | 302 (205 Vs 97) | Olaparib | Standard CT (Capecitabine or Eribulin orVinorelbine) | 72.2/28.8/0 Vs 63.9/36.1/0 | 146 (71.2) Vs 69 (71.1) | 60 (29.3) Vs 26 (26.8) | 7.0 Vs 4.2 | 19.3 Vs 17.1 |
| EMBRACA | 431 (287 Vs 144) | Talazoparib | Standard therapy | 53.3/44.3/2.1 Vs 58.3/39.6/1.4 | 176(61.4) Vs 90(62.5) | 46 (16.0) Vs 30 (20.8) | 8.6 Vs 5.6 | 19.3 Vs 19.5 |
| BROCADE | 284 (97 Vs 99) | VCP | PCP | 92/5 Vs 93/6 | 23(23.7) Vs 37(37.4) | NA | 14.1 Vs 12.3 | 28.3 Vs 25.9 |
| | (94 Vs 99) | VT | PCP | 91/3 Vs 93/6 | 28(30.6) Vs 37 (37.4) | NA | 7.4 Vs 12.3 | 19.1 Vs 25.9 |
| BROCADE-3 | 509 (337 Vs 172) | VCP | PCP | NA | 19% | 8% | 14.5 Vs 12.6 | 33.5 Vs 28.2 |
| SWOG S1416 ** | 321 | Veliparib + Cisplatin | Placebo + Cisplatin | 69/41Vs 57/43 | 51(32) Vs 49(31) | 14(9) Vs 18(11) | 6.2 Vs 6.4 | 14.2 Vs 14.6 |
| BRAVO | - | Niraparib | Physician choice CT | Study was prematurely closed after an interim analysis showed too many patients were not completing the necessary assessments in the control arm, and it was no longer suitable as a registration trial. | | | | |

| Adverse Events (%) | OlympiAD | EMBRACA | BROCADE(VCP & VT Vs PCP) | BROCADE-3 | SWOG S1416** | Odds Ratio for Adverse Events |
|---|---|---|---|---|---|---|
| Anemia Grade ≥3 | 33 (16.1) Vs 4 (4.4) | 112 (39.2) Vs 6 (4.8) | 16 (17.2) &7 (7.5) Vs 17 (17.7) | 91(27) Vs 29(17) | 35(23) vs 11(7) | 3.01 (1.14,7.93) *P*=0.03 |
| Neutropenia Grade ≥3 | 19 (9.3) Vs 24 (26.4) | 60 (20.9) Vs 44 (34.9) | 52(55.9) &34(36.6) Vs 53 (55.2) | 175(52) Vs 86 (50) | 71(46) vs 29(19) | 0.80 (0.40, 1.62) *P*=0.53 |
| Leukopenia Grade ≥3 | 7(3.4) Vs 9 (9.9) | 19 (6.6) Vs 11(8.7) | 15(16.1) &11(11.8) Vs 11 (11.5) | NA | 42 (27) Vs 11 (7) | 1.19 (0.42,3.38) *P*=0.74 |
| Nausea/Vomiting Grade ≥3 | 0 Vs 1 (1.1) | 8 (2.7) Vs 4(3.2) | 2(2.2) &5(5.4) Vs 3 (3.1) | NA | 28(18) Vs 16(10) | 1.45 (0.85,2.46) *P*=0.17 |
| Diarrhea Grade ≥3 | 1 (0.5) Vs 0 | 2 (0.7) Vs 7 (5.6) | 4(4.3) & 2(2.2) Vs 7(7.3) | NA | NA | 0.33 (0.13, 0.85) *P*=0.02 |
| Fatigue Grade ≥3 | 6 (2.9) vs 1 (1.1) | 5 (1.7) Vs 4 (3.2) | 5(5.4) &3(3.2) Vs 8(8.3) | NA | 8(5) Vs 9(6) | 0.73 (0.40,1.33) *P*=0.30 |
| Treatment discontinuation due to any AE | 10 (4.9) Vs 7(7.7) | 17 (5.9) Vs 11 (8.7) | | NA | NA | 0.72 (0.39,1.34) *P*=0.30 |

Table 2: Side effect profile of PARP inh arm vs. CT armNA: Not available**side effect includes all 154 pts in experimental arm and 149 in control arm

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# Machine learning model of gut microbiota predicts neratinib induced diarrhea in patients with breast cancer

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**Background: Neratinib is a potent small molecule tyrosine kinase inhibitor (TKI) of human epidermal growth factor receptors (HER1,2,4). One of the major side effects of neratinib is diarrhea. The human gut contains a dense microbiome ecosystem that is essential in maintaining a healthy host physiology, and its disruption may lead to increased risk of toxicities from cancer therapy. In this study, we aimed to develop a machine learning model based on analysis of gut microbiota data to predict neratinib-induced diarrhea.**
**Methods: Patients were enrolled in a phase II trial evaluating safety and tolerability of neratinib in older adults with HER2+ breast cancer (NCT02673398). Neratinib was administered as single agent, 240 mg oral daily in a 28-day cycle. Stool samples were collected at baseline and during treatment for 16S rRNA gene sequencing. Using microbial relative abundance data, we developed gradient-boosted tree models with two nested loops of cross validations to classify whether diarrhea would occur or not after treatment onset. For the inner validation loop, we used ten-fold cross validation to determine the optimal model from hyper-parameters including regularization. For the outer validation loop, we utilized a leave-one-patient-out cross validation to test this model on the hold-out patient's baseline data and the predictions were used for model assessment.**
**Results: A total of 11 patients and 50 longitudinal stool samples were collected. The median age was 66 years. 73% developed grade ≥ 1 diarrhea attributed to neratinib. Shannon diversity index of gut microbiome was not associated with diarrhea. For predictive modeling, the outer validation loop Area Under the Receiver Operating Characteristic Curve (AUROC) and Area Under the Precision Recall Curve (AUPRC) were 0.92 and 0.97, respectively. The two most important taxa predictive of protection from diarrhea were *Ruminiclostridium* 9, and *Bacteroides* sp. HPS0048. We found that patients with a larger relative abundance of *Ruminiclostridium* 9 and *Bacteroides* sp. HPS0048 have reduced risk of neratinib-related diarrhea.**
**Conclusions: The machine learning model can identify breast cancer patients at risk of diarrhea prior to neratinib use. Future studies are required to validate this finding.**

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# Real-world evidence of platinum-based chemotherapy for the treatment of BRCA-positive metastatic breast cancer in a cohort of 33,878 women in the United States

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Background The choice of chemotherapy for women diagnosed with metastatic breast cancer (BC) has been evolving as new agents and clinical trial results become available. Current NCCN guidelines recommend sequential single chemotherapeutic agents and combination therapy including platinum-based regimens for patients with high risk disease. Platinum-based chemotherapies are recommended for triple-negative breast cancer (TNBC) and, in particular, for a more defined population of TNBC with a BRCA mutation that may have particular sensitivity to platinum agents due to the impaired ability to repair DNA damage inherent in these patients.[1] Here, we aim to leverage real world data to ascertain the use of platinum-based treatments in BRCA-mutation positive (BRCA+) metastatic BC patients, characterized by their hormonal receptor status.

Methods Optum's electronic health records (EHR) database was used to identify a cohort of women with 1) confirmed BC ICD-9/ICD-10 diagnosis between 2008 and 2018, 2) at least 12 months of history in the EHR, 3) at least one distant metastasis diagnosis (per ICD-9/ICD-10, or from physician notes), and 4) no previous diagnosis of other primary cancers in previous 12 months. BRCA-mutation status, ER, PR and HER2 test results were used to create relevant biomarker subgroups. Distinct lines of therapy (LOT) in the post-metastatic period were established using business rules, and the extent of use of platinum-based treatments, overall and of specific platinum regimens, were analyzed in various LOTs.

Results Among 33,878 metastatic BC patients receiving a systemic chemotherapy, 8.7% were treated with a platinum-based regimen, while among the subgroup who were BRCA+, the proportion receiving platinum-based regimens was higher at 12.3%. In LOT2 and LOT3, the proportion receiving platinum regimens was 3.9% and 2.5% for the overall cohort, compared with 5.2% and 3.0% for the BRCA+ cohort. Within the BRCA+ cohort, the use of platinum-based regimens in TNBC patients was substantially higher than in other patients, accounting for 21.6%, 15.3% and 14.2% of patients in LOT1, LOT2 and LOT3 respectively, compared with 8.7%, 3.1% and 1.7% in ER+/PR+ patients (Table 1). The choice of specific platinum-containing combination regimens differed by biomarker cohorts; the combination of carboplatin and paclitaxel was most common in TNBC patients, while a quadruplet regimen was most used in the ER+/PR+ cohort.

Conclusions Real-world evidence on use of platinum-based regimens in metastatic BC patients revealed differences across BRCA and hormonal status phenotypes. Women with TNBC had higher use of platinum agents than other subgroups across all lines of treatment. The observation that the use of platinum-based chemotherapy, including combination regimens, was highest in TNBC across lines of treatment highlights the persistent unmet need around alternative therapies for women affected with TNBC and BRCA+ disease.

Table 1. Use of platinum-based regimens in women with metastatic BC in LOTs 1-3

| | All metastatic BC | BRCA+ | | |
|---|---|---|---|---|
| | | All BRCA+ | ER+/PR+ | TNBC |
| N (treated with LOT1) | 33,878 | 5,649 | 4,228 | 782 |
| Age at LOT1 start (in years): Median (IQR) | 63 (53-73) | 54 (46-64) | 54 (46-64) | 54 (45-62) |
| Total proportion (%) of platinum-based regimens in LOT1 | 8.7% | 12.3% | 8.7% | 21.6% |
| REGIMEN | | | | |
| Carboplatin+paclitaxel | 1.8% | 2.8% | 1.4% | 8.3% |
| Carboplatin+docetaxel+pertuzumab+trastuzumab | 1.7% | 2.8% | 2.6% | 0.4% |
| Carboplatin+docetaxel+trastuzumab | 1.2% | 1.9% | 1.8% | 0.3% |
| Carboplatin+gemcitabine | 0.9% | 1.4% | 0.7% | 5.5% |
| Carboplatin | 0.7% | 0.8% | 0.5% | 1.9% |
| Carboplatin+docetaxel | 0.3% | 0.4% | 0.2% | 1.3% |
| Cisplatin | 0.3% | 0.4% | 0.2% | 1.0% |
| Other platinum-based regimens | 1.9% | 2.0% | 1.4% | 2.9% |
| N (treated with LOT2) | 21,148 | 4,197 | 3,317 | 495 |
| Total proportion (%) of platinum-based regimens in LOT2 | 3.9% | 5.2% | 3.1% | 15.3% |
| N (treated with LOT3) | 13,937 | 2,959 | 2,523 | 226 |
| Total proportion (%) of platinum-based regimens in LOT3 | 2.5% | 3.0% | 1.7% | 14.2% |

Footnotes[1] Isakoff, SJ. Triple-Negative Breast Cancer: Role of Specific Chemotherapy Agents. Cancer J 2010;16: 53-61

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# Salt-inducible kinases suppress tumour function and regulate drug resistance in breast cancer

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**Background: Salt-inducible kinases (SIKs) belonging to an AMP-activated kinase (AMPK) family, have functions in tumourgeniesis and metastasis in many solid tumours. However, the role of SIKs in breast cancer is not clear. In this study we aimed to determine the function of SIKs (SIK1, SIK2 and SIK3) in human breast cancer. Method: A cohort of breast cancer tissues (n=102) were analysed using qPCR to determine changes in SIK expression (SIK1, SIK2, SIK3 and housekeeping GAPDH ) between cancer and normal tissues and different aetiologies of cancer. In addition, a breast disease spectrum array (TMA) was probed for SIK expression at the protein level. SIK1, 2 and 3 were knocked down using shRNA in the human breast cancer cell lines MCF-7 and MDA-MB-231 and changes in cell behaviour were assessed using a number of cell function assays.Results: At the messenger level, expression of SIK2 was lower in breast cancer than normal tissue (p=0.0179), while expression of SIK1 and SIK3 had no significant difference between breast cancer and normal tissue. SIK3 expression was associated with ER status in the cohort (p=0.02). The level of SIK2 expression was significantly different in Stage I and Stage III. While SIK3 expression was significantly higher in ER positive breast cancer than ER negative breast cancer. Further analysis using Kaplan-Meier survival was performed for SIKs expression in an online database (http://kmplot.com/analysis/index.php?p=background) which showed that that an increased expression of SIKs was associated with good prognosis in the breast cancer cohort (p<0.01). Moreover, IHC staining correlation of SIKs in tumour with different clinicopathological characteristics showed a SIK1 Klein score significantly higher in ER positive breast cancer than ER negative breast cancer; in SIK3, a higher Klein score was observed in breast cancer with higher Grade, negative lymph node and higher TNM stage (p <0.05). *In vitro*, reduced expression of SIK2 and SIK3 increases the proliferation of breast cancer cells. However, SIK2 and SIK3 had differential effects on breast cancer cell adhesion. Knockdown of SIK2 only enhanced the adhesion of triple negative breast cancer cells (MDA-MB-231), while knockdown of SIK3 decreased the adhesion of both MDA-MB-231 and MCF 7 cells. Knockdown of SIK1 and SIK3 increased the invasion of MDA-MB-231 cells (p<0.05). Knockdown SIK1 increased the barrier but knockdown of SIK2 and SIK3 decreased the barrier of the breast cancer cells (p<0.05). We also determined the effect of possible chemotherapeutic resistance in these cell lines: the cells were treated with various concentration of chemotherapy drugs and placebo and found that reduced SIKs increased the resistance of breast cancer cell to paclitaxel and cisplatin.Conclusion: In conclusion, we show that low expression of SIK1,2 and 3 in breast cancer was correlated with poor prognosis and chemotherapy resistance of breast cancer. Reduced SIKs promote tumour metastasis by enhancing tumour function and tight junction. SIKs could be potential biomarkers for prognosis and chemotherapy sensitivity in breast cancer.**

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# In depth single cell profiling of a case of bone metastases with associated organoid models reveals a precision medicine approach to treatment

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Occurring in 65-80% of metastatic breast cancer (BC), bone metastasis (BoM) is the major cause of BC related mortality. Under current standard of care, 5 year overall survival for patients with BoM is 20-25%, warranting the need of improved treatments. Like other cancers, BC BoM has high inter- and intra-patient heterogeneity. Thus, understanding disease evolution and heterogeneity of BoM at the individual patient level will be key to guide precise application of targeted therapies. In this study, we describe in depth histologic and single cell molecular characterization of a case of invasive lobular breast cancer (ILC) metastasis to bone.

We collected fixed primary tumor (ER+/PR-/HER2- ILC) and fresh pelvis and tibia BoMs from a patient. H&E/IHC staining and whole exome sequencing (WES) of DNA and RNA of the samples were performed. Organoids were derived from the two BoMs and single cell RNA sequencing was applied to these cultures and the BoMs.

Based on H&E/IHC staining, this case evolved from a ER+ primary ILC to ER- BoM with mixed lobular and ductal carcinoma features. WES revealed 208 missense somatic mutations in the BoMs. 15 were predicted as BC drivers, two of which are druggable including PIK3CA (E545K) and BRCA1 (D1834H, H399P). Notably, BRCA1 (D1834H) was not found in the primary tumor. Based on RNA sequencing, estrogen signaling was downregulated, while TGF-β, Wnt beta catenin and PI3K signaling, epithelial to mesenchymal transition (EMT) and angiogenesis were upregulated, all of which have been reported to be potential targets in BoMs.

scRNAseq of BoMs revealed 5 major cell populations and pronounced heterogeneity. The two BoMs showed similar cellular compositions, including epithelial (30-50%), fibroblasts (50%), immune (5-10%), osteoclasts (1-2%) and endothelial cells (1-2%). Within epithelial cells, there were 5 major clusters exhibiting unique transcriptomic features, including a TNF-α signaling high cluster, two clusters showing high partial EMT (pEMT) signatures majorly regulated by PRRX1/2, TWIST1/2, and FOXS1, a cluster in active cell proliferation, and a cluster showing high signatures related to endocrine resistance. In fibroblasts, 3 clusters were identified representing ECM remodeling, angiogenesis (VEGFA high) and myofibroblasts. Immune cells majorly composed of macrophages, CD4+, CD8+ and Treg T cells. 2.2% tumor and 3.2% T cells express PDL1, exceeding the 1% threshold to select patients eligible for anti-PDL1 therapy. Based on CellPhoneDB, epithelial cells with high pEMT signature show the most interactions and uniquely interact with Treg cells through TNFSF4-TNFRSF4 which has been reported to promote Treg cell proliferation, and is investigated in clinic for immune therapy.

Organoids were developed to evaluate therapeutic potential of targetable mutations, upregulated genes and susceptible cell populations. WES showed organoids preserved the mutational signatures of the matched tumor. scRNAseq showed all epithelial populations in the tumor were preserved in the matched organoids at comparable abundance. Consistent with the BRCA1 and PIK3CA mutations, organids were responsive to a PARP (Talazoparib: $IC_{50}$ 1.3uM/1.3uM) and PI3K (Alpelisib: $IC_{50}$ 9uM/4uM) inhibitor. We are currently examining the therapeutic potential of inhibiting pEMT, TNF-α, and genes upregulated in BoM.

In summary, we have demonstrated a precision medicine approach to understand the evolution and heterogeneity of BC BoM. We have identified potential therapeutic targets and evaluated those in patient-specific organoids, thereby providing insights for the design of a precision medicine based clinical treatment strategy.

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# Locoregional treatment in de novo metastatic breast cancer: An overview of the current evidence

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**Background: Patients presenting with de novo metastatic breast cancer (dnMBC) is considered incurable but treatable. Despite the advances in systemic therapies, the role of locoregional treatment (LRT, primary tumor surgery and/or radiotherapy) for dnMBC remains controversial.**
**Aim: To review and discuss the present evidence of surgery- and radiation-based treatment strategies for dnMBC.**
**Settings and design: A systematic review and meta-analysis of the literature were carried out.**
**Methods: We did a systematic review and meta-analysis of observational studies and randomised controlled trials (RCTs) published from database inception to Feb 28, 2020, which reported on survival outcomes of LRT in patients with dnMBC. Studies were identified by searches in PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and by hand searching of previous publications. The review and meta-analysis were conducted to assess the effect of LRT on overall survival (OS). Robustness of pooled estimates from random-effects models was considered with sensitivity analyses, meta-regression, and subgroup analyses. All statistical analyses were performed with Stata 16.0.**
**Findings: Data on 714 patients in 3 RCTs and 173476 patients in 39 observational studies were included. In total 174190 patients, 76711 patients (44.04 %) underwent LRT ± systemic therapy, and 97479 patients (55.96 %) received systemic therapy alone (STA). Observational data showed LRT significantly improved overall survival (HR=0.63; 95%CI, 0.57 to 0.69, P<0.001, $I^2$=96.3%). The subgroup analysis found a favorable impact on survival in both patients undergoing surgery plus radiotherapy and surgery. However, the pooled outcomes of prospective trials suggested a 19.0% reduction in mortality which was not statistically significant (HR=0.81; 95% CI, 0.57 to 1.14, P=0.06, $I^2$=64.4%).**
**Interpretation: Due to the paucity of RCTs exploring LRT in patients with dnMBC, this was a meta-analysis which included retrospective and prospective data; both sets provide a complete picture of the effect. However, withstanding for retrospective bias, separate analyses was conducted to specifically examine the prospective trials. Findings from observational studies and RCTs associated with LRT and OS in these patients were inconsistent. Given the retrospective nature of observational studies, its results cannot be used as level I evidence to support LRT in patients with dnMBC. As level I evidence, prospective data suggest that the relationship between the LRT and survival benefit in these patients could not be causal. Although these trials have been criticized due to systemic therapy protocols which differ from standard modern treatments, they continue to provide important data. Ongoing well-designed prospective studies, including ECOG 2108 trial, are awaiting mature data.**
**Conclusions: Based on the results of current level I evidence, LRT should not be part of routine clinical practice in patients with dnMBC but might be performed in specific patients.**
**Key words: Locoregional treatment; De novo metastatic breast cancer; Systematic review; Meta-analysis**

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# A spatially resolved single cell atlas of the human breast

**Kai Kessenbrock. UCI, Irvine, CA**

**The human breast consists of lobules connected to an intricate network of ducts that are surrounded by fatty tissues, designed to produce and transport milk to nourish offspring. Histopathology has identified 10 major cell types based on morphological features but have provided limited information on cell states - the transcriptional programs of cell types that reflect different biological functions. In this study we have generated an unbiased 'cell atlas' of the normal human breast to define the cell types and cell states using single cell RNA sequencing and spatial transcriptomics methods. We performed 3' microdroplet based single cell and nuclei RNA sequencing of 248,687 stromal cells and 89,301 nuclei from 35 women with pathologically normal breast tissues that were collected from mastectomies and reduction mammoplasties. Unbiased expression analysis identified four major cell types: adipocytes, epithelial cells (luminal and basal), fibroblasts and endothelial cells and defined their transcriptional programs. Additionally, 8 minor cell types were identified in the breast, including macrophages, T-cells, natural killer cells, mast cells, pericytes, apocrine cells, neurons and smooth muscle cells. Our data revealed hundreds of novel markers of these cell types and defined their transcriptional programs and cell states. Most cell types had multiple transcriptional programs including luminal epithelial cells (hormone receptor positive and secretory), basal epithelial cells (myoepithelial or basal), endothelial cells (E1, E2, E3), myeloid cells, T-cells and fibroblasts (F1-F4) and provided insight into developmental lineages. We further delineated the spatial organization of these cell types and cell states within the tissue architecture via a 34 antibody CODEX ultra-high plex immunofluorescence imaging experiment. Antibodies were targeted against epithelial, endothelial and immune cells and imaging data were acquired at single cell resolution from breast tissues measuring up to 35mm$^2$. Cell phenotypes were independently clustered, correlated to transcriptomic data and cellular neighborhoods were mapped using nearest neighbor approximations. The breast cell atlas data provides an invaluable normal reference for the research community to understand how normal cell types are reprogrammed in diseases such as breast cancer.**

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# Low dose tamoxifen for breast cancer prevention and mammographic density reduction - a randomized controlled trial

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Introduction: Tamoxifen prevents breast cancer in high-risk women and reduces recurrence in the adjuvant setting but comes with side-effects. The optimal dose to increase uptake and retain therapeutic effect is unknown. We tested if the efficacy of low-dose tamoxifen is non-inferior to standard dose using mammographic density as a proxy for therapy response and if lower doses are associated with fewer symptoms.Methods: Healthy pre- and postmenopausal women attending a mammography screening program aged 40 to 74 years were invited to participate. N=2,314 screening women were investigated for eligibility. Exclusion criteria were women with a low mammographic density (BI-RADS A), high blood pressure, pregnancy, use of hormonal therapy, previous cardiovascular disorder, uncontrolled diabetes, any previous cancer. N=1,440 women entered a six-months double-blind placebo-controlled randomized dose-determination trial that was conducted in 2016-2019. Women were allocated into six months oral daily administration of 1, 2.5, 5, 10, and 20 mg of tamoxifen or placebo.Mammographic density was assessed as radiographic dense fibro-glandular tissue using a fully automated density tool. Symptoms were assessed using a self-reported questionnaire including vasomotor, gynecological, sexual, and joint pain symptoms. Non-inferior reduction of mammographic density and fewer severe symptoms in lower doses were compared with standard dose 20 mg. Post-hoc analyses were performed by menopause status. Both per protocol and intension to treat populations were analyzed.Results: Premenopausal (N=566) and postmenopausal (N=873) participants were recruited to the study. Premenopausal women showed non-inferior reduction in mammographic density following 2.5, 5 and 10 mg tamoxifen compared with the median 9.7% decrease observed in the 20 mg group
(Table 1). No reduction in density was seen in postmenopausal participants. Severe vasomotor symptoms (hot flashes, cold and night seats) were reduced by approximately 50% in the 2.5 mg group compared with the 20 mg group (Table 2).Conclusion: Premenopausal women experienced fewer side effects with non-inferior decrease in breast density at lower dose of tamoxifen (2.5 mg) compared with standard dose (20 mg). A low dose of tamoxifen could be used for prevention and to increase sensitivity of a mammogram in premenopausal women.

Table 1. Non-inferior dense area reduction at six-months in the 2.5 mg arm compared with the standard dose 20mg arm.

| | All women | | | Premenopausal | Postmenopausal |
|---|---|---|---|---|---|
| Dose | Proportion (97.5%CI) | p-value | Holm p-value | Proportion (95%CI) | Proportion (95%CI) |
| 0 mg | 41.0 (29.2,100) | 0.101 | 0.203 | 33.9 (15.0,52.8) | 44.6 (33.3,55.9) |
| 1 mg | 40.8 (28.1,100) | 0.125 | 0.203 | 33.3 (17.9,48.8) | 46.1 (31.9,60.3) |
| 2.5 mg | 55.3 (44.2,100) | <0.01 | <0.01 | 71.9 (57.7,86.0) | 44.2 (31.2,57.2) |
| 5 mg | 54.8 (44.8,100) | <0.01 | <0.01 | 77.3 (64.4,90.1) | 38.5 (26.8,50.1) |
| 10 mg | 54.5 (42.9,100) | <0.01 | <0.01 | 72.7 (59.6,85.8) | 42.6 (28.9,56.3) |
| 20 mg | 50.0 (ref.) | | | 63.8 | 41.2 |

The table shows the proportions of women that had a larger decrease than median density decreases in the 20 mg arm (-9.7%) at six-months, stratified by menopausal status and tamoxifen dose.

Table 2. Significantly lower prevalence ratios of severe vasomotor symptoms by 50% at six-months in the 2.5 mg arm compared with the standard dose 20 mg arm.

| | All women | Premenopausal | Postmenopausal |
|---|---|---|---|
| Dose | PR (95%CI) | PR (95%CI) | PR (95%CI) |
| 0 mg | 0.41 (0.27,0.62) | 0.10 (0.02,0.39) | 0.56 (0.36,0.88) |
| 1 mg | 0.48 (0.33,0.71) | 0.37 (0.19,0.75) | 0.56 (0.35,0.89) |
| 2.5 mg | 0.47 (0.32,0.71) | 0.37 (0.18,0.78) | 0.54 (0.33,0.88) |
| 5 mg | 0.72 (0.51,1.01) | 0.36 (0.18,0.75) | 0.97 (0.65,1.42) |
| 10 mg | 0.76 (0.55,1.06) | 0.68 (0.39,1.19) | 0.81 (0.54,1.22) |
| 20 mg | 1 (ref.) | 1 (ref.) | 1 (ref.) |

The table shows the prevalence ratios (PR) of severe vasomotor symptoms stratified by menopausal status and tamoxifen dose.

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# Change in intra-lesion heterogeneity on CT predicts long-term survival following treatment with CDK4/6 inhibitors in hormone receptor-positive metastatic breast cancer (MBC)

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Background: CDK 4/6 inhibitors are currently standard of care for patients CDK 4/6 inhibitors but currently lack validated predictive markers. We evaluated whether changes in intra-lesional heterogeneity, extracted computationally from routine computed tomography (CT) of MBC could predict survival following treatment with CDK 4/6 inhibitors.
Methods: 33 patients with ER+ breast cancer metastasized to the liver who received palbociclib in combination with anti-estrogen therapy were identified from a registry. For each patient, CT exams were acquired prior to treatment and following initiation of treatment (median time between scans of 106 +/- 48.6 days). Liver metastases were manually delineated on all scans with consultation of radiology reports. On each scan, gray level co-occurrence matrix (GLCM) entropy, a computational measure of intra-lesional heterogeneity, was calculated and averaged across all metastatic lesions and its change over treatment was computed. For comparison, response was also assessed via RECIST v1.1: 65% of patients had objective response/stable disease, while 35% had progressive disease on scan following initiation of treatment. Imaging metrics were assessed individually and in a multivariate comparison including clinical features for association with overall survival (OS) via a cox proportional hazards model.
Results: Change in intra-lesion heterogeneity was associated with OS with a hazard ratio [HR] of 2.82 (p=0.019). An increase in entropy between the pre- and treatment scan was associated with poorer viability on treatment including CDK inhibitors, indicating that a favorable response can be distinguished by a decrease in intra-lesion heterogeneity. RECIST response was also associated with OS (HR=0.24, p<0.001). In a multivariable comparison with clinical variables, change in GLCM entropy and response per RECIST criteria both demonstrated multivariate significance. Neither the heterogeneity measure on the pre-treatment scan (HR=0.56, p=0.23) nor the scan acquired during treatment (HR=1.51, p=0.27) treatment scans alone were significantly associated with overall survival.
Conclusions: The change in lesion heterogeneity on clinical imaging following the initiation of treatment was found to offer independent value in distinguishing patients with favorable survival following CDK 4/6 inhibitor treatment.

Multivariate association of imaging features and clinical variables with overall survival

| | Hazard ratio (HR) | p-value |
|---|---|---|
| Change in Heterogeneity | 4.67 | 0.019 |
| RECIST response | 0.16 | 0.003 |
| PR status | 1.01 | 0.99 |
| HER2 status | 1.13 | 0.92 |
| Age | 1.04 | 0.26 |
| Pathology | 0.77 | 0.39 |
| Line of Treatment | 1.36 | 0.12 |

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**Publication Number: PS4-42**

# Kiss1, the kiss1 receptor (kiss1r) and the protein kinase c (pkc) family identifies patients with clinical outcome in clinical breast cancer

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**Background: Kiss1, also known as Kisspeptin-1 and metastin, is a protein coded by the *KISS1* gene (1). The receptor for KISS1, KISS1R (also known as G-protein coupled receptor 54 or GPR54 is coded by the *KISS1R* gene. Kiss1 and Kiss1R have been indicated in a number of pathophysiological conditions, including metabolic and reproductive abnormalities and the protein complex has been well indicated in the development and progression of a number of solid cancers including the metastatic potential of cancer cells (1) and in clinical cancers including breast cancer (2). Here, the intracellular events associated with KISS1/KISS1R signalling have been explored, including focal adhesion kinase and phospholipase-C (PLC) pathways where we employed a protein kinase platform together with a clinical breast cohort in order to explore protein kinases that are involved in KISS1 signalling and the clinical significance. Methods: A protein kinase microarray (Kinexus850) was employed to detect the cellular kinase responses to exogenous Kisspeptin stimulation. Kiss1, Kiss1 receptor (KISS1R or GPR54) and the prospective members of the protein kinase C (PKC) family members were assessed for the expression in a Cardiff breast cancer cohort and were analysed against the pathological and clinical outcomes of the patients. Results. Using the Kinexus protein kinase platform, we identified that some key members of the protein kinase C family were upregulated in response to treatment with exogenous Kisspeptin. These members include Protein kinase C (PKC)-gamma, PKC-iota, PKC-zeta and PKC-delta, which are potential downsteam targets of KISS1/KISS1R. In our clinical cohort, KISS1 was significantly correlated with the expression levels of PKC-iota (p=0.01) and PKC-gamma (p<0.001). Similarly, KISS1 receptor (KISS1R) was also significantly correlated with both PKC-gamma and PKC-iota. Neither PKC-delta nor PKC-zeta showed a correlation with KISS1 and KISS1R in the clinical cohort. When KISS1, KISS1R, PKC-gamma and PKC-iota were collectively analysed against clinical outcome of the patients, the four molecules identified a subset of the patients who had all survived the ten year followup period (OS) and with no breast cancer related incidence (DFS). The subgroup consisted of all Her-2 negative tumours but with variable nodal and disease stages. Multivariate analyses indicate that the collective expression pattern of KISS1, KISS1R, PKC-gamma and PKC-iota is an independent prognostic factor for disease free survival in breast cancer patients. Discussion: Protein kinase C (PKC) family members, including PKC-gamma and PKC-iota, are important downstream intracellular events in response to KISS1/KISS1R activation. These protein kinase C members together with KISS1/KISS1R protein complex identify a subset of patients with breast cancer who have favourable prognosis.**

**References 1. Lee JH, Miele ME, Hicks DJ, Phillips KK, Trent JM, Weissman BE, Welch DR. KiSS-1, a novel human malignant melanoma metastasis-suppressor gene. J Natl Cancer Inst. 1996, 88:1731-7. 2. Tracey A Martin [1], Gareth Watkins, Wen G Jiang. KiSS-1 Expression in Human Breast Cancer. Clin Exp Metastasis, 2005;22:503-11**

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# A fast and effective 3D preclinical assay system comprised of patient derived breast cancer microtumors combined with DigiWest protein signaling pathway analyses for therapeutic response prediction (Project PRIMO)

**Nicole Anderle[1], Felix Ruoff[1], Simge Yuez[1], Andre Koch[2], Andreas Hartkopf[2], Sara Brucker[2], Michael Pawlak[1], Markus Templin[1] and Christian Schmees[1]. [1]NMI Natural and Medical Sciences Institute at the University of Tubingen, Reutlingen, Germany[2]Department of Gynecology, University of Tubingen, Tubingen, Germany**

**In the era of personalized medicine, the ability of pre-selecting individualized therapeutic options and pre-defining their suitability in advance of clinical treatment might facilitate decision making in breast cancer treatment and hence, improve patient outcome. In order to preclinically validate anti-cancer drug efficacy, it is crucial to design a model system that reveals the influence of cellular interactions of the tumor microenvironment and cellular heterogeneity on drug response. Within the PRIMO (Personalized Medicine for tailored cancer therapies) project, such a 3D preclinical model system comprised of patient-derived microtumors (PDM) and autologous tumor-infiltrating lymphocytes (TILs) isolated from fresh primary breast cancer tissue using limited digestion and subsequent culture in defined media in the absence of serum is established. Herein, the heterogeneous cellular composition of isolated PDM is analyzed by FFPE immunohistochemistry and compared to corresponding primary tumor tissue. The composition of autologous TILs influencing individual treatment responses is characterized by multi-color flow cytometry detecting different cell populations, such as tumor-specific $CD8^+$ or regulatory $CD4^+$ T-cells. By using the DigiWest technology, a proprietary high throughput immune assay screening tool, in-depth protein profiling of up to 200 analytes from low amounts of PDM material is performed. The generated protein profiles of PDM are compared to their corresponding primary tumor tissue as well as the pathological receptor grading. Furthermore, differences in activation of key signal transduction pathways are detected and related to treatment responses to small molecules, chemotherapeutics as well as immunotherapeutic agents within PDM and PDM-TIL co-cultures assessed by a functional viability assay in a microplate format. To expand this preclinical model system, we established PDM-co-cultures adding further immune cell types including natural killer (NK) cells or dendritic cells (DC).**

**In summary, immunohistochemical analyses combined with protein profiling of breast cancer PDM enables drug-mode-of-action analyses, biomarker identification together with personalized therapeutic sensitivity prediction. The platform presented here expands the preclinical repertoire of relevant test systems for efficacy testing of drugs and investigational compounds, pre-identified by protein pathways as well as genetic profiling in personalized medicine of breast cancer.**

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# Heterogeneous tumor microenvironment in metastatic breast cancer for insufficient anti-PDL1 IgG delivery and its efficacy

**Yan ting Liu, Shreya Goel, Megumi Kai, Thao Nguyen and Kenji Yokoi. Houston Methodist Research Institute, Houston, TX**

**Although immune-checkpoint inhibitors have improved the survival of patients with various types of metastatic tumor, intra- and inter-patient heterogeneities in the response of multiple tumors to the therapy have significantly limited clinical benefits. Understanding the specific driving forces behind these heterogeneities will facilitate a better understanding of therapeutic resistance. Research has revealed that tumors in patients and established cancer cell lines are composed of multiple clones with different phenotypes. Our goal is to dissect these complexities and decipher mechanisms of tumor heterogeneities and resistance to immunotherapy. We have established single cell-derived clonal populations from parental, polyclonal 4T1, murine breast cancer cells. In vitro studies, while parental cells formed the heterogeneous types of colonies in a clonogenic assay, established clones created clone dependent uniform colonies. Each clone showed different growth rates, response to chemotherapy, and produced different amounts of cytokines. Then, 4T1 parental cells, clone 1, or clone 16 cells were injected into the spleen of mice to create multiple experimental liver metastases. Seven days after the inoculation, tumor-bearing mice were implanted with the window chamber above the liver, intravenously (iv) injected with fluorescently labeled anti-PDL1 IgG, and delivery of the antibody to individual liver metastasis was imaged using intravital microscopy (IVM). Then, mice were imaged using IVM for 7 days to determine the therapeutic effect on individual tumor growth. In another set of tumor-bearing mice, either isotype IgG or anti-PDL1 IgG were iv injected and the effect on the survival was evaluated. We found that the delivery of fluorescently labeled anti-PDL1 IgG and therapeutic effect was heterogeneous among liver metastases originated from 4T1 parental cells. We also found that there was an inverse correlation between the amount of the anti-PDL1 IgG delivered to the tumor and individual tumor growth. Liver metastases originated from clone 16 cells accumulated significantly more amount of the anti-PDL1 IgG and most of the tumors disappeared within 7 days. On the other hand, the anti-PDL1 IgG delivery to clone 1 cell-derived tumor was significantly reduced than parental and clone 16 cell-derived tumors and none of the tumors responded to the therapy. Thus, limited therapeutic efficacy can be attributed to the limited anti-PDL1 IgG delivery to the tumor. The survival of the tumor-bearing mice was correlated with the level of anti-PDL1 IgG delivery. While the anti-PDL1 therapy could extend the survival of mice-bearing clone 16 derived tumors, mice-bearing parental cells, and clone 1 cells didn't respond to the therapy. To elucidate the mechanism for the difference in anti-PDL1 Ab delivery, the effect of the therapeutics on tumor growth, and survival, we evaluated the expression of PDL1 protein in tumors by immunohistochemical analysis. PDL1 expression was higher in clone 16 tumors compared to parental and clone 1 tumor. Next, we evaluated the amount of blood vessels in tumors, because the difference in the antibody delivery can be attributed to the amount of angiogenesis. Interestingly, there was no significant difference in the amount of blood vessels, indicating the expression level of the target protein is crucial to determine the amount of the antibody delivery. Regarding the immune microenvironment, there was no difference in the amount of CD8 cells inside tumors. Thus, heterogeneity in anti-PDL1 IgG delivery and its therapeutic efficacy was explained by heterogeneous PDL1 expression in polyclonal tumors. Evaluation of heterogeneity in PDL1 expression in the patient's tumor shall be considered for personalizing the therapy.**

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# Clinicopathological follow-up of breast ductal carcinoma in situ diagnosed on biopsies: A single institutional study of 575 patients

**Mingfei Yan, Phillip Bomeisl, Hannah Gilmore and Aparna Harbhajanka. University Hospitals Cleveland Medical Center, Cleveland, OH**

**Background: Despite the risk of being upgraded, most DCIS remain as an indolent lesion without developing invasive disease. Therefore, it is important to stratify DCIS patients into different upgrading risk groups and to guide precise therapeutic decisions. This study aims to understand the prevalence of DCIS upgrading, and to investigate clinicopathological features that correlate with the risk of DCIS upgrading. Besides, the status of hormonal receptors (ER and PR) and HER2 are compared in both DCIS and the upgraded invasive counterparts. Materials and Methods: We collected 575 patients with a diagnosis of DCIS on biopsies, and followed up their final diagnosis on excision as well as the status of axillary lymph node involvement. Several clinicopathological factors were analyzed by both univariate and multivariate analysis to understand the risk factors associated with DCIS upgrading. The status of ER, PR, and HER2 were also compared between DCIS and their upgraded invasive counterparts. Results: The overall upgrading risk for DCIS was 19.1%, and factors associated with higher upgrade risk on multivariate analysis include ultrasound-guided biopsy ($p<0.0001$), DCIS with suspicious microinvasion ($p<0.0001$) and DCIS diagnosed in the left breast ($p=0.026$). Patients younger than 40-year-old also showed higher upgrade risk, which was only significant on univariate analysis ($p=0.0128$). DCIS with high nuclear grade and papillary or micropapillary features had the highest upgrade risk, while DCIS with apocrine features had the lowest upgrade risk; however, both nuclear grade and histological type of DCIS did not show statistically significant association with DCIS upgrade. Over 80% of ER+/PR+ and ER-/PR- DCIS remained the same ER/PR status in their invasive counterparts, and 33.6% of the upgraded DCIS had HER2-amplification in the invasive component. In addition, ER+/PR- DCIS (63.4%) had the highest risk of developing HER2-amplified invasive carcinoma, while ER-/PR- DCIS (40.9%) was most likely to develop triple-negative breast carcinoma. DCIS had an overall 7.9% risk of developing axillary lymph node metastasis, for which 5.3% were macrometastasis and 2.6% were micrometastasis. However, the risk of developing lymph node macrometastasis was much higher in upgraded DCIS patients (12%) than the non-upgraded patients (0.74%). Finally, for the upgraded cases, microinvasive carcinoma were more likely to be ER-/PR- (37%) and triple-negative (15.4%) as compared to more extensively developed invasive ductal carcinoma (22.5% to be ER-/PR- and 8.9% to be triple-negative), and had much lower risk of developing axillary lymph node macrometastasis (4.4% for microinvasive carcinoma and 14.7% for invasive ductal carcinoma). Microinvasive carcinoma also had a higher chance of having HER2 amplification (53.9%) than invasive ductal carcinoma (29.5%). Conclusion: Suspicious microinvasion on biopsy was the only pathological parameter that was significantly associated with DCIS upgrade on excision. Other clinical parameters associated with DCIS upgrade included ultrasound-guided biopsy and left laterality of the lesion. Besides, DCIS with different ER/PR status showed distinctive HER2 status in their invasive counterparts, and ER+/PR- DCIS was most likely to develop HER2-amplified invasive carcinoma. However, most of the ER/PR status were consistent between DCIS and invasive counterparts. DCIS generally had a low risk of developing axillary lymph node metastasis, but the risk was significantly increased for upgraded cases with invasive carcinoma other than microinvasion. Finally, microinvasive carcinoma was more likely to be ER-/PR- and triple-negative, and had a significantly higher chance of HER2 amplification.**

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# Clinical outcomes with neoadjuvant chemotherapy plus dual anti-HER2 therapy in patients with operable/locally advanced breast cancer: Single institution experience

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Background: Pertuzumab, a monoclonal antibody targeting subdomain II of HER2 and blocking dimerization, was approved by the FDA in 2013 as neoadjuvant therapy in combination with trastuzumab + chemotherapy for HER2+ locally advanced or early-stage breast cancer patients (pts). TCHP (Docetaxel/Carboplatin/Trastuzumab/Pertuzumab) is a popular, non-anthracycline neoadjuvant therapy. In the TRYPHAENA trial, pathologic complete response (pCR) rate was 63.6% with 6 cycles of neoadjuvant TCHP (47.5% in ER+/PR+ and 81.1% in ER-/PR- tumors). We previously reported (SABCS 2015) our institutional experience with neoadjuvant TCHP in 75 pts with operable/locally advanced HER2+ breast cancer (10/2013 - 12/2015). Now we report our updated experience of 230 pts (10/2013 - 12/2019) with neoadjuvant chemotherapy + dual anti-HER2 therapy.

Patients & Methods: Medical record search identified HER2+ pts (T1c-T3/N0-3 or Tany/N1-3) treated with neoadjuvant chemotherapy + dual anti-HER2 therapy from 10/2013 to 12/2019. Collected information included pt and tumor characteristics at diagnosis, details of neoadjuvant therapy, clinical, radiologic, & pathologic assessment of tumor response, type of breast and axillary nodal surgery, and long-term disease outcomes.

Results: 230 pts (229 female, 1 male) met the inclusion criteria; median age: 52 yrs (range 25-79); Clinical stage: I (2%), II (78%) , III (20%); ER+ and/or PR+ 70% ; ER-/PR- 30%. 228 pts received TCHP and 2 pts AC then THP. 170 pts (74%) received 6 cycles of TCHP without dose reduction; 49 pts (21%) received 6 cycles, but with dose reduction (most commonly due to diarrhea, nausea, neutropenia, and anemia); 11 pts (5%) received < 6 cycles (7 of those also needed dose reduction). Mean left ventricular ejection fraction was 62.0% pre-treatment, and 60.9% post-treatment.

Of the 230 pts who underwent breast surgery (1 had no breast primary at presentation), 86 pts (38%) had breast conserving surgery, 19 (8%) unilateral mastectomy, and 124 (54%) bilateral mastectomy. Axillary assessment was by SLNB in 75% and ALND in 25% (with/without SLNB). Among 138 pts with cN0 and axillary assessment, 124 had SLNB (4 had + nodes), 14 had ALND (11 had + nodes). Among 91 pts with cN1-3, 47 had SLNB (1 had + nodes) and 44 had ALND (27 had + nodes).

Overall pCR rate (ypT0/Tis, ypN0) was 59%. pCR rate was 50% for ER+ and/or PR+, and 79% for ER-/PR-. pCR by Stage: I (50%), II (60%), III (55%). At median follow-up of 2.9 years, 221 pts (96%) were alive with no evidence of disease; 8 pts (3.5%) have experienced recurrence (6 distant, 1 locoregional, 1 unknown site), and 1 pt died after developing AML as the only event.

The table below presents details on the 8 pts who suffered recurrence: 4 had clinical stage II disease, and 4 clinical stage III. All pts had hormone receptor + tumors at diagnosis. 7 of 8 pts (88%) with recurrence did not have pCR at surgery. Most common sites of distant metastases as first event were liver and bone. Of the 8 pts with recurrence, 6 are alive with disease (median follow-up 2.8 years). There was 1 death due to disease progression, and 1 pt was lost to follow-up.

Conclusions: Our updated results continue to demonstrate the clinical safety and efficacy of neoadjuvant therapy with TCHP for operable/locally advanced HER2+ breast cancer. Our pCR rates are similar to those observed in the TRYPHAENA trial. Longer follow-up is required to evaluate the long-term clinical outcomes with this regimen.

**Recurrence Data**

| Patient Number | Age at Diagnosis | Date of Diagnosis | Hormone Receptor at Diagnosis | Clinical Stage at Diagnosis | Type of Breast Surgery | pCR | Pathologic Stage at Surgery | Date of Recurrence | Time to Metastases (Years) | Site of Recurrence |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 65 | 11/19/14 | Positive | cT2N1 (IIB) | Left Mastectomy | Yes | ypT0N0 (0) | 4/6/17 | 2.4 | Liver, Bone |
| 2 | 36 | 6/15/15 | Positive | cT2N0 (IIA) | Bilateral Mastectomy | No | ypT3N0 (IIB) | 3/19/18 | 2.8 | Liver |
| 3 | 54 | 6/29/15 | Positive | cT2N3 (IIIC) | Left Mastectomy | No | ypT1bN1a (IIA) | 10/2/19 | 4.3 | Bone |
| 4 | 57 | 7/1/15 | Positive | cT2N3 (IIIC) | Left Lumpectomy | No | ypT1cN1a (IIA) | 2/4/19 | 3.6 | Bone, Soft Tissue |
| 5 | 56 | 8/20/15 | Positive | cT2N0 (IIA) | Left Lumpectomy | No | ypT1aN0 (IA) | 6/28/18 | 2.8 | Lymph Node |
| 6 | 26 | 4/29/16 | Positive | cT4N0 (IIIB) | Bilateral Mastectomy | No | ypT2N1 (IIB) | 12/13/17 | 1.6 | Liver |
| 7 | 53 | 9/27/16 | Positive | cT3N3 (IIIC) | Bilateral Mastectomy | No | ypT3N3 (IIIC) | Not Known | Not Known | Not Known |
| 8 | 31 | 9/3/17 | Positive | cT2N1 (IIB) | Bilateral Mastectomy | No (clinical progression) | ypT3N2a (IIIC) | 6/25/18 | 0.8 | Lungs |

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# Prognostic value of neutrophil to lymphocyte ratio in patients with breast cancer in a Mexican population

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**Background: Inflammatory serum markers (IBM) have emerged as prognostic factors in solid tumors. In breast cancer (BC) in particular, an elevated neutrophil to lymphocyte ratio (NLR) has been linked to lower overall survival (OS) and disease-free survival (DFS), although a standard cutoff value has not been established. In Mexico there is no information regarding NLR as a prognostic marker in BC. The aim of the present study was to assess NLR as prognostic factor in BC patients in a Mexican population.**
**Methods: This single-center retrospective and descriptive study included patients, >18 years old with histological diagnosis of BC who were treated at Medica Sur oncological center in Mexico City between January 2008 and December 2019. The patients were divided into two groups according to their NLR. NLR was calculated using the following formula: absolute neutrophil count / absolute lymphocyte count (mm3). NLR was considered as elevated (>2), and as low (≤2) based on data from previous studies. The primary endpoint was OS. Statistical analysis was performed with SPSS v25. The associations between PNI and clinicopathologic characteristics were analyzed using Pearson's χ2 test. Kaplan-Meier and log-rank test methods were used for survival analysis. The prognostic value of the pre-treatment NLR was assessed by univariate and multivariate analysis. P<0.05 was considered to indicate a statistically significant difference. This study was approved by our scientific and bioethical committee.**
**Results: A total of 110 patients were included in the final analysis. All patients had infiltrating ductal carcinoma; 18.2% were triple negative, 23.6% over-expressed HER 2 and around 51% had hormone receptor expression. 15.5% had metastatic disease. Median follow-up was 65 months. Mean NLR at diagnosis was 2.82 (SD 2.59). Mean NLR in patients with triple negative BC (TNBC) was significantly higher than in patients with non TNBC (p= 0.055), no other statistically significant associations were found between mean NLR and clinical characteristics. Median OS was not reached in two groups, but the 100 months OS was higher in NLR ≤2 group vs NLR > 2 group (90 vs 78%) (p= 0.079). In univariate and multivariate analysis, triple negative histological subtype and elevated NLR were independent prognostic indicators of poor survival.**
**Conclusion: An elevated pretreatment NLR was an independent prognostic factor, associated with lower OS in patients with BC with local and advanced disease, although statistically significant association was not found. NLR is an accessible and minimally invasive marker with clinical value for evaluation of the prognosis of BC patients, especially in resource-limited settings.**

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# Understanding genomic testing in real-world populations at outcomes4Me (GENOME)

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**Background:** National guidelines including NCCN and ASCO clearly state the indication of genomic profiling for all patients diagnosed with advanced or metastatic breast cancer. Despite this, there remains a large gap between those guidelines and real-world practice. Increasing numbers of therapies have been approved or are under investigation for specific genomic mutations including PIK3CA, NTRK, BRCA, and most recently immunotherapy based on PD-L1 and microsatellite status. Accordingly, it is critical that advanced and metastatic breast cancer patients are offered and receive genomic testing. We explored patients' knowledge and perception of genomic testing as well as their testing status using the Outcomes4Me™ app, a digital application that helps breast cancer patients engage in their care.
**Methodology:** The study was conducted virtually on the Outcomes4Me™ mobile app. Eligible patients (n=203) had stage III/IV breast cancer and resided in the United States. Participants were surveyed on their awareness of Comprehensive Genomic Profiling (CGP), if they have been tested, incentives and barriers to testing, and their willingness to talk to their doctors to learn more/initiate genomic testing. Participants were also able to access educational content on CGP through the app. Analyzed data included: tested vs not tested, cancer subtype and stage, geographic location, and time since diagnosis.
**Results:** Participants represented all 4 breast cancer subtypes, were well-distributed in time since diagnosis, and were located across 43 states. 105 (52%) of patients were HR+HER2-, 152 (75%) were metastatic, and 51 (25%) were stage III/advanced. Most patients (59%) were at least somewhat aware of the availability of CGP and 60% of participants were at least somewhat familiar with CGP. However, only 56 out of 203 eligible surveyed patients (28%) had been tested. Of those patients that were not tested (n=147), only 73 patients (50%) were at least somewhat aware or familiar with CGP. Further, 88% of patients that were not tested said they were interested in genomic testing and 85% said they were likely to ask their doctor about getting genomic testing, after learning about CGP.
**Conclusion:** Despite under-testing, many advanced and metastatic patients are interested in learning more and getting genomic testing. These results are important because they demonstrate the discrepancy between patients' willingness to get genomic testing and the extent of genomic testing being offered to patients. They also highlight the importance of educational digital apps such as the Outcomes4Me™ app in raising awareness and providing access to CGP, which can ultimately improve outcomes. In fact, many studies have shown that ~40% of patients with HR+HER2- advanced breast cancer have a PIK3CA mutation, where now a new therapy (alpelisib) targeting this mutation is FDA approved. Additional data needs to be collected to identify barriers to genomic testing and how to overcome such barriers to decrease the gap with current guidelines.

***Chart 1: Results from patient-reported surveys***

| Dimension | Value | N (%) |
|---|---|---|
| Stage | Stage IV (Metastatic) | 152 (75) |
| | Stage III (Advanced) | 51 (25) |
| Subtype | HR+HER2- | 105 (52) |
| | HR+HER2+ | 36 (18) |
| | HR-HER2- | 30 (15) |
| | HR-HER2+ | 12 (6) |
| | Unknown | 20 (10) |
| Time from Diagnosis | <6 months | 46 (23) |
| | 6 months - 1 year | 35 (17) |
| | 1-2 years | 42 (21) |
| | 2-5 years | 43 (21) |
| | >5 years | 37 (18) |
| Testing Status | Had genomic testing | 56 (28) |
| | Did not have genomic testing | 147 (72) |
| Awareness | Very aware or somewhat aware of CGP | 120 (59) |
| | Not very aware or not at all aware of CGP | 83 (41) |
| Familiarity | Very familiar or somewhat familiar with CGP | 123 (60) |
| | Not very familiar or not at all familiar with CGP | 80 (40) |
| Interest in GCP (non-tested) | Very interested or somewhat interested | 129 (88) |
| | Not very interested or not at all interested | 18 (12) |
| Likeliness of talking to their Doctor (non-tested) | Very likely or somewhat likely | 125 (85) |
| | Not very likely or not at all likely | 22 (15) |
| HR+HER2- (stage III/IV) | Tested | 34 (32) |
| | Not Tested | 71 (68) |
| Interest in learning more about GCP (non-tested HR+HER2-) | Very interested or somewhat interested | 64 (90) |
| | Not very interested or not at all interested | 7 (10) |
| Likeliness to talk to their doctor about CGP (non-tested HR+HER2-) | Very likely or somewhat likely | 60 (85) |
| | Not very likely or not at all likely | 11 (15) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS11-42**

# Treatment patterns and clinical outcomes among patients (pts) with HER2- advanced breast cancer (ABC) and germline *BRCA1/2* mutation(s) (g*BRCA1/2*mut): results from a US real-world study

**Elias Obeid[1], Rohan C Parikh[2], Elizabeth Esterberg[2], Bhakti Arondekar[3], Abigail Hitchens[2], Lillian Shahied Arruda[3] and Alexander Niyazov[4].**
**[1]Fox Chase Cancer Center, Philadelphia, PA;[2]RTI Health Solutions, Research Triangle Park, NC;[3]Pfizer Inc., Collegeville, PA;[4]Pfizer Inc., New York, NY**

**Background: g*BRCA1/2* mutation(s) represents ~5% of HER2- ABC. Recently poly ADP-ribose polymerases inhibitors (PARPi) have demonstrated improved clinical outcomes and favorable pt reported outcomes in g*BRCA1/2*mut HER2- ABC pts. Optimal treatment sequencing has not been established. We assessed real-world treatment patterns and clinical outcomes by line of treatment (LOT) among adult pts with g*BRCA1/2*mut HER2- ABC.**
**Methods: Oncologists retrospectively reviewed charts (July 2019-June 2020) of quasi-random selected pts ≥18 y, with g*BRCA1/2*mut HER2- ABC who received ≥1 cytotoxic chemotherapy (CT) regimen(s) for ABC between Jan 2013-April 2018. Descriptive analysis was performed for treatment patterns for the first 3 LOT. Clinical outcomes (PFS by LOT and survival rates) were estimated using the Kaplan-Meier method. PARPi clinical outcomes data was immature given its recent launch. Additional analyses evaluating outcomes in pts receiving PARPi are planned.**
**Results: This is a placeholder abstract. Results will be provided during the final submission.**
**Funding: Pfizer**

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**Publication Number: PS1-43**

# Axillary surgery after neoadjuvant chemotherapy in patients treated for an operable breast cancer with a proven initially positive axillary node: Preliminary results of identification and removal of the initially positive axillary node

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**BackgroundAlmost half of the patient with initially metastatic axillary node, treated with neoadjuvantchemotherapy (NAC) for a large operable breast cancer, has no axillary lymph node involvementat the time of surgery after NAC. Sentinel lymph node detection (SLND), performed after NAC,has a high false negative rate (FNR) when compared to FNR after primary surgery. GANEA 3 isa French prospective multi institutional ongoing trial, aimed at assessing the impact of targeting,before NAC, the initially positive node and removing it after NAC. The main objective of GANEA3 trial is the accuracy of this initially positive node to predict pathological status of the otheraxillary nodes after NAC. A total of 385 patients are required.ObjectiveThe current abstract assessed preliminary results of the detection rate of the clipped node and thedifferent methods to find it during axillary surgery based on the first 41 patients.Patients and MethodThis study is part of GANEA 3 Trial validated by scientific national board (clinicialtrials.gov:NCT03630913).Inclusion criteria: TNM stage T1-T3 N1 infiltrating breast carcinoma, indication of NAC, andsigned consent form,Exclusion criteria: more than 5 suspicious axillary nodes, inflammatory cancer, local relapse,mental disorder, pregnancy or no contraceptive method, contra-indication to NAC, NACinterrupted due to progressive disease.Design: Patients treated for an early breast cancer with NAC, axillary sonography with fine needlecytology before NAC to select patients with a proven lymph node involvement. Initially positive node identification warranted, for example with a clip. After NAC patients underwent the removalof the clipped node, a SLN detection with the combined method (patent blue and technetium) andan axillary lymph node dissection (ALND). In order to find the clipped node, during surgery thesurgeon attempted to find it with palpation and sonography. Each surgical specimen was then x-rayed before pathological examination.Studied parameters were clipped node and SLND detection rate, and the methods used to find theclipped node.ResultsFrom January 2019, to November 2019, 41 patients were enrolled, from 13 institutions, withinitially positive axillary node clipped, NAC courses and surgery after NAC.Median age was 53 (31-75), pathological subtype infiltrative ductal carcinoma (n=40) andinfiltrative lobular carcinoma (n=1), a median of 7 courses of NAC (1-16).SLN detection rate was 90% (37/41). A median number of 2 sentinel nodes were removed (1-7).The clipped node was removed in 100% of cases. The clipped node was identified by thesurgeon palpation (n=11), an axillary wire (n=13), per operative axillary sonography (n=4),surgical specimen radiography (n=11), the pathologist (n=2).The clipped node was part of SLN in 29 cases (70%). It was part of axillary lymphadenectomyspecimen in 6 cases (14.5%) and was find alone as an isolated node in 6 cases (14.5%).ConclusionThe clipped node was always found after NAC. It was mostly always part of SLN or ALNDspecimens. Further studies are needed in order to help the surgeon to remove only the clippednode.**

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# Locoregional recurrence in patients with early-stage triple-negative breast cancer receiving neoadjuvant systemic therapy: Patient characteristics and clinical outcomes

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**Background: Recurrence is common among patients with early-stage triple-negative breast cancer (ESTNBC). There is minimal real-world evidence describing the patient characteristics and clinical outcomes following recurrence among patients receiving neoadjuvant chemotherapy for ESTNBC. Methods: This retrospective, observational study aimed to describe the demographic and clinical characteristics and clinical outcomes in ESTNBC patients experiencing locoregional recurrence in the US community oncology setting in the Concerto HealthAI Definitive Oncology Dataset. Eligibility criteria included female sex, age 18+ years, diagnosis of stage II, IIIA or IIIB ESTNBC between 3/2008 and 3/2016, and receipt of definitive surgical resection following neoadjuvant systemic therapy. Descriptive methods were used to evaluate patient characteristics and treatment patterns in this population. Locoregional recurrence was defined as recurrence in the same breast and/or regional nodal recurrence as documented by the provider in the medical record. Results: Of 308 patients who received neoadjuvant treatment for ESTNBC, 27.3% patients (n=84) observed recurrence, within which 25.0% (n=21) were locoregional and 75.0% (n=63) were metastatic. All 21 patients with locoregional recurrence were 65 or younger, with mean age of 50.6 (SD 8.7) at initial diagnosis. They were primarily White (47.6%, n=10) or African American (42.9%, n=9). Over half of patients were stage II at initial diagnosis (61.9%, n=13), while 38.1% (n=8) were stage III. The majority had ductal histology (90.5%, n=19) and had Grade 3 tumors (90.5%, n=19). Of the 21 patients with locoregional recurrence, less than one-tenth (9.5%, n=2) had achieved pathologic complete response (pCR) prior to their recurrence, compared to 41.2% (n=127) of the 308 patients receiving neoadjuvant treatment. In terms of treatment following locoregional recurrence, two-thirds of patients received radiation therapy (66.6%, n=14) with median duration of 47.5 days. Over half of patients (57.1%, n=12) had mastectomy following recurrence, while 14.3% (n=3) had partial mastectomy (breast conserving surgery). Most patients (85.7%, n=18) received systemic chemotherapy after recurrence. Median duration of systemic therapy following locoregional recurrence was 108 days. Nearly one-half (47.6%, n=10) had a subsequent metastatic diagnosis and nearly one-third (28.6%, n=6) had a record of death. Median time from locoregional recurrence to metastatic diagnosis was 36.6 months, but median time from locoregional recurrence to death was not reached. Conclusions: Among patients who received neoadjuvant therapy for ESTNBC in the real-world setting, nearly 7% (n=21) experienced locoregional recurrence. Nearly one-fourth of those patients had a prior pCR which potentially suggests a higher risk of recurrence associated with ESTNBC patients. Chemotherapy was the mainstay of treatment following recurrence. Most patients also received radiation therapy and surgery, but despite those nearly one-half of the patients went on to have a subsequent metastatic diagnosis. This probably reflects the limitations of existing treatment modalities for ESTNBC patients. Future studies with a bigger sample size could confirm our findings. Our study provides some benchmark perspective to such future studies.**

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# Phase I study of adoptive immunotherapy for advanced MUC1* positive breast cancer with autologous T cells engineered to express a chimeric antigen receptor, huMNC2-CAR44 specific for a cleaved form of MUC1 (MUC1*)

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**Background: Chimeric antigen receptor (CAR) T cell therapy targeting CD19 results in marked tumor regression for patients with B-cell malignancies. It would be ideal to extend the success of CAR T cell therapy to common epithelial cancers. MUC1* is a post-translationally modified/cleaved form of mucin 1 (MUC1) that is frequently expressed on breast tumors, functions as a growth factor receptor, and is a promising antigen for CAR T cell therapy. Minerva Biotechnologies developed a CAR T (huMNC2-CAR44) that specifically recognizes the cleaved form of MUC1* and does not bind to full-length or MUC1* negative cells. huMNC2-CAR44 product consists of autologous T cells transduced with a lentiviral vector encoding humanized MNC2-scFv (MUC1* targeting head), sequences from CD8 $\alpha$;; leader, hinge and transmembrane domains, 4-1BB and CD3ζ domains. Trial Design: NCT04020575 is a phase I study evaluating the safety and anti-tumor activity of adoptively transferred autologous T cells genetically modified to express huMNC2-CAR44 in patients with metastatic MUC1* breast cancer. After screening, leukapheresis is performed, CD8+ and CD4+ T cells are selected, transduced with huMNC2-CAR44, expanded, and antigen stimulated *in vitro*. Lymphodepletion with cyclophosphamide and fludarabine is followed 36-96 hours later by infusion of huMNC2-CAR44 CAR T cells in escalating doses ($3.3 \times 10^5$ CAR+ T cells/kg - $1 \times 10^7$ CAR+ T cells/kg). Eligibility: Key inclusion criteria include metastatic breast cancer of known ER, PR and HER2 status which has MUC1* membrane expression > or = 30% by immunohistochemistry, measurable or evaluable disease, receipt of standard systemic therapies known to confer benefit, age >18, informed consent, adequate organ function, and KPS > or = 60%. Patients with active autoimmune disease or uncontrolled infection, contraindication to cyclophosphamide, anticipated survival < 3 months, and/or untreated CNS metastases are not eligible. Specific Aims: The primary objective is to identify the maximum tolerated dose of huMNC2-CAR44 T cells by CTCAE v5 and Lee criteria. Secondary objectives include persistence and phenotype of adoptively transferred huMNC2-CAR44 T cells and preliminary antitumor activity in all patients with measurable disease by RECIST 1.1. Exploratory objectives include trafficking of huMNC2-CAR44 T cells to tumor sites, effector function of huMNC2-CAR44 T cells *in vivo*, association between tumor MUC1* expression and huMNC2-CAR44 T cell persistence and response, change in tumor immune microenvironment by multiplex immunohistochemistry in pre and post-treatment tumor biopsies. Statistical Design: Dose escalation or de-escalation is tested in cohorts of 3 patients each using standard "3+3" dose-finding targeting a T cell dose that is associated with a true DLT rate < 33% and > than 17%. DLT period is between day 0 and 28. Once the MTD has been determined, up to 15 more patients will be enrolled in each of 3 expansion cohorts (Luminal, HER2 positive, and TNBC) to estimate the anti-tumor activity in these patient populations and to inform future huMNC2-CAR44 T cell trials. Present accrual: Study is open to screening and enrollment in dose escalation. Up to 69 patients may be enrolled in dose escalation and expansion phases. Contact information: To refer patients or obtain more information, please contact immunotherapy@seattlecca.org.**

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# The utility of PET-CT after the second cycle of neoadjuvant chemotherapy for monitoring early metabolic change to predict pathologic response

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## INTRODUCTION

Neoadjuvant chemotherapy (NAC) is increasingly utilized in the treatment of Breast Cancer to downsize the tumour, improve surgical outcome and to achieve a complete pathological response (pCR). Current regimes result in response rates of 40-80% depending on the subtype of the tumour and the presence of pCR, noted in 13-26% patients, is considered an indicator of excellent prognosis. An additional advantage of NAC is the assessment of the in vivo chemo-responsiveness of the tumor.FDG-PET/CT (fluorodeoxyglucose positron emission tomography/computed tomography) provides morphologic as well as functional imaging. Preliminary studies suggest it provides a more accurate evaluation of tumour response compared to other techniques. Moreover, studies suggest its utility in identifying non-responders early during NAC so as to enable a switch to an alternate more effective regimen, thereby preventing avoidable toxicity associated with an ineffective drug regimen.In this study, we evaluated metabolic changes on FDG-PET after 2 cycles of NAC to predict pathological response to NAC.

## PATIENTS AND METHODS

A prospective cohort of patients with newly diagnosed, non-metastatic, T1-4, N1-2/3 breast cancer, undergoing NAC from October 2012 to December 2019 at a tertiary referral center, were entered in this study. The tumor size was assessed by the same surgeon at baseline and after every cycle of NAC. FDG-PET/CT was performed before commencement of NAC (PET1) and after the 2nd cycle of NAC (PET2) and the early metabolic response (ΔSUV max i.e. change in maximum standardized uptake value) was determined. All patients underwent surgery on completion of NAC and the pathological response following surgery served as the reference standard for the evaluation of the therapy response on FDG-PET/CT. Patients were classified into Responders [pCR and Minimal Residual Disease (MRD)] and Non-responders [Gross Residual Disease (GRD)] as per the classification of Honkoop et al. Receiver operating characteristic analysis was performed to identify an optimal threshold value of reduction rate (RR) of maximum standardized uptake values (ΔSUVmax) to accurately predict pathological response.

## RESULTS

Out of 135 patients, 4 patients had bilateral cancer, resulting in 139 breast lesions assessed at baseline by FDG PET CT of which 51.07% were Luminal, 21.58% HER2 + and 27.34% TNBC. The mean age was 49 years (range 27-72), 54.81% were premenopausal, 45.19% post-menopausal, 85 (61.15%) were stage II cancers and 54 (38.84%) had stage III cancers. The overall pCR rate was 24.46%, 65 (46.76%) were Responders (pCR+MRD) and 74 (53.23%) Non-responders (GRD). The mean PET1 SUVmax of the tumors in Responder group was 14.5 and of Non-responder group was 9.4. The mean PET2 SUVmax for Responders was 4.28 and Non-responders was 7.52. The RR after the second course of NAC (ΔSUV), was significantly higher for Responders, 62.38% (±24.79) as compared to Non-responders 25.81% (±57.57), ($p < 0.0001$). The optimal ΔSUV threshold to discriminate between Responders and Non-responders was 51% (69.35% sensitivity; 69.12% specificity) with area under the curve being 0.744. The negative predictive value for histopathologic Non-responders was 71.2 (CI 62.2- 78.8).

## CONCLUSIONS

Metabolic change in FDG/PET-CT after 2 cycles of NAC can predict pathological response and, a ΔSUVmax of more than 51%, can differentiate Responders from Non- responders. Early determination of Non-responders could help identify a group which may benefit from an early change to an alternate regimen.

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# Prediction of breast ductal carcinoma in situ recurrence using histomics analysis of stromal features from hematoxylin and eosin stain-based images

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**OBJECTIVE**
It remains a challenge to predict individual risk for recurrence after primary treatment of ductal carcinoma in situ (DCIS). While DCIS is contained within the duct, prior studies have pointed to the importance of stromal collagen in cancer progression. Using hematoxylin and eosin (H&E) stain-based images, we studied the collagen structure surrounding DCIS in a case-control cohort of women to determine whether stromal collagen could provide additional risk information.

**METHODS**
We present a quantitative histology image analysis pipeline (termed “histomics”) that consists of collagen segmentation, quantitative feature extraction and statistical analysis to predict recurrence. A cohort of 73 patients with DCIS (33 cases with recurrence matched with 40 controls) were retrospectively analyzed. H&E images were obtained from pathologic slides and regions-of-interest (ROI) of the collagen in the stroma adjacent to DCIS was automatically segmented using an in-house trained deep learning algorithm. A total of 123 histomics features (intensity, statistical and textural) were then extracted from the segmented ROI for each patient. Kruskal-Wallis test and receiver-operating characteristic methodology was used to assess performance of the features to differentiate patients with and without recurrence.

**RESULTS**
We found substantial variations in recorded H&E signal between samples, and the intensity and statistical features did not reach statistical significance. However, twelve percent of the textural features had an AUC between 0.62 to 0.61 with p-value between 0.06 to 0.08. Two textural histomics features in particular were significantly associated with DCIS patient recurrence; inverse variance (AUC: 0.64, p-value: 0.046) feature based on grey-level cooccurrences matrix (GLCM) and complexity (AUC 0.65, p-value: 0.025) feature based on neighborhood grey tone difference matrix (NGTDM).

**CONCLUSION**
Textural stromal features extracted from H&E image-based histomics indicate association of some features with tumor progression in DCIS. H&E image based histomics features can be a promising quantitative tool to develop predictive signatures of recurrence in patients with DCIS. We are processing additional patients through our quantitative image analysis pipeline to determine the significance of histomics features compared to conventional clinical features for the prediction of DCIS recurrence.

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# The prognostic impact of breast cancer subtype based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) statuses for end-stage disease

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**Background: Most patients with metastatic cancer request information regarding their prognosis, most notably when death is clearly approaching. Several clinical indices are used to predict the prognosis of end-stage cancer based on performance status and clinical factors. For example, the Palliative Prognostic Index (PPI) includes a range of scores from 0-15 based on factors that include performance status, oral intake, presence of edema, dyspnea at rest, and delirium. For scores greater than six, survival for an additional three weeks was predicted with a sensitivity of 80% and a specificity of 85%. However, the predictive power of these indices is currently insufficient; the quality of life of end-stage breast cancer patients would be markedly improved with a more accurate prediction model. Breast cancer subtypes based on the hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) statuses are important prognostic factors with respect to the outcome of initial breast cancer therapy; the subtype defined by these parameters was also identified as an independent prognostic factor for outcomes in cases of metastatic breast cancer. However, the prognostic impact of breast cancer subtype with respect to end-stage disease remains unclear. In this retrospective observational study, we evaluated the relationship between survival time and associated clinicopathological factors, including breast cancer subtype, in order to develop a more accurate prognostic model for end-stage breast cancer patients. Methods: Seventy-three patients with end-stage breast cancer who were admitted to our hospice care unit from January 2014 to December 2018 were enrolled in the study. Patients in this unit were not provided with anticancer therapy but did receive highest-quality supportive care. The primary endpoint was survival time from the admission. Patient information, including age, PPI, disease-free interval (DFI), the number of treatments for the metastatic disease, metastatic site, and breast cancer subtypes were collected from medical records. Breast cancer subtypes included Luminal (Lum), Lum-HER2, HER2, and triple negative (TN) with respect to those that were HR+HER2−, HR+HER2−, HR−HER2+, and HR−HER2−, respectively. The study was approved by the ethical committee of the Oikawa Hospital (OHCT022). Results: The median survival time was 23 days (1-359 days). From the univariate analysis, PPI scores of less than six were associated with significantly shorter survival (14 days vs. 36.5 days, P = 0.001). Patients diagnosed with Lum-HER2 subtype, those who were older and were without liver metastasis, those with a shorter DFI, and those who underwent fewer treatments for metastatic disease showed a tendency toward a favorable prognosis, although these findings did not reach statistical significance. Multivariate logistic regression analysis revealed that a PPI score less than six (P = 0.001), Lum-HER2 subtype (P = 0.003), absence of liver metastasis (P = 0.001), and DFI lower than the median (33 months; P = 0.028) all contributed to longer survival time. Discussion & Conclusion: In addition to the PPI, breast cancer subtype can be used to provide more precise prognoses for end-stage breast cancer patients. Survival of patients diagnosed with the Lum-HER2 subtype was longer than that observed among those with any of the other subtypes who had not undergone any anticancer treatment for metastatic disease; these results suggest that anti-HER2 therapy may be associated with critical immunological modifications. Taken together, our results indicate that breast cancer subtype should be included to provide a more accurate prognostic model for end-stage breast cancer patients.**

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# Impact of educational workshops on patient-provider communication among Spanish-speaking metastatic breast cancer survivors and their caregivers: Results from the *frankly speaking about cancer: Cáncer de seno métastatico* evidence-based educational workshops

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**Background: Latina metastatic breast cancer survivors, in particular those of low socioeconomic status, often receive unsatisfactory medical care and experience poor physician-patient communication and relationships.[1] Patient education about metastatic breast cancer can improve communication between Latina survivors and caregivers and their health care team.[2] This analysis explores participants' experiences gained from Cancer Support Community's national evidence-based educational program, *Frankly Speaking about Cancer: Cáncer de seno metástatico (Metastatic Breast Cancer)*.**

**Methods: *Frankly Speaking about Cancer (FSAC): Metastatic Breast Cancer* is a comprehensive psychosocial educational program that provides information about current treatments, side effect management, and social and emotional challenges of an advanced breast cancer diagnosis. *FSAC: Metastatic Breast Cancer* was originally created in English and was then translated into Spanish to make the program more accessible to Spanish-speaking metastatic breast cancer survivors and caregivers in the US. 75 participants from 22 workshops across the country between 2018 and 2020 completed program evaluation surveys in Spanish and provided self-reported data on factors including pre- and post-workshop knowledge and intentions for patient-provider communication. Descriptive analyses and pre-and post-workshop comparisons were conducted to assess workshop outcomes.**

**Results: Most workshop participants were metastatic breast cancer patients/survivors (n=46); the remainder served in the caregiving capacity and included spouses/partners (n=19) and family members (n=10). The average age of participants was 61 years old (s.d.= 24.14 years). Among those with metastatic breast cancer, more than half (54%) received the diagnosis within the last two years; and only 29% reported being moderately to highly involved in their treatment decisions. 76% of respondents reported experiencing emotional distress due to their/their loved one's cancer. Pre- and post-survey results show a significant gain in reported knowledge about metastatic breast cancer ($\chi^2$= 13.4, $p$ <.05). Caregivers of Latina metastatic breast cancer survivors also demonstrated a significant gain from pre- to post-workshop in knowledge about metastatic breast cancer treatment options, confidence to participate in treatment decision-making with their health care team, and confidence in asking questions about side effects of metastatic breast cancer and its treatment. As a final point, 68% of cancer patients/survivors and 72% of caregivers reported that because of the workshops, they felt better prepared to emotionally cope with their metastatic breast cancer experience.**

**Discussion: Our findings indicate that educational workshops in Spanish can play a role in enhancing Latina patients' self-perceived knowledge about metastatic breast cancer and empowering patients and caregivers to become active participants in their treatment decisions. These results underscore the importance of providing culturally specific educational resources to support patients and caregivers in their interactions with their health care team and advance breast health equity among Latinas.**

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# Sco-101 is a novel oral drug that reverses antiestrogen resistance in breast cancer cells

**Jan Stenvang[1], Ida CB Madsen[2], Katrine Hartfelt[3], Haatisha Jandu[1], Signe L Nielsen[4], Palle Christophersen[5] and Nils Brunner[1]. [1]Scandion Oncology, Copenhagen, Denmark[2]University of Copenhagen, Copenhagen, Denmark[3]Uniersity of Copenhagen, Copenhagen, Denmark[4]University of Copenahgen, Copenhagen, Denmark[5]Saniona, Copenhagen, Denmark**

**Breast cancer is the most frequent cancer diagnosed in women and 80% of all cases of breast cancer patients present with estrogen receptor (ER)-positive disease. Treatment with antiestrogens most notable tamoxifen and faslodex are effective for a large proportion of ER-positive breast cancer. However, antiestrogen resistance eventually arises in all patients with advanced disease. Thus, antiestrogen resistance represents a major problem in the clinical management of breast cancer patients and there is currently no treatment to overcome resistance to antiestrogens. SCO-101 is an oral drug currently being tested in a Phase II clinical trial enrolling metastatic colorectal cancer patients with drug resistant disease (ClinicalTrials.gov Identifier: NCT04247256). In the current work, we investigated the potential of SCO-101 to act in combination with the antiestrogens tamoxifen or fulvestrant (faslodex) in antiestrogen resistant breast cancer cell lines (MCF-7/LCC-2, MCF-7/LCC-9, T47D/TR1) and - as a negative control - the ER negative MDA-MB-231. Treatment effects were investigated by MTT cell viability assays, siRNA knock-down experiments and western blots. SCO-101 only had minor inhibitory effects on cell viability when administered alone. Interestingly, when combining SCO-101 with tamoxifen or fulvestrant in MCF-7 or T47D antiestrogen resistant breast cancer cells, an additive to synergistic effect on cell viability was observed. In contrast to these results, SCO-101 in combination with antiestrogens had no effects on the triple negative MDA-MB-231 cell line, indicating the ER and or PR (progesterone receptor) is important for the effect of SCO-101 in antiestrogen resistant breast cancer cells. As SCO-101 has been described to targets the volume-regulated anion channel (VRAC), in which LRRC8A is the essential subunit, we investigated whether knockdown of LRRC8A would impact the treatment outcome. No apparent changes in response to SCO-101 and antiestrogens were observed upon the knockdown. Additionally, the protein level of LRRC8A was examined upon treatment with anti-estrogens +/- SCO-101 and the treatment did not alter LRRC8A protein expression. Our findings strongly suggest that SCO-101 interferes with antiestrogen resistance in breast cancer and we have recently received an EURECA Eurostars grant to further investigate the molecular mechanisms of action for SCO-101 in reversing antiestrogen resistance, to investigate drug response in 3D breast cancer models, and to conduct a Phase Ib dose escalation clinical trial with SCO-101 and faslodex in patients with antiestrogen resistant ER positive breast cancer.**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS1-44**

# Impact of a standardized protocol for management of axilla after neoadjuvant chemotherapy in breast cancer patients at a cancer center

**Marina de Paula Canal, Caroline Rocha, Marina Sonagli, Almir Bitencourt, Solange Sanches, Monique Tavares, Cynthia Osorio and Fabiana Baroni Makdissi. Accamargo Cancer Center, Sao Paulo, Brazil**

**Background: Axillary lymph node status is one of the most important prognostic factors in breast cancer (BC). Neoadjuvant Chemotherapy (NACT) has been indicated for locally advanced tumors, and for HER2-positive and triple negative tumors larger than 2.0 and 1.0 cm, respectively, regardless of axillary status. This approach allows to assess biological response of the tumor, predicting prognosis and may permit more conservative surgeries in breast and axilla. However, there is no consensus about the best approach on management of axilla after NACT.**
**Objective: To evaluate the rate of axillary downstaging after NACT in BC patients using a standardized protocol with a clip marker placement on positive lymph nodes prior to chemotherapy at a Cancer Center.**
**Methods: This single-center, Institutional Review Board (IRB)-approved, retrospective study evaluated 471 BC patients who underwent NACT from January/2014 to December/2018. All included patients were evaluated for histological type, clinical T and N stages before NACT, modality of breast surgery (mastectomy vs. lumpectomy), type of axillary dissection (Axillary Lymph Node Dissection [ALND], sentinel lymph node biopsy [SLNB], or SLNB followed by ALND), placement or not of a clip marker in axillary lymph nodes before NACT, reason for the ALND and the pathological response by residual cancer burden (RCB) criteria. Patients were divided in two groups, before and after institution of a standardized protocol for axillary management after NACT in January/2017, which consists of: (1) biopsy of clinically suspect axillary lymph nodes before NACT, and placement of a clip marker in one positive lymph node in patients with 1-2 suspected lymph nodes (N1); (2) SLNB after NACT using blue dye and radioactive isotope injection; (3A) in the presence of clip marker in an axillary lymph node, confirmation of its extraction is performed through radiography of**
**the surgical specimen and, (3B) in the absence of clip markers on axillary lymph nodes, removal of at least 03 sentinel lymph nodes should be performed; (4) no further axillary dissection is performed if all SLN are negative on frozen section analysis; any residual lymph node disease and/or absence of previously placed clip marker on SLNB specimen indicate ALND.Results: Patients' mean age was 47 years (range 24-87 years), 67.2% (n=316) were cT2-T3, 83.5% (n=393) cN+ (N1 and N2), 62.6% (n = 295) had mastectomy. ALND was performed in 64.7% (n=303) patients, SLNB in 33.3% (n=156) and SLNB followed by ALND in 1.9% (n=9). In the subgroup of N+ patients (n=385), it was possible to perform SNB in 25.6% (n=98). 165 of 471 patients (35%) were included in standardized protocol for axillary management; the rate of SLNB in N+ patients was statistically higher in this group when compared to patients treated before the implementation of the protocol (34.4% vs. 22.8%; p=0.025).Conclusion: The results of the present study demonstrate a significant increase in sparing ALND after the implementation of a standardized protocol for management of axilla after NACT. However, further multi-institutional studies are still needed to support its widely adoption, as well as clinical trials to assess overall and disease-free survival in those patients who had omitted ALND after NACT.**

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# Senescence-related methylation changes following therapy as potential biomarker for CDK4/6 inhibitor activity

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***Introduction*Classically, cancer therapy approaches lead to tumor cell death or an alternative fate such as senescence. Senescent cells remain viable but without proliferation markers. Senescent cells secrete factors with diverse actions that influence surrounding cells, the extracellular matrix (ECM) and the immune system, a phenomenon termed the senescence-associated secretory phenotype (SASP). Cyclin-dependent kinase 4/6 inhibitors (CDKi) are game-changers in the therapy of metastatic hormone receptor-positive, HER2-negative breast cancer. A potential mechanism of the action of these agents is induction of senescence in breast tumor cells, going beyond cell cycle arrest. However, senescence can be studied mainly using invasive biopsies, and therefore the prevalence and importance of senescence in patients are largely unknown. Moreover, only few circulating biomarkers exist to predict activity or measure CDKi effects. In order to develop a correlative liquid biopsy for CDKi activity, we have analyzed epigenetic (methylation) changes following therapy-induced senescence *in vitro*. We sought to identify (un)methylated loci that will be affected by different approaches and later can be discovered in circulating cell-free DNA.**

***Methods*We have treated luminal breast cancer MCF-7 cells with Doxorubicin, CDKi (Palbociclib) or by irradiation. This protocol resulted in up to 80% of cells with senescence-related beta-galactosidase activity. DNA methylation was profiled using Illumina Infinium MethylationEPIC 850K BeadChip. Differentially methylated loci (mDNA) were identified using GenomeStudio and Minfi. Analyses were done using GREAT, CSGene, and Reactome databases. Methylation age was analyzed using the Horvath Methylation Calculator. Statistical significance was defined as $p<0.05$, $q<0.1$.**

***Results*Significantly differentially methylated sites (in comparison to untreated cells) were revealed as following: 9111 sites in Doxorubicin treated cells, 3828 sites in Palbociclib treated cells, and 694 sites in irradiated cells. These loci comprise 1%, 0.45%, and 0.08% of analyzed methylation sites, respectively. 324 loci were similarly changed following the three treatment options ('common sites'). We found that the 'geographic' distribution of intragenic and intergenic methylation sites (5' UTR, gene body etc.) in all treated cells was similar. Gene set over-representation analysis revealed that sites associated with genes of the 'collagen metabolic process' set were significantly altered in drug-treated cells. Pathway investigation of the 324 'common sites' revealed that ECM-related 'focal adhesion assembly' is the most significant pathway involved. Specific analysis of senescence-related gene sets showed that 15.1% (76/503) of senescence genes changed after Doxorubicin treatment, 6.2% (31/503) after Palbociclib and 1% (5/503) after irradiation. Pathway analysis of these genes showed that drugs affected the 'oxidative stress-induced senescence' pathway, while irradiated cells had SASP-related genes affected.Despite the above mentioned methylation changes, age calculation based on methylation clock showed that all samples had similar age (6), regardless of manipulation.**

***Conclusion*Single treatment of MCF-7 cells with known senescence inducers results in changes in methylation patterns. A significant number of common loci changed following all types of treatments, suggesting them as potential surrogate loci of senescence. Also, we have reproduced the well-known interplay between collagen and senescence/SASP.This preliminary data sheds light on epigenetic changes following treatment-induced senescence. Further studies are needed to validate whether these methylation changes can be found *in vivo* in tumors and in patients' cell-free DNA following therapy with CDKi.**

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# A remote-directed “virtual” clinical trial in metastatic breast cancer to determine feasibility of evaluating patient response to immunotherapy using spliceosome mutational markers (SF3B1): The PRISMM trial (NCT04447651)

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**Background:**
Next-generation sequencing (NGS) is becoming increasingly routine in patients with advanced cancers, and rare mutations may occasionally be identified. Evaluating the efficacy of targeting rare mutations is challenging given the low observed frequencies, which can result in slow accrual to clinical trials. The internet and social media have revolutionized the way we receive information and connect with each other, and may potentially be leveraged to identify patients with rare mutations. Spliceosome mutations, such as SF3B1, occur in approximately 4% of breast cancers. The Park Lab has demonstrated that somatic cell knock-in of an SF3B1 hotspot mutation results in new mRNA transcripts can be translated into aberrant proteins. These preliminary data suggest that spliceosome mutations could produce a high number of neoantigens, which may increase sensitivity to immune checkpoint inhibitors (ICI). Indeed, since response rates to immunotherapy in patients with metastatic breast cancer is low, identifying biomarkers predictive of response is critical. We therefore designed a remotely directed “virtual” clinical trial to determine the feasibility of evaluating Patient Response to Immunotherapy using Spliceosome Mutational Markers (PRISMM, NCT04447651). Methods: The is a prospective feasibility trial in which patients will be identified via a social media campaign that directs potential participants to a landing page where they can fill out an online form. Patients will need to self-identify as having metastatic breast cancer (any receptor status) with an SF3B1 mutation (main eligibility criteria); once this information is confirmed by the study team, outside records will be obtained and their case will be reviewed at an institutional Molecular Tumor Board; ICI may be recommended or not. Recommendations from the Board will be provided to the patient and local oncologist, who will then decide whether to proceed with the Board’s recommendation or not. Efficacy of next line therapy will be followed by physician and patient questionnaires every one to three months. During routine blood collection, we will evaluate plasma tumor DNA (ptDNA) and peripheral blood mononuclear cells (PBMCs) at baseline and three months. The primary objective of this study is to evaluate the feasibility of conducting a prospective study using online recruitment tools, and the feasibility of real-time case review by a centralized Molecular Tumor Board to assist in therapeutic decision making. Secondary objectives include evaluating the clinical effect of ICI including progression-free and overall survival, correlate SF3B1 mutations in ptDNA with tissue-based NGS, and describe immunopharmacodynamic changes by PBMC evaluation. We anticipate screening approximately 5000 patients via our social media campaign to identify 60 eligible patients. We will conduct efficacy interim analysis after 23, 35, 47, and 56 patients are enrolled. The response rate of 1% 5%, 10%, and 20% correspond to 99.8%, 74.7%, 24.9%, and 1.1% chance that the study will stop early with an average sample size of 26.2, 41.3, 53.6, and 58.7 patients enrolled and treated respectively. If the true response rate exceeds 15% the Board will continue to make recommendation for ICI in patients with SF3B1 mutations. For more information please contact us at PRISMM@jhmi.edu.

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# Pyrotinib in the treatment of women with advanced HER2 positive breast cancer: A multicenter, prospective, real world study

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**Backgrounds: Pyrotinib (an irreversible pan-ErbB receptor tyrosine kinase inhibitor) plus capecitabine have been approved for patients with advanced HER2 positive breast cancer in China. However, the efficacy of pyrotinib in patients with different baseline characteristics in the actual clinical practice has not been reported. This study analyzed the anti-tumor activity and toxicity of pyrotinib in real world setting. Methods: Total 36 hospitals in China participated in the real-world study. Patients with histologically confirmed advanced HER2 positive breast cancer were included in the analyses. All patients received pyrotinib-based therapy were given pyrotinib once a day in a 21-day cycle. The primary endpoint was progression-free survival (PFS). Secondary endpoints included adverse events (AE), objective response rate (ORR), disease control rate (DCR), and overall survival (OS). Results: Periodic analysis results were reported in this study. A total of 231 patients (median age: 53 years [26-78]) were enrolled from February 17, 2019 to June 11, 2020. Among them, 156 (67.53%) patients had visceral metastatic lesions and 39 (16.88%) had brain metastases. HR+, HR-, or unknown HR status for primary tumor accounted for 52.82%, 45.45%, 1.73%, respectively. 206 (89.18%) patients were previously administered with anti-HER2 drugs. Among them, 156 patients had received single type of anti-HER2 drug (153 patients with trastuzumab, 3 patients with trastuzumab biosimilar); 50 patients had received trastuzumab and some other drugs (lapatinib, pertuzumab, T-DM1, trastuzumab biosimilar, and antibody-drug conjugate). 88 (65.67%) patients received pyrotinib-based therapy as a second or further line of treatment. 177 (76.62%) patients initiated pyrotinib treatment at 400 mg, 52 (22.51%) patients started with 320 mg, and 2 (0.87%) patients had a starting dose of 160mg. Treatment regimens were pyrotinib plus capecitabine (95/231), pyrotinib combined with other chemotherapy drugs (41/231), pyrotinib combined with anti-HER2 treatments (57/231), and pyrotinib monotherapy (30/231), pyrotinib combined with endocrine therapy, radiotherapy or antiangiogenic drugs (8/231). Among the 134 patients available for efficacy evaluation, 1 (0.75%) patient achieved complete response (CR), 30 (22.39%) patients had partial response (PR), 86 (64.18%) patients achieved stable disease (SD), and 17 (12.69%) patients had progression disease (PD), resulting in an ORR of 23.14% and DCR of 87.31%. Patients received pyrotinib-based therapy as their first, second, and later lines of treatment had a DCR of 82.05%, 90.91%, and 87.27%, respectively. Among patients receiving ≥3 lines treatment, no statistical significance of the DCR was observed, nonetheless, patients received pyrotinib plus capecitabine had a numerically lower DCR than those received pyrotinib combined with other chemotherapy drugs (85% vs. 92.86%, *P*=0.704). This is an early stage of data analysis, median progression-free survival has not yet been reached. The most common AE was diarrhea (81.68%), but only 16 (7.93%) patients reported Grade ≥ 3 diarrhea which could be well controlled. Other AEs included leukopenia (31.69%), neutropenia (30.69%), anemia (27.23%), increased alanine aminotransferase (15.36%), decreased appetite (11.39%), and stomatitis (6.44%). No treatment-related death occurred. Conclusions: Pyrotinib demonstrated an encouraging efficacy and manageable safety profile in patients with advanced HER2+ breast cancer. More data would be analyzed and reported in the future.**

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# Validation study results for a personalized prevention education aid in breast cancer risk reduction

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BackgroundOptions for breast cancer risk reduction include endocrine medications (tamoxifen, raloxifene, aromatase inhibitors) and lifestyle modifications (increasing exercise, reducing BMI, or alcohol intake). At present, there are limited patient-facing resources that provide information on personalized risk and prevention strategies. To address this unmet need, the Breast Health Decisions (BHD) Tool was designed to educate and empower women in the WISDOM (Women Informed to Screen Depending on Measures of risk) Study, a preference-tolerant randomized control trial comparing personalized risk-based screening to traditional annual screening. The tool supports Aim 4 of the WISDOM Study: test whether risk-based screening, including individualized risk assessment and targeted risk reduction education for those in the top 2.5% risk, enables higher uptake of preventive interventions. We conducted a study of the first 100 participants counseled using the BHD Tool to assess its impact on risk-reduction strategies.
MethodsThe BHD Tool, built on the Salesforce platform, integrates WISDOM Study risk assessments to generate personalized education about risk and risk reduction, using concise wording, 8th-grade reading level or lower, and visual representations to support shared decision making for high-risk women. Changes to improve usability were incorporated from an initial pilot study. The study population was WISDOM Study participants in the top 2.5% 5-year risk by age, excluding mutation carriers. 5-year risk was calculated using the Breast Cancer Surveillance Consortium risk modified by a polygenic risk score. The tool was available through the participants' online study portals. Study staff contacted these participants to schedule consultations via Zoom with a WISDOM Breast Health Specialist, who navigated the participant through the tool during an interactive 45-minute consultation. Participants could decline the consultation and use the tool independently. A survey was conducted afterward to assess the tool's utility in motivating women to pursue risk-reducing options.
ResultsWe surveyed 100 high-risk participants who used the BHD Tool. 65% found it very helpful in understanding their breast cancer risk. 27 participants listed additional lifestyle improvements that they were practicing or hoping to begin, including yoga, walking, breast exams, self-exams, yard work, dietary improvements, meditation, and stress reduction. 37% of participants agreed that the tool eased their breast cancer worries and anxiety, while 44% were neutral and 17% disagreed. At the time of presentation, we will present 3-month follow up data and report which preventive actions were actually taken and barriers encountered.

| Survey question | | Number of participants (N=100) |
|---|---|---|
| Interested in reducing chance of developing breast cancer | | 97 |
| Currently participating in a breast cancer risk reducing activity* | | 77 |
| | Reducing alcohol intake | 35 |
| | Losing weight | 60 |
| | Increasing exercise | 27 |
| | Risk reducing medications | 5 |
| Considering participating in a breast cancer risk reducing activity* | | 72 |
| | Reducing alcohol intake | 12 |
| | Losing weight | 26 |
| | Increasing exercise | 24 |
| | Risk reducing medications | 22 |

**Participants can choose more than one risk-reducing activity*

ConclusionsThe BHD Tool synthesizes up-to-date chemoprevention literature in a patient-friendly interface to help educate women about their prevention options and to facilitate future discussions with a provider to empower informed decisions. Data from the first 100 high-risk women who used this tool suggest that the majority of women presented with information about their risk are interested in reducing it. More are considering lifestyle measures than medications. The BHD tool will be made available to all women in the personalized arm of the WISDOM Study. Future improvements include making the tool accessible to clinicians who counsel high-risk women.

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# Expression of the claudin transmembrane tight junction protein family (CLDN) and the prediction value of a claudin subset to the clinical outcome of patients with breast cancer

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**Background: Tight Junction (TJ) proteins are directly or indirectly involved in breast cancer progression and metastasis where the mutual adhesiveness of cancer cells is significantly weaker than normal cells and so reduced cell-cell interaction results in a loss of normal tissue architecture (1). This adhesiveness is in addition to the role of the proteins in the control of the barrier functions of epithelial and endothelial cells. The claudin family (CLDN) of transmembrane proteins, the largest protein family of the tight junctions, are located in the TJ of cells of epithelial and endothelial origin where they are key in the maintenance of TJ function and have been increasingly shown to have important roles during key steps in the progression of cancer. We have previously demonstrated that the expression of some TJ molecules (occludin, claudins -5, -16, -20) are associated with disease progression in breast cancer (2-5). This study sought to evaluate the possible clinical and prognostic value of the entire CLDN family, in patients with breast cancer. Methods: Members of the claudin family of transmembrane TJ proteins were assessed and correlated with clinical and pathological parameters at the messenger level in a Cardiff breast cancer cohort. Breast cancer primary tumours (n=114) and matched background tissue (n=30) were processed for RNA extraction. RNA was reverse transcribed and quantified before analysis by Q-PCR CLDN-1 to -24. The expression profile was analysed against the clinical and pathological information and most importantly the clinical outcome of the patients. Results. Mammary tissues expressed varying levels of CLDNs. However, the levels of CLDN1, CLDN3, CLDN4, CLDN11, CLDN19, and CLDN22 were found to be significantly aberrant in breast cancer tissues compared with normal tissues. Members of the family, namely CLDN10, CLDN11, and CLDN18 were found to have a significant predictive value to the prognosis when using the Nottingham Prognostic Index. Of the claudin family, we identified eight members whose expression was negatively correlated with long term survival, and three members positively correlated with the survival. A comprehensive bioinformatic analyses of these CLDN members revealed a highly significant signature in predicting the clinical outcome. A favourable CLDN signature predicted a subset of the patients who all survived the ten-year followup, compared with those with unfavourable signature (69.1%), p<0.0001 (Log ranked). Likewise, the CLDN signature also successfully predicted the occurrence of breast cancer related incidence (97.6% vs 61.8%, p<0.0001). Multivariate analyses confirmed that the CLDN signature has a highly significant value as an independent predictor for both overall survival (p=0.001) and disease-free survival (p=0.001). Moreover, the predictive power was more profound for patients with ER negative and Her2 negative tumours. Discussion: Claudins, key tight junctional transmembrane proteins, have important prognostic value in human breast cancer. Together with their pivotal roles in controlling the adhesiveness and permeability of the cell layers, this family is a key player in the development and progression of breast cancer.**

**References 1. Martin TA. 2011 Frontiers in Bioscience 16(3):898-936. 2. Martin TA et al. Anticancer Research 2016 36 (3):1287-1293 3. Esparza et al. J Exp Clin Cancer Res. 2012; 31(1): 43. 4. Martin TA et al. 2013 1(3)e1-10. 5. Martin et al. J Cell Biochem. 2008 105(1):41-5**

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# The significance of body mass index and absolute lymphocyte count as a prognostic factor for disease-free survival in Korean breast cancer patients

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**Introduction: The purpose of our study is to identify the association between body mass index (BMI) and absolute lymphocyte count (ALC), and to determine the effect of these two factors on the prognosis of breast cancer patients.Methods: We retrospectively identified 16,375 healthy female and 1,226 primary invasive breast cancer patients from Gangnam Severance Hospital. BMI and complete blood count (CBC) information at the time of diagnosed was collected. A multivariate Cox proportional hazard model was used to variable associated with disease-free survival (DFS).Results: BMI and ALC has positive correlation in breast cancer patients as well as health female (both *P* < .001). However, the effect of BMI and ALC on prognosis was the opposite. Overweight and obese had worse DFS (HR, 2.00; 95% CIs, 1.36-2.96; *P* < .001) than underweight or normal weight, but patients with high ALC had better DFS than those with low ALC (HR, 0.42; 95% CIs, 0.28-0.63; *P* < .001). When the risk stratification group was divided according to BMI /ALC, the high-risk group who had high BMI and low ALC had worse DFS than low-risk group (HR, 2.61; 95% CIs, 1.51-4.51; *P* = .001). In subgroup analysis, Her2-overexpressing and early stage tumor was more affected by BMI/ALC.Conclusions: The impact of BMI and ALC on prognosis in breast cancer was the opposite although BMI and ALC had positive correlation. Patients with high BMI and low ALC had worse DFS than others. Weight management is essential to breast cancer patients, and additional study about correlation between BMI and ALC affecting prognosis is needed in the future.**

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# Translational breast cancer research consortium 044 trial: Randomized phase 2 study of pembrolizumab and carboplatin versus carboplatin alone for chest wall recurrence of breast cancer

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Background: Chest wall recurrence may occur in up to 30% of patients with breast cancer, and is associated with a high morbidity and mortality. We hypothesized that immunotherapy may be beneficial in this setting because of the inflammatory nature of this disease, and the association of chest wall disease with lymphovascular invasion. Combination immunotherapy and chemotherapy may have a synergistic effect. In this study, we combined pembrolizumab, an anti-programmed cell death 1 (PD-1) antibody with carboplatin, in patients with chest wall disease. This combination has previously been shown to be effective in advanced lung cancer.
Trial design: This is a 2:1 randomized phase II study of pembrolizumab and carboplatin (Arm A) versus carboplatin alone (Arm B) in patients with chest wall involvement from breast cancer. Pembrolizumab is dosed at 200 mg IV every 3 weeks, and carboplatin is dosed at AUC 5 IV every 3 weeks. Patients on Arm A have the option to continue on pembrolizumab alone after 6 cycles of combination treatment (Arm Ax). Patients on Arm B have the option to cross-over to pembrolizumab (+/- carboplatin) after 6 cycles of carboplatin alone (Arm Bx). Patients with HER2 positive disease may continue trastuzumab in addition to the study treatment. Patients undergo chest wall biopsies and peripheral blood collection for correlative studies at enrollment and after 2 cycles of treatment, and also imaging with CT chest, abdomen, and pelvis, and bone scan every 3 cycles.
Eligibility criteria: Patients must have chest wall involvement from breast cancer, with or without distant metastases. Patients may have triple-negative breast cancer, hormone receptor positive, HER2- disease (after two prior lines of hormone therapy), or refractory HER2 positive disease. Patients may have received any number of lines of prior chemotherapy. A prior platinum is allowed as long as there was not disease progression on this agent.
Specific Aims: 1. (Primary aim) Disease control rate in the chest wall and other distant sites at 18 weeks of treatment using RECIST 1.1 criteria, 2. progression-free survival, 3. toxicity, 4. response based on tumor PD-L1 expression, and 5. response based on irRECIST. Exploratory aims include evaluating: 1. Soluble PD-L1 expression, 2. changes in tumor and peripheral blood immune composition, 3. peripheral blood circulating tumor cells, 4. peripheral blood cell-free DNA, and 5. the association of MYC with PD-1 and TIM-3 on tumor cells, based on preclinical data to suggest that MYC may upregulate these inflammatory markers.
Statistical Methods: 84 patients (56 in Arm A and 28 in Arm B) are being enrolled at 7 sites in the Translational Breast Cancer Research Consortium. The study is powered to determine a 20% difference in disease control rates between arms (HR 0.52, $\alpha$= 0.10, ß=0.20). A futility analysis was originally planned to occur for Arm B after 18 patients are enrolled, but a subsequent amendment has enabled an earlier assessment after 14 patients were enrolled.
Accrual: Present accrual is 40 patients. (NCT03095352). This trial is funded in part by Merck and a Development Program Grant from the University of California San Francisco.
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# Surgical management of the axilla in breast cancer in Latin American countries: Surgeon´s conduct

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**IntroductionAfter knowing the safety of the sentinel lymph node and the omission of axillary dissection inpatients with clinically negative and / or positive (1-2 lymph nodes) breast cancer withconservative surgery and the evidence from the ACOSOG Z011 randomized clinical trial andother evidence caution against proceeding with the use of axillary lymph node dissection inbreast cancer patients; a standardization of this practice is established globally, however indeveloping countries where treatments are affected by their availability, little is known aboutthe frequency of acquisition of these practices.MethodsAn online survey was carried out in different Latin American countries, which was distributedvia electronic link and QR code, with an open invitation to congresses and medical associations.The study lasted from August 16th, 2019 to April 30th, 2020. Surgeons with low, intermediateand high clinical practice in breast cancer were categorized, their type of clinical practice(private or public) and the period of clinical practice after discharge of the specialty.ResultsIn total, 260 replies were collected from surgeons from 10 different countries: Bolivia (1),Colombia (15), Ecuador (6), El Salvador (19), Guatemala (12), Nicaragua (12), Mexico (182),Paraguay (1), Peru (1) and Venezuela (11).Of these, the group that participated the most was the Surgical Oncologists (surgeons andgynecologists with a subspecialty in oncology), representing 82% of the participants, the rest ofthe participants being: Mastologists, Gynecologists and General Surgeons.The age group with the highest participation was 30-40 years old with 51.92% of the total(135), followed by the 41-50 year old group with 24% (63). 60% of the participants reported aprofessional practice of 10 years or less. In addition to referring to a mixed but mostly publicpractice in 48%, however, 56.93% of the participants reported a low practice (10 or less casesof breast cancer per month) of which between 60-100% of the occasions they offer earlysurgical treatment to their patients; responding that they always perform Sentinel Ganglion incN0 only 50% of the total, however it was mentioned that on average 85% of the occasions it isobtained between 2-3 lymph nodes number. The question was asked about completing theaxillary dissection when having 1-2 positive nodes with the scenarios of "always complete""almost always" "only in mastectomy" "only in breast conservation" and 63% answered thatalways or almost always will perform axillary dissection, 38.83% even referred the probabilityof doing it with micrometastasis in the setting of conservative surgery. In an exploratory manner, a question was added about the possibility of sentinel node after neoadjuvanttherapy, for which 52% answered that they would not perform such a procedure.ConclusionThe result of this survey shows a trend of resistance of less extensive surgical treatments in theaxilla for patients with breast cancer. Thus, reflecting that Latino populations are perhapsoverexposed to locoregional treatment; similar findings were reported by Dr. Morrow in astudy published in 2018 which showed the substantial variation in surgeon acceptance formore limited procedures.**

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# Energetics and lifestyle in inherited syndromes (ELLIE'S study)

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**Background: US women have a 1 in 8 lifetime chance of developing breast cancer (BC), with an estimated 10% resulting from a hereditary BC gene mutation. Individuals with mutations in genes such as *BRCA1* and *BRCA2* have an increased risk of breast and ovarian cancer, as well as other types of cancers. At present, there are more than a dozen other hereditary cancer related genetic mutations that have an associated moderate to high risk of developing cancer. Along with an ability to identify and characterize risk in individuals with a hereditary cancer mutation, there is a need to study modifiable factors such as dietary intake and physical activity in relation to an individual's risk for cancer.**

**Obesity and poor physical fitness are independently associated with an increased risk of BC and recurrence. There is a paucity of data on the impact of BMI, obesity, and physical activity on primary and recurrent BC in genetic mutation carriers. Women with a moderate penetrance gene mutation are at a high risk for BC and yet are likely to have an impact from modifiable risk factors. The impact of obesity, diet, and physical activity on BC risk and outcomes needs to be further characterized in genetic mutation carriers.**

**Methods: A short REDCap electronic survey was disseminated on social media and through our advocate partner Facing our Risk of Cancer Empowered (FORCE). Eligible participants include males or females, ≥18 years with a hereditary cancer genetic mutation. The survey includes questions regarding personal health, weight, height, metabolic risk factors, reproductive history as well as personal and/or family history of cancer and gene mutation status. In addition, includes a standardized assessment for diet (14-Item Mediterranean Diet Tool) and physical activity (IPAQ and modifiable PAQ). The first 1000 participants are compensated for their time with a $10 e-card. The survey is available in English and Spanish. The Spanish version was developed in collaboration with JUNTOS Kansas City.**

**Objectives: To establish a cohort and describe obesity rates, physical activity, metabolic factors, and nutrition in a cohort of individuals that have an increased risk of cancer due to a hereditary cancer genetic mutation.**

**Results: A total of N = 1,117 surveys have been completed as of June 30, 2020. Of them, 61.2% were removed from final analysis due to incomplete surveys, internet bots, and multiple single-user entries. A total N = 443 surveys have been verified and included in this analysis. Demographics: 98.6% female (n= 437), 94.4% white (n = 418) and median age 46 (range 19 – 77 yrs). Mutations represented in the cohort include: *BRCA2* (39.0%), *BRCA1* (29.1%), *CHEK2* (13.1%), and *ATM* (5.9%) and < 5%: *PALB2*, *RAD51D*, and *TP53*. Median BMI 24.9 ± 6.06 stdv. BMI 25 to < 30: 26.4% (n = 117). BMI 30 or > 30: 23.47% (n = 104). 61.3% responders are currently trying to lose weight. Attempts at weight loss: No attempts: n = 60 (13.5%), at least 1: n = 55 (12.4%), 2-5: n = 211 (47.6%), 6 or more: n = 117 (26.4%). Limitations to exercise include motivation (26.9%), time (23.5%), not liking exercise (15.6%), and lack of gym memberships (12.4%). 74.9% (n = 332) responded that they are interested in participating in future studies. The Spanish survey was made available 3/3/2020, no responses to date.**

**Conclusion: Individuals harboring a hereditary cancer genetic mutation are interested and willing to participate in research focused on lifestyle modifications and association with cancer risk. Rates of being overweight or obese are high and many have made multiple attempts at weight loss and find common barriers to exercise. Social media is a feasible platform to recruit to a lifestyle research project in a rare population. Additional steps to limit internet trolls, bots, and repetitive responses are necessary but did not impede recruitment. Further effort and collaboration are needed to expand the survey to underrepresented minorities.**

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# Termination of trastuzumab-based treatment after complete response in HER2-positive metastatic breast cancer

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**Background: Trastuzumab has been used for HER2 positive breast cancer treatment for more than 20 years. The ratio of HER2 overexpression in breast cancer patients is about 20%. In this study, we aim to evaluate the prognosis of HER2 positive breast cancer patients with long term received trastuzumab and examined the predictors of complete response.**
**Method: In this study, we included the patients with HER2 positive metastatic breast cancer received long-term trastuzumab. Demographic, clinical, pathological, and treatment data of the patients retrospectively recorded. Response rates of trastuzumab-based treatment evaluated by RECIST. The prognosis of the patients and predictors of complete response assessed with Kaplan-Meier analysis and logistic regression analysis, respectively. Also, the prognosis of the patients whose trastuzumab-based treatment was terminated was evaluated.**
**Results: Median follow-up was 123.3 months (range, 32.2-330.3). Eighty patients included the study, and the median age of the patients was 43 (22-68). The patients received trastuzumab-based treatment with a median of 62 months (range, 12-191). The number of de-novo metastatic patients was 27 (33.8%). All patients had a pathological HER2 overexpressed tumor that scored 3+ (71.3%) by ımmunohistochemistry (IHC) or scored 2+ (28.7%) by IHC confirmed with FISH. In all patients, five-, ten-, and, fifteen – years overall survival were 96.1%, 86.8%, and 60.5%, respectively. A complete response was detected at 60 (75%) of the patients. The median time to complete response was 14.4 months (range, 2.4-47.8). In logistic-regression analysis: age at diagnosis (p=0.543), menopausal status (p=0.074), bisphosphonates treatment (p=0.682), palliative radiotherapy (p=0.935), and de-novo metastatic disease (p=0.405) were not statistically significant predictors for complete response. However, the number of metastatic sites (p=0.016), and the use of endocrine therapy (p=0.019) with trastuzumab were statistically significant. During the study period, trastuzumab-based treatment of twelve patients was terminated, four (33.3%) patients continue to receive aromatase inhibitör, and eight (66.7%) patients received no treatment. After termination of trastuzumab, at a median follow-up 44.7 months (range, 11.6-66.6), recurrence was not detected in the patients.**
**Conclusions: In this study, we found that trastuzumab-based therapy can provide full recovery of HER2 positive metastatic breast cancer. For the patients with a long-term complete response, discontinuation of trastuzumab-based treatment should be considered. Also, hormone-positive patients should continue to receive aromatase inhibitör. The use of endocrine therapy with trastuzumab and the number of metastatic sites are predictors of the complete response**

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**Pd-l1 expression among different subtypes of chinese breast cancer patients**

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**Background Immunotherapies such as PD-L1 inhibitors have shown promising efficiency in breast cancer (BC) patients. However, treatment responses for immunotherapies are diverse since the immunogenicity of breast cancer is heterogeneous. Specific subtypes such as hormone receptor (HR)-positive, human EGF receptor 2 (HER2)-positive, and triple-negative breast cancer (TNBC) have shown heterogeneity in immunogenicity. Therefore, precisely identification of patients potentially benefit from immunotherapy is important. Previous studies have proved PD-L1 expression and tumor mutational burden (TMB) as predictive biomarkers for immunotherapy. Here, we report the PD-L1 expression and TMB status in Chinese BC patients with different subtypes. Using comprehensive molecular analysis, we also characterized the genomic features related to these biomarkers.**
**Methods Tumor samples from 112 Chinese patients with BC were collected and subjected to next-generation sequencing (NGS) and immunohistochemical (IHC) analysis. NGS were performed in a laboratory accredited by College of American Pathologists (CAP) and certified by Clinical Laboratory Improvement Amendments (CLIA) using validated panel targeting 450 cancer genes. Genomic alterations, included including single base substitution, short and long insertions/deletion (Indel), copy number variation, gene fusion, and rearrangement, were assessed. Tumor mutational burden (TMB) was measured by an algorithm developed in-house. Tumor tissues were analyzed for PD-L1 expression by IHC with 22C3 or 28-8 antibodies, respectively. Results The 112 Chinese BC patients consisted of 87 HR+ (77.7%), 19 TNBC (17.0%) and 6 HR-/ HER2 + (5.3%), with a median age of 47.5 years old (range 24-81). Of all patients, 42.0% were positive for PD-L1 expression (CPS≥1), including 30.4% PD-L1 (1≥CPS>10) and 11.6% PD-L1 (CPS≥10). PD-L1 expression were observed in HR+ BCs (41.4%) as well as in TNBC (47.4%) and HR-/ HER2+ (33.3%) subtypes, no significant difference were observed among the three subtypes. 8.9% patients were TMB-High (≥10 muts/Mb) with median TMB of 3.4 muts/Mb (range 0-80.8). TMB was slightly correlated with PD-L1 expression (Kendall tau = 0.241; P =0.01). 17.0% of PD-L1 positive patients and 3.1% of PD-L1 negative patients were TMB-High (p=0.016). Patients with PD-L1 CPS≥10 had significantly higher median TMB (7.1 vs. 3.1 muts/Mb, p<0.001). Moreover, patients with TMB-High were significantly elder than TMB-Low (median age, 57.5 vs. 47, p=0.012). In PD-L1 positive patients, the most frequently mutated genes were *TP53* (66%), *PIK3CA* (36%) and *ERBB2* (30%); In TMB-High patients, the most frequently mutated genes was *PIK3CA* (80%), followed by *TP53* (60%) and *ERBB2* (40%).**
**Conclusion Our data shows that the PD-L1 expression has no significant difference among HR+, TNBC and HR-/ HER2+ subtypes. These data provide the hypothesis that PD-L1 expression positive in different subtype breast cancers may benefit from immune treatment, including HER2 and Luminal subtypes. Otherwise, there was a correlation between PD-L1 expression and TMB, High TMB was also observed in PD-L1 negative patients, which may enrich the subgroup of patients who could benefit from immunotherapy. The verification of integrated predictive biomarkers for immunotherapy in BC is further needed.**

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# Simvastatin induces ferroptosis in breast cancer cells by inhibiting GPX4 and sensitizes chemotherapy

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**Background The incidence of breast cancer ranks the first among female malignant tumors. Although the effect of breast cancer treatment strategies has been very ideal and the mortality rate of breast cancer has decreased, some patients are still not sensitive to these, which eventually leads to rapid recurrence, metastasis and poor prognosis. Ferroptosis is a kind of Regulated cell death, which induced by accumulation of lipid peroxidation products and Reactive Oxygen Species (ROS). It is quite different from apoptosis and autophagy in cell morphological characteristics and biochemical indicators. According to the latest studies, ferroptosis can reduce the activity of GPX4 (Gutathione Peroxidase 4) in cells and accumulate ROS and lipid Peroxidase products through iron metabolism, ROS metabolism, amino acid metabolism and lipid metabolism, etc., thus causing ferroptosis. Ferroptosis is a hotspot in the study of drug resistance and metastasis of breast cancer. Simvastatin is a kind of commonly used oral cholesterol-lowering drugs, belongs to the HMG CoA reductase inhibitors. Some clinical studies have shown that statins can reduce the risk of a variety of cancers, including breast cancer, and the risk of recurrence. Other basic experiment show lipophilic statins have anti-cancer effect. Simvastatin is the most lipophilic of all statins in use. Recent studies have found that simvastatin can be used in combination with docetaxel to enhance the effect of chemotherapy in prostate cancer, but has not been reported in breast cancer. In this study, we investigated whether simvastatin could induce ferroptosis in breast cancer by inhibiting GPX4 and play the role of chemotherapy sensitization in combination with docetaxel. Methods (1) CCK8 assay was used for cell proliferation in vitro by simvastatin and docetaxel in breast cancer cells MDA-MB-231 and MCF-7. (2) The anti-cancer effect of simvastatin in vivo was verified by xenograft experiments in nude mice. (3) GPX4 mRNA and protein levels were detected by qPCR and Western blot. (4) GPXs activity test, ROS level test and MDA level test were used for ferroptosis detection.(5) the expression of ferroptosis-related genes ACSL4, PTGS2 and NOX1 was detected by qPCR.(6) anti-tumor effect of simvastatin combined with docetaxel in breast cancer cells mda-mb-231 and McF-7 was detected in vitro by CCK8 method.(7) By MDA-MB-231 tumor xenograft models surveyed anti-tumor activity of simvastatin and docetaxel. Results CCK8 results showed that simvastatin significantly inhibited cell proliferation in breast cancer cells MDA-MB-231 and MCF-7 ($P<0.001$), with the $IC_{50}$ values of MDA-MB-231 was 4.67um and MCF-7 was 81.53um,. In the xenograft experiments of nude mice, it was found that compared with the control group, the tumor volume of the simvastatin group was significantly reduced. In qPCR and Western blot, simvastatin was found to significantly inhibit GPX4 mRNA and protein expression. Compared with the control group, in breast cancer cells MDA-MB-231 and MCF-7 , simvastatin can reduce the activity of GPXs and increase the level of ROS and MDA, thus causing ferroptosis in breast cancer cells. qPCR showed that ferroptosis -related gene ACSL4 and PTGS2, which are related to lipid metabolism, and ROS metabolism were significantly increased. In the xenograft experiments of nude mice, it was found that compared with the control group and the single drug group, the tumor volume of simvastatin combined with docetaxel group was significantly reduced. Conclusion Simvastatin can inhibit the proliferation of breast cancer cells both in vivo and in vitro, inhibit the expression of breast cancer cell MDA-MB-231 and MCF-7 GPX4, and induce ferroptosis. Besides, simvastatin sensitizes the effect of docetaxel.**

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# Pik3ca mutations among hormone receptor positive and HER-2 negative advanced breast cancer patients in Finland

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**Background: Several new medicinal products have been introduced for the treatment of advanced breast cancer (aBC) in recent years, many of which are indicated for a specific patient population. One of these compounds is alpelisib, a phosphatidylinositol 3-kinase (PI3K) inhibitor, which has shown efficacy in the treatment of hormone receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer (aBC) harboring phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) "hotspot" mutations, i.e. mutations affecting the helical (E542K and E545K) and kinase (H1047R) domains. In this retrospective register-based study, the frequency of *PIK3CA* gene mutations as well as survival among HR+/HER2- aBC patients in Finland was analyzed.**
**Methods: This study utilized retrospective register-based data from the Hospital District of Southwest Finland (Auria Biobank), which covers approximately 20% of the population in Finland. Patients diagnosed with aBC between 2004–2013 were identified using ICD-10 code C50* (breast cancer) together with customized text mining algorithms to extract metastatic patients. Tumor biomarker data including estrogen receptor (ER), progesterone receptor (PR), and HER2 status were used to identify HR+/HER2- patients. The formalin fixed paraffin embedded (FFPE) tumor tissue samples available for these patients in the Auria Biobank's tissue archives were screened for *PIK3CA* mutations with next generation sequencing. Study follow-up period was defined to start from the date of aBC diagnosis and to continue until death or end of 2016, whichever occurred first. Clinical pathology and survival data were collected from the Auria Biobank and electronic medical records of the Hospital District of Southwest Finland. Overall survival (OS) was estimated using the Kaplan-Meier method.**
**Results: Altogether 444 adult female patients with aBC were identified. HR and HER2 status were available for 377 patients (85%), out of which 274 (73%) were HR+/HER2-. Representative FFPE tumor samples were available for 187 patients and *PIK3CA* was successfully screened in 161 patients. Out of the sequenced HR+/HER2- samples, 53.4% showed mutation in the *PIK3CA* gene and 46.6% wild type (wt) *PIK3CA* gene. Approximately one third (32.3% n=52) of the samples represented *PIK3CA* hotspot mutations and 18% (n=29) of these displayed more than one *PIK3CA* variant. The most common *PIK3CA* hotspot mutation was H1047R. HR+/HER2- patients with the wt *PIK3CA* gene showed slightly shorter OS compared to patients showing *PIK3CA* hotspot mutations (18.9 months (95% CI: 14.1-25.1) vs. 22.3 months (95% CI: 17.0-26.3). Higher portion of the wt patients also developed metastases within 1 year from the primary diagnosis compared to the patients with *PIK3CA* hotspot mutations (41.3% vs. 25.0%). At the time of diagnosis, 92.0% of the wt and 84.6% of the *PIK3CA* hotspot mutated population was 50 years or older, respectively.**
**Conclusion: Approximately one third of the HR+/HER2- aBC patient cohort in Finland had at least one variant of *PIK3CA* hotspot mutations in line with the SOLAR-1 clinical trial population. The OS did not differ markedly between the patients with wt and hotspot mutated *PIK3CA* gene. The short OS of the patients is probably due to the fact that the patients were treated before the availability of CDK4/6is as a treatment option.**

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# Identifying relevant parameters that characterize the early response to NAT in breast cancer patients using a novel personalized mechanistic model integrating *in vitro* and *in vivo* imaging data

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**The early determination of response to neoadjuvant therapy (NAT) in triple-negative breast cancer would enable the treating oncologist to adapt the therapeutic regimen of a non-responding patient (e.g., by changing dosage, dose schedule, prescribed drugs), and thereby improve treatment outcomes while avoiding unnecessary toxicities. To address this challenge, we propose to use personalized, *in silico* forecasts of tumor response to therapeutic regimens *via* a mechanistic mathematical model calibrated with patient-specific longitudinal multi-parametric magnetic resonance imaging (MRI) data acquired early in the course of NAT.**

**Here, we extend our mechanistic model to include a new term describing the synergistic effects of NAT drug combinations and identify the driving parameters involved in its formulation by means of a sensitivity analysis. Our model describes tumor cell dynamics as a combination of proliferation, which is regulated by a logistic term, and mobility, which is described as a diffusion process constrained by the local tumor-induced mechanical stress. Tumor cell density is extracted from diffusion-weighted MRI data, while tissue mechanical properties are defined from segmented $T_1$-weighted MRI data. We adjust the tumor proliferation rate in response to NAT drug combinations with a recent model of drug synergy, MuSyC, which accounts for distinct types of synergistic drug effects (synergy of potency *vs.* synergy of efficacy). We also consider the heterogeneous intratumoral delivery of drugs by means of perfusion maps estimated from dynamic contrast-enhanced MRI data.**

**We use Sobol's method for the sensitivity analysis of two different tumors - one well-perfused and one poorly-perfused. We simulate a four-cycle NAT protocol in which NAT drugs are delivered every 14 days, and assess the total effect ($S_T$) of each parameter on the mean relative difference of tumor cell density with respect to a control simulation of tumor growth without NAT. Sensitivity analysis results directly depend on the definition of the parameter space, which we construct by combining two approaches. First, we experimentally constrain parameter ranges using time-resolved, high-throughput, automated microscopy assays to capture the changes in proliferation rates of various breast cancer lines (HCC1143, SUM149, MDAMB231, and MDAMB468) caused by two standard drug combinations: paclitaxel with carboplatin and doxorubicin with perfosfamide (metabolic derivative of the pro-drug cyclophosphamide), and fitting the MuSyC model to these data. Second, we scale the resulting *in vitro* parameter ranges to clinically-relevant *in vivo* ranges by running an *in silico* study with our mechanistic model of breast cancer growth and NAT response.**

**Our results show that, out of the ten parameters involved in the synergy term, three have a dominant role in the dynamics of breast cancer during NAT ($S_T$ > 0.1): synergistic potency, the maximal change in tumor cell proliferation by the slowest decaying drug, and its concentration producing half of maximal effects. The other parameters have marginal (0.02 < $S_T$ < 0.1) to negligible effect ($S_T$ < 0.02). Ongoing studies are assessing the ability of our mechanistic model to forecast NAT response over a small patient cohort after patient-specific calibration of the driving parameters identified in the present study.**

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# Breaking the silent struggles: Development of a cancer caregiver support program

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**Background/Purpose: 4.6 million Americans serve as unpaid caregivers for someone with cancer. The burden of caregiving poses challenges to one's physical, psychological, financial and spiritual health. Our project aimed to explore caregiver needs and provide comprehensive information and practical guidance to enhance coping during and after treatment. Methods: We conducted targeted interviews with 50 caregivers of patients with high risk cancers (brain, head and neck, lung, gastrointestinal, gynecologic, breast and hematologic cancers) to prioritize and discuss their most pressing concerns. Caregiver quality of life and well-being was assessed using validated tools that were measured at baseline and 6 months later. A Caregiver Resource Manual was developed with a list of tangible resources and provided to all families. Supportive interventions included counseling, palliative care, referral to nutrition and support groups.**

**Results: The interviewed caregivers included spouses, children, friends and parents. At baseline, 55% of patients had stage IV disease. Within 6-months, 38% of patients expired or progressed, 59% stayed in remission or remained stable on treatment. At baseline, 65% of caregivers reported moderate/high distress, 39% scored moderately/high in feeling their life was imposed upon, and 58% scored moderately/high in difficulty meeting their own medical needs. After intervention, moderate/high scores improved by 25% in distress, 18% in feeling life was imposed upon and 12% in attending to medical needs. The well-being survey found an 8% increase in all aspects assessed.Conclusion: Our project recognized patients and caregivers as one unit of care with information and support needed for both. The interventions improved caregiver stress and overall well-being. We found a gap in adequately preparing families for progressive nature of disease highlighting the need for proactive palliative care in the future.**

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# Radiological response pattern predicts disease-free survival in breast cancer patients undergoing neoadjuvant chemotherapy

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**Purpose** Pathological complete response (pCR) predicts improved survival in breast cancer patients undergoing neoadjuvant chemotherapy (NAC). However, the prognosis of patients with non-pCR remains unclear. The aim of this study was to evaluate the effect of radiological response pattern on breast cancer patients' outcome.

**Method** A total of 396 breast cancer patients who underwent neoadjuvant chemotherapy between 2010-2017 at Seoul St. Mary's Hospital were retrospectively reviewed. Among them, patients who underwent 4-6 cycles of neoadjuvant chemotherapy and underwent response evaluation every 2 cycles using breast MRI were included for analysis. Early and late response ratio was calculated from breast MR images using the longest diameter of the main tumor. Early response ratio was calculated as post-2 cycle NAC / pre-NAC ratio. Late response ratio was calculated as post-4 cycle NC / post-2 cycle NAC ratio. Radiological response pattern was divided into three groups; fast-slow responder meaning early response ratio > late response ratio + 20%, slow-fast responder meaning late response ratio > early response ratio + 20% and constant responder meaning the difference between initial response ratio and later response ratio is lower than 20%. Survival analysis was done using the Kaplan-Meier method and multivariate analysis by Cox regression. Disease-free survival (DFS) was defined as locoregional recurrence, contralateral breast recurrence and distant metastasis.

**Result** A total of 177 patients were included for analysis. Among them 19 (10.7%) patients were pCR, 122 (68.9%) patients had partial response, 29 (16.4%) patients had stable disease and 7 (4.0%) patients had progressive disease. Median follow-up period was 50 months (range, 3-112 months). Radiological response pattern was significantly associated with disease-free survival in univariate analysis ($p$=0.042). Fast-slow responders had significantly worse disease-free survival (DFS) in univariate analysis compared to slow-fast responders and constant responders ($p$=0.042, 5-year DFS 67.6%, 88.3% 67.6%). Radiological response pattern continued to be statistically significant by multivariable analysis ($p$=0.037).

**Conclusion** Our results showed that fast-slow responders have worse survival compared to constant or slow-fast responders. Radiological response patterns may be useful to more accurately assess prognosis, especially when considering adjuvant chemotherapy.

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**Metastatic tissues display organ specific immune infiltration archetypes; lessons from a rapid autopsy tissue collection study**

**Colt Egelston, Weihua Guo, Eliza R. Bacon, Kena Ihle, Diana Simons, Christian Avalos, Jlayi Tan, Jian Ye, Lei Wang, Minhui Lim, James R. Waisman and Peter P Lee. City of Hope, Duarte, CA**

**Immune composition in the tumor microenvironment (TME) of patient tumors has proven to play a central role in the development of metastases and response to therapy. Evidence has suggested that the metastatic TME is immune aberrant, however difficulty in obtaining biopsies of metastatic tumors has made assessment of the immune TME difficult. Here we utilize a rapid autopsy tissue collection protocol to assess the infiltration and composition of the immune TME in numerous metastatic tissue sites, paired disease-free tissue sites, and the associated tissue draining lymph nodes. Post-mortem tissues were collected from nine metastatic breast cancer patients shortly after death through City of Hope's "Legacy Project for Rapid Tissue Donation" Program. The average post-mortem interval (PMI) for tissue collection was 6 hours. Collected specimens include metastatic lesions and paired non-cancer samples from every cancer-involved organ, disease-free specimens from non-involved major organs, distant and tumor-draining lymph nodes (both cancer-infiltrated and disease free), as well as blood and spleens. Immediately following collection, specimens were processed into single cell suspension for flow cytometry. Over 80 immune cell phenotypes were assessed, including CD8+ and CD4+ T cell subsets, B cell subsets, natural killer (NK) cells, tumor associated macrophages (TAMs), dendritic cell subsets, and other immune cells. Tumor infiltrated tissues were found to have comparable immune cell densities and composition compared to paired disease-free tissues of the same organ type. However, immune cell densities in metastatic tissues and disease-free tissues were significantly different between organ types, with lung immune infiltration consistently being greater than liver, brain, and skin tissues. Differences in immune composition between tissue sites were also observed. Notably, liver tissues favored the presence of IL-2 producing central memory CD8+ T cells, while lung tissues favored the presence of CD8+ tissue resident memory T cells and CD16+ NK cells. Relative to disease-free lung tissues, tumor infiltrated lungs contained diminished frequencies of CD8+ tissue resident memory T cells and altered B cell and monocyte phenotypes. Increased levels of targetable immune pathways were observed, including increased PD-L1 and CTLA-4 expressing cells in skin metastases, and increased GARP+ B cells in bone marrow metastases. These data suggest that immune monitoring and trafficking of metastatic tissues site is dictated by organ type, which can be altered in composition by tumor infiltration. Further studies such as these may reveal organ-specific mechanisms of response to therapeutic interventions. Identity of organ location for tumor metastases may guide choices for immunotherapeutic interventions.**

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# The impact of progesterone receptor negativity on oncologic outcomes in estrogen receptor positive breast cancer

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**BACKGROUND: Estrogen receptor (ER) status provides invaluable prognostic and therapeutic information in breast cancer (BC). When clinical decision making is driven by ER status, the value of assessing progesterone receptor (PgR) status is less certain. AIM: To describe the clinicopathologic features of ER positive (ER+) /PgR negative (PgR-) BC and to determine the effect of PgR negativity on oncologic outcomes in ER+ disease.METHODS: Consecutive female patients with ER+ BC managed in a single institution between 2005-2015 were included. Clinicopathological features of PgR- BC were determined. Factors associated with PgR- disease were assessed using binary logistic regression. Oncological outcome was assessed using Kaplan-Meier curves and Cox regression analysis.RESULTS: 2660 patients were included with a median age of 59.6±13.3 years (21-99). Median follow-up was 97.2 months (3.0-181.2). 2208 cases were PgR+ (83.0%) and 452 were PgR- (17.0%). Being postmenopausal (OR:1.656, 95% Confidence interval (CI):1.249-2.195, *P*<0.001), presenting with symptoms (OR:1.712, 95% CI:1.302-2.249, *P*<0.001), invasive ductal subtype (OR:1.514, 95% CI:1.166-1.966, *P*=0.002) and grade 3 tumours (OR:2.198, 95% CI:1.683-2.870, *P*<0.001) were all associated with PgR- status. In patients receiving neoadjuvant chemotherapy (n=308), pathological complete response rates were 10.1% (25/247) in patients with PgR+ disease, versus 18.0% in those with PgR- disease (11/61) (*P*=0.050). PgR negativity independently predicted worse disease-free (HR:1.632, 95%CI:1.209-2.204, *P*=0.001) and overall survival (OS) (HR:1.774, 95%CI:1.324-2.375, *P*<0.001), as well as worse OS in ER+/HER2- disease (*P*=0.004). CONCLUSIONS: In ER+ disease, PgR- tumours have more aggressive clinicopathological features and worse oncological outcomes. Neoadjuvant and adjuvant therapeutic strategies should be tailored according to PgR status.**

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# Budget impact of introducing neratinib for third-line treatment of HER2+ metastatic breast cancer in the United States

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**Background** Neratinib, an oral, irreversible tyrosine kinase inhibitor of multiple HER receptors, was recently approved in combination with capecitabine (neratinib doublet regimen) in the United States (US) for adults with HER2+ metastatic breast cancer (mBC) who have received 2 or more anti-HER2 therapies. Clinical trials showed that neratinib plus capecitabine significantly improved progression-free survival versus lapatinib plus capecitabine. There are several existing and potential treatment options for this population with varying efficacies, side effect profiles, and costs.

**Objective** This analysis estimates the budget impact for US health care payers of adding a neratinib doublet regimen to the currently available third-line HER2+ mBC treatments in the US.

**Methods** A budget-impact model was developed to compare health care payer costs associated with third-line treatment of HER2+ mBC over 5 years between a treatment setting with neratinib and a treatment setting without neratinib for a hypothetical 1-million-person commercial plan of adults over age 18. The treatment options considered in the model include neratinib doublet regimen, oral combination therapy with lapatinib and capecitabine (lapatinib doublet regimen), tucatinib plus capecitabine plus trastuzumab (tucatinib triplet regimen), and intravenous fam-trastuzumab deruxtecan-nxki (DS-8201 single agent). The population eligible for treatment was calculated based on prevalence and incidence of HER2+ mBC and progression to third-line HER2-direct treatment; estimates were obtained from the published literature. The impact of including neratinib doublet regimen was assessed under two market share scenarios: one in which all regimens had equal market share and a second in which a clinical expert provided judgement on projected uptake of the regimens over the five-year period. In the treatment setting without the neratinib regimen, market shares for neratinib were distributed equally to the other treatments. Treatment duration, dosing, adverse event incidence, and monitoring requirements were obtained from key clinical trials and prescribing information. Drug acquisition costs, unit monitoring costs, and adverse event costs were obtained from wholesale acquisition costs, fee schedules, and the Healthcare Cost and Utilization Project, respectively. The total incremental costs and per-member-per-month (PMPM) costs were calculated by comparing total health plan costs in the treatment setting with neratinib with costs in the treatment setting without neratinib over a 5-year period. Costs were presented in 2019 US dollars.

**Results** It was estimated that 47 patients would be eligible for third-line HER2 mBC treatment in the first year, with an additional 17 incident patients becoming eligible each subsequent year. Average monthly costs per treated patient were $15,037, $9,283, $27,759, and $14,826 for neratinib doublet regimen, lapatinib doublet regimen, tucatinib triplet regimen, and DS-8201, respectively. When market shares were assumed to be even across regimens, the treatment setting with neratinib doublet regimen reduced total annual health plan costs by $1.4 million ($0.02 PMPM) over 5 years compared with the treatment setting without neratinib doublet regimen. Cost reductions for the treatment setting with neratinib doublet regimen were $575,738 ($0.01 PMPM) over 5 years when market shares were based on clinical expert estimates.

**Conclusions** The introduction of neratinib over the course of 5 years has the potential to reduce US health plan costs for the treatment of patients with HER2+ mBC by reducing the usage of more expensive treatment regimens.

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# Magnetic seeds to aid targeted axillary dissection

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**Introduction: Indications for accurate removal of a previously identified, involved or highly suspicious axillary lymph node include: 1) after neoadjuvant chemotherapy (NACT) to ensure pathological assessment of the correct index node (targeted axillary dissection, TAD) 2) for women with an abnormal/indeterminate node on imaging who may be able to avoid axillary lymph node clearance (ALNC) because they meet Z0011 criteria or may be eligible for POSNOC trial inclusion 3) guided removal of a specific axillary lymph node (eg Rotter's node recurrence, diagnostic biopsy, inclusion of specific node in ALNC). Dual localisation is either not viable or has an unacceptably high false negative rate in these scenarios and marking of the index node is advised. Although conventional markers are often used prior to NACT, finding that marked node at surgery can pose a challenge. Wire localisation has variable outcomes and scheduling constraints. Magnetic seed localisation, with Magseed™, allows for easy placement and excision of targeted nodes. Seeds can be accurately placed, do not migrate and can now be placed many months prior to surgery, at the start of NACT. The aim of this study was to report our early experience. Methods: Patients were identified by searching an imaging database for women who had undergone ultrasound (US)-guided Magseed™ insertion into an abnormal axillary lymph node between August 2018 and July 2020. Data on intended use and surgical outcomes were collected retrospectively from electronic patient records (EPR). Patients were categorised into 3 groups as described above. Results: 37 patients were identified, 17 in group 1, 13 in group 2 and 7 in group 3. Only 1 patient had complications with Magseed™ insertion, requiring a second attempt to successfully mark the required node. In 1 patient the Magseed™ was found on the surgical drape, thought to have been lying adjacent to the node intended for excision, this patient was therefore excluded from further evaluation in the results, as were 3 patients with missing data. One patient has yet to come to surgery, all other Magseeds™ have been successfully retrieved. Group 3 indications were disparate, and this group will not be described further. Group 1 - in 10 of 15 patients post NACT the Magseed™-marked node was found to be the sentinel node by routine mapping techniques (Technetium 99 +/- Patent V blue dye injection), identified as either hot or hot and blue. Of the 15 patients, 6 remained node positive on intra-operative assessment and underwent ALNC whilst 9 (60%) were spared ALNC. 2 patients avoided false negative results as the Magseed™-marked node contained residual disease yet was neither hot nor blue. Group 2 - Ten patients underwent sentinel lymph node biopsy using routine mapping techniques and Magseed™-guided excision of a specifically targeted node. In 7 the Magseed™-marked node was found to be a sentinel node (hot or hot and blue). Only 3 patients had sufficient disease to warrant completion ALNC. Conclusion: Insertion of a magnetic seed into a biopsy-proven positive node prior to planned TAD or into an abnormal node identified at diagnosis facilitates specific node retrieval for pathological assessment, with minimal associated complications, and has wide versatility. Magnetic seed localisation reduces the false negative rate and provides confidence in the correct assessment of the axilla thereby sparing patients unnecessary ALNC if they have had a complete pathological response to NACT or have limited axillary disease. The ability to insert the seed prior to the surgical date allows for flexibility with scheduling in comparison to wire localisation.**

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**Prognostic significance of tumor-infiltrating lymphocytes and neutrophil-to-lymphocyte ratio in patients with breast cancer receivingneoadjuvant chemotherapy**

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**Introduction and objectives: Tumor infiltrating lymphocytes (TILs) and neutrophil-to-lymphocyte ratio (NLR) play a prognostic role in early stage breast cancer (BC). There is no evidence about the combined effect of both factors. Our objective was to evaluate the integrated clinical significance of TILs and NLR in patients with early BC treated with neoadjuvant therapy. Materials and methods: Retrospective, single-center analysis of a cohort of patients with early BC treated with neoadjuvant chemotherapy between 2001-2010. Pre-treatment TILs ($CD3^+$-TIL count) was evaluated using a tumor tissue microarray. NLR was calculated within one month of cancer diagnosis. TILs (logarithmic transformed) and NLR were analyzed as continuous variables. Survival analysis was performed using multivariable Cox regression models. Results:A total of 121 patients were included. Median age: 56 years. Cancer stage at diagnosis: 16% IIA, 28% IIB, 33% IIIA, 7% IIIB and 16% IIIC. Molecular subtype: 64% hormone receptor(HR)-positive (12% HER2-positive), 11% HER2-positive HR-negative and 22% triple-negative. Pathological complete response (pCR): 16.5%. Median follow-up: 12 years. Pre-treatment TIL analysis was available in 71 patients (59%) and NLR in 101 (83%). There was no correlation between both variables (Spearman's Rho: 0.03, p = 0.98). In the univariate analysis, the NLR showed a negative prognostic value for overall survival (OS) (HR 1.23, 95%CI 1.11-1.36; p <0.001, C-index: 0.64 95%CI 0.52-0.77, p = 0.69). The effect was opposite for TILs (HR: 0.76 95%CI 0.61-0.95, p = 0.02; C-index: 0.69 95%CI 0.57-0.81, p = 0.69). The linear approximation was adequate, and there was no suspicion of non-proportionality of the hazards. In the multivariate analysis, including or not cancer staging after neoadjuvant therapy, NLR remained as an independent variable (HR 1.18, 95%CI 1.04-1.33; p = 0.01) and a statistic trend for TILs was also observed (HR 0.83, 95%CI 0.65-1.07; p = 0.16). Given the limited sample size, the multivariate analysis did not provide clear evidence of an additive effect. Nevertheless, the combined analysis of both parameters showed a better fit with respect to the two variables separately (Akaike Information Criterion for the combined model, for TILs and for NLR: 106, 133 and 214, respectively). Conclusion:The integrated characterization of TILs and NLR identifies different prognostic subgroups in early BC patients receiving neoadjuvant chemotherapy. Future validation of these findings in large, multicenter cohorts might allow treatment optimization by means of new strategies such as immunotherapy.**

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# Insurance coverage, employment status, and financial wellbeing of young women diagnosed with breast cancer

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**Research Objective: The objective of this study was to evaluate the insurance, employment, and financial experiences of young (age ≤ 39 years) female breast cancer patients and assess factors associated with any changes in their financial situation. Previous literature has shown that younger women are more likely to be diagnosed with late-stage disease that requires more-intensive treatments, while significant medical expenditures, productivity losses, financial hardship, and changes in employment and work productivity have been found in patients of all ages. Methods: A sample of women who were diagnosed with breast cancer between the ages of 18 and 39 years and residing in the states of California, Florida, Georgia, and North Carolina were identified. The sample included women who were (1) diagnosed with ductal carcinoma in situ (D05.90; 8500/2) or invasive breast cancer (C50; 8500/3) between January 2013 and December 2014; (2) between the ages of 18 and 39 years at the time of diagnosis; and (3) alive at the time of data extraction. We contacted 3,659 women by mail; 2,927 were alive with deliverable addresses. Of those, 830 women returned completed surveys, yielding a response rate of 28.4%. The survey instrument included 66 questions on demographics, insurance status, employment history, out-of-pocket cost, and overall financial well-being. Multivariate analysis was used to identify factors associated with financial decline. Principal Findings: About half of the women (47.4%) reported that treatment expenditures were higher than anticipated, and almost two-thirds (65.3%) had not discussed treatment costs with their care team. Almost a third of the patients (31.8%) reported treatment nonadherence due to cost. Factors associated with not receiving recommended care included very young age (<35 years) at diagnosis, self-insurance, the presence of comorbid conditions, and a late-stage diagnosis. Conclusions: Young female breast cancer patients experienced considerable financial burden regardless of insurance coverage. Most respondents made employment decisions that would allow them to keep their health insurance coverage. Knowledge about the financial consequences of breast cancer can help patients factor cost and employment into treatment decisions. Implications for Policy or Practice: This study highlights the burdens that many young women with breast cancer face, regardless of employment or insurance status, raising the possibility of target policy intervention. The strengths of this study include a unique focus on young breast cancer patients, identification of patients from population-based cancer registries, and the utilization of multifaceted insurance/financial indicators.**

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# Factors causing delayed resolution of breast lymphoedema

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IntroductionBreast lymphoedema impacts the quality of life and cosmesis in women undergoing breast conserving surgery for cancer. The assessment of breast lymphoedema is complex and challenging. The varied reported incidence (0-94%) is due to lack of awareness, poor reporting, subjective characterisation, absence of standardised definitions and tools for diagnosis and monitoring. Extensive research has been done on secondary limb and trunk lymphoedema following lymph node surgery and/or radiotherapy. However, there is a lack of data on breast lymphoedema. Disruption of lymphatics due to advanced oncoplastic procedures, axillary surgery, modified incisions and adjuvant radiotherapy may contribute to this problem. The objective of this study is to identify the causes of delayed resolution of breast lymphoedema.

Methods A retrospective audit was carried out in women who underwent breast conserving surgery between 2011-2017.Only patients with breast oedema, seen in the lymphoedema clinic were included in the study. Data on body mass index (BMI), types of incisions, breast procedures, axillary surgery, histopathology, adjuvant treatment including the extent of adjuvant radiotherapy was collated from the hospital database.

Breast lymphoedema was diagnosed by clinical examination and/or by a Delfin lymph scanner (DLS). DLS is a mobile non-invasive device which uses tissue dielectric constant (TDC) for measuring subcutaneous tissue water. A reading of 45% or higher was accepted as indicative of breast lymphoedema in our unit. Percentage water content (PWC) value was recorded only in 55 patients using DLS.

ResultsDuring the study period, 1905 patients underwent breast conserving surgery, out of which 120 (6.3%) were documented as having breast lymphoedema. The median time from surgery to assessment in the lymphedema clinic was 11 months. On univariate analysis, a high BMI (>30) and radiotherapy with boost lead to non-resolution of breast oedema. The median time taken for resolution of symptoms was 18 months. Other factors such as lateral skin crease incisions, single incisions to perform both breast and axillary surgery, oncoplastic procedures and re-excisions were not statistically significant. Using a DLS, the median PWC value was 56% in this cohort.

Conclusions Our study shows that high BMI and radiotherapy with boost leads to delayed resolution of breast lymphoedema. The Delfin lymph scanner may be a potential tool for monitoring breast oedema but further prospective studies are required for validation of this tool.

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# Computerized image analysis of nuclear morphological features reveals differences in phenotype and prognosis of disease free survival of early stage ER+ breast cancers for South Asian and North American women

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Background: Breast cancer is the most common cancer worldwide. There has been emerging interest in studying differences in breast tumor phenotypes between South Asian and South American women given that racial/ethnic disparities in incidence and mortality have been demonstrated in multiple studies. South Asian women are more likely to be diagnosed with an advanced stage breast tumor despite lower incidence than in North American women. There is evidence that computer-extracted nuclear morphological features on H&E slide images may be associated with breast cancer aggressiveness, specifically recurrence and disease free survival. However, studies have mostly focused on North American women. In this work, we evaluated whether there is a difference in computer extracted features of nuclear morphology from H&E tissue slide images between South Asian (SA) and North American (NA) women and we also investigated how these differences could impact the development of population specific breast cancer prognostic models. Methods: H&E slides of breast tumors from patients who were diagnosed with ER+ early stage invasive breast cancer from Tata Memorial Centre, India (SA: 69 (20 recurrence)) and from University Hospitals Cleveland Medical Center (NA: 121 (20 recurrence)), along with outcome information were collected. All slides were digitized on either a Ventana DP 200 or a Roche Ventana iScan HT slide scanner. For each image, a conditional Generative Adversarial Network model was employed to segment the individual nuclei, which were used to generate 241 nuclear features including nuclear architecture, shape, orientation disorder, and texture features. Half of the patients (95) were randomly selected as the training set ($S_{tra}$) with the remaining patients as the hold-out validation set ($S_{test}$). Three elastic net regularized Cox regression models ($M_{SA}$, $M_{NA}$, $M_{SA+NA}$) were trained fitting between the nuclear features and disease free survival (DFS) respectively for SA subset, NA subset, and SA & NA set in $S_{tra}$. The top five prognostic features were identified respectively from each of the three models ($M_{SA}$, $M_{NA}$, $M_{SA+NA}$) which were further validated on $S_{test}$ to evaluate their prognostic value in prediction of DFS. Results: We found that the prognostic features identified by $M_{NA}$ and $M_{SA+NA}$ were mostly shape features (three out of five for $M_{NA}$, four out of five for $M_{SA+NA}$), while the prognostic features identified by the model specifically trained with the SA population ($M_{SA}$) were mostly texture features (three out of five), possibly reflecting chromatin patterns in the cell. $M_{SA}$ yielded a better performance (Hazard Ratio=4.99 (p=0.00928, CI=1.32-18.9) from log-rank test between model derived high and low risk categories) on SA population in $S_{test}$ compared to $M_{NA}$ and $M_{SA+NA}$. Conclusion: We found that nuclear histomorphometry features were different between breast cancer patients from South Asia and those from North America. The prognostic capability of the computational pathology-based models for South Asian women could be significantly improved by taking into account population-specific information. An additional independent validation set is needed to confirm the preliminary findings presented here.

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# Association between tumor mutation profile and clinical outcomes among Hispanic Latina women with triple-negative breast cancer

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**Triple-negative breast cancer (TNBC) represents approximately 15-20% of all breast cancer types. It is more common among African American (AA) and Hispanic-Latina (HL) women and has more aggressive course. The biology of TNBC in HL women has been poorly characterized, but some data suggest that molecular drivers of breast cancer might be different. Chemotherapy remains the only option for those patients. There is no clinical tool to help medical oncologist with the decision about appropriate individual chemotherapy, as well as no way to predict long-term outcomes. The aim of the study was to characterize individual patient gene expression profiles and to identify the relationship with clinical outcomes.Patients and Methods: From 2012-2019, we collected formalin-fixed paraffin-embedded tumors (FFPE) from women with TNBC. All specimens were carefully examined by pathologists for adequacy and for a hormonal status. We analyzed gene mutation profiles of collected tumors and associated results with individual patient's clinical history and outcomes.Results: Of 25 patients with TNBC, 24 (96%) identified as HL, one patient as NHL. Twenty-one (84%) had stage III/IV disease, and four (16%) had stage II at the diagnosis. Most commonly mutated genes were: TP53, Notch, AKT, MEP3K, PIK3CA and EGFR. Compared to other international cancer databases mostly included NHW, AA and Asian women, our study demonstrated statistically significant higher frequencies of those among HL women. With TNBC. Also a worse clinical course was among those patients whose tumor had mutations in Notch and PIK3CA. Conclusion: In conclusion, this study is the first to identify the most common genetic alterations among HL women with TNBC. Our data strongly support the notion that molecular drivers of breast cancer could be different in HL women. Therefore, a deeper understanding of the biological mechanisms behind Notch, PIK3CA mutation, might lead to a new treatment approach.**

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# Adaption of the EORTC quality of life breast cancer module for male breast cancer - phase I

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**Background: Approximately 1% of all new cases of breast cancer (BC) occur in men. Care of male BC is largely based on extrapolation from treatment strategies and management of symptoms in women. The impact of BC diagnosis and therapy on Quality of Life (QoL) in women with BC is well documented. Comprehensive, prospective data about QoL in men treated for BC are sparse. Due to the lack of a validated male BC QoL questionnaire, we previously evaluated the QoL of the male BC using the original EORTC QLQ-C30 and breast module QLQ BR23 with "female" items replaced by male-specific items from the EORTC QoL prostate module (EORTC QLQ-PR25). The development of a validated worldwide questionnaire for male BC is sponsored by EORTC QoL Group and will be completed in cooperation with EORTC Breast Group and the International Male BC Program (a cooperation between EORTC-BCG, TBCRC, within the BIG and NABCG networks) Trial design: The evaluation of the QoL issues relevant for male BC, as well as the translation of issues into items to build the tool for QoL assessment in male BC will be carried out through four phases: *1.* A systematic Literature review *2.* Interviews with patients *3.* Interviews with Health Care Professionals (HCP) *4.* Consultation of experts in Oncology and QoL Inclusion criteria: • Histologically proven early BC or metastatic BC in male patients • Age ≥ 18 years • Ability to understand and fill out questionnaires • Written informed consent Exclusion criteria: • Other cancer in the past 5 years except non-melanotic skin cancer • Patients participating in interventional clinical studies with QoL as primary endpoint • Any condition potentially hampering compliance with the study protocol Aims: The study proposes to carry out an evaluation of the QoL issues relevant for male patients with BC, and translating the issues into questions to build the tool for an adequate QoL assessment in these patients. The specific aims are: 1) To carry out an evaluation of the existing EORTC QLQ-BR 45 (adapting for male BC) and for suitability of use in male BC patients 2) To carry out an evaluation of the EORTC QLQ-PR25 (adapting for male BC) for suitability of use in male BC patients 3) To provide recommendations to the EORTC on a suitable assessment approach to assess QOL in male BC Statistical methods: A systematic literature review to assess what factors are unique to male BC patients in influencing their QoL and what QoL measures exist for them will be performed. This will be conducted by reviewing all studies with male BC participants and including investigator brochures describing side effects in male BC patients, as well as by evaluating issues captured by other existing EORTC modules. The final list of potential QoL issues relevant to the male BC will be tested for relevance and importance in semi-structured qualitative interviews with patients and HCP. A total of 2-5 patients per year will be recruited from collaborating hospitals/countries. At least 40 in total will be interviewed before, during, or after treatment for male BC. At least 2 experts/country from the all collaborating centres will be included in the interview to discuss and consider the potential issues. Finally, the issue list will be translated into questions to build the tool for a QoL assessment in male BC patients. Present accrual and target accrual This study started in October 2019. A systematic literature review has been completed. Seventeen centres from worldwide are participating in the study. New centers may still join. Contact information for people with a specific interest in the trial Vesna Bjelic-Radisic**
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# Real-world patient characteristics, utilization patterns, and outcomes of US patients with HR+/HER2- metastatic breast cancer treated with abemaciclib

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**Background Abemaciclib is the most recent oral cyclin-dependent kinase 4 and 6 inhibitor (CDK4&6i) to receive FDA approval to treat hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (MBC). We used administrative claims data to describe patient characteristics, real-world utilization patterns, and outcomes in a US patient cohort upon initiating abemaciclib treatment for HR+, HER2- MBC.Methods This retrospective observational study analyzed medical and pharmacy claims from the IBM® MarketScan® Research Databases (Commercial and Medicare Supplemental) between 1-Jan-2007 to 31-Jan-2020. Patients (≥18 years) newly initiating abemaciclib between 1-Sept-2017 and 31-Oct-2019 were included if they had ≥2 breast cancer diagnoses, ≥2 secondary neoplasm diagnoses, evidence of HR+ disease, continuous enrollment ≥6 months before and ≥90 days after abemaciclib initiation (index date), and absence of therapies suggesting HER2 positivity. Patients were grouped by concomitant therapy (+aromatase inhibitor [AI], +fulvestrant [F], 200mg abemaciclib monotherapy [200mgMono], or +other), and stratified by prior CDK4&6i use (yes/no). Line of therapy (LoT) and reason for discontinuation were not able to be determined from this dataset. Baseline demographic, clinical, and treatment characteristics were summarized with descriptive statistics. Kaplan-Meier methods assessed time-to-discontinuation, defined as a gap of 60-days without an abemaciclib fill, following exhaustion of days' supply from prior fills, or initiation of a different CDK4&6i (ie, palbociclib or ribociclib).Results There were 454 patients included in this analysis (mean [SD] age=57.7 years [10.8]; 98.9% female). Prevalence of new abemaciclib initiators was 29.3% (n=133) in the +AI group, 35.0% (n=159) in the +F group, 10.4% (n=47) in the 200mgMono group, and 25.3% (n=115) in the +other group. Prior CDK4&6i use within each regimen ranged from 37.6% (+AI) to 60.0% (+other). Visceral metastases were present in 50.4% in the +AI group; 49.7% in the +F group; 55.3% in the 200mgMono group; and 47.8% in the +other group. Nearly 75% (n=331) of all abemaciclib initiators began treatment with a 150 mg dose. Chemotherapy use in the 6-month pre-index period was observed for 18.8% in the +AI group; 21.4% in the +F group; 51.1% in the 200mgMono group; and 21.7% in the +other group. Median length of follow-up for all abemaciclib initiators was 321 days (IQR 195-482). Among those without prior CDK4&6i use, the median time-to-discontinuation for the +AI group was not reached (NR) (95% CI, 430 days-NR), the +F group was 531 days (95% CI, 281-NR), the 200mgMono group was 141 days (95% CI, 80-NR), and the +other group was 392 days (95% CI, 300-NR). In the subset with prior CDK4&6i use, the median time-to-discontinuation for the +AI group was 196 days (95% CI, 125-NR), the +F group was 146 days (95% CI, 93-225), the 200mgMono group was 140 days (95% CI, 86-NR), and the +other group was 191 days (95% CI, 113-280).Conclusion These real-world data complement pivotal abemaciclib clinical trial results by examining abemaciclib use among a more heterogeneous patient population in a clinical practice setting. The sizeable number of patients with prior CDK4&6i use, visceral metastases, and prior chemotherapy at abemaciclib initiation suggests many patients had very advanced disease and/or were in later stages of their treatment paradigm. Claims data lack many variables of clinical relevance needed to fully understand disease severity in the study population, such as LoT and degree of endocrine sensitivity; these limitations should be considered when interpreting CDK4&6i administrative claims studies.**

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# Inhibition of breast cancer stem cells in 2- and 3-dimensional culture by novel salinomycin analogs

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**Breast cancer remains one of the leading cancers among women and an estimated 90% of breast cancer deaths are due to metastasis. Cancer stem cells (CSCs) are a sub-population of cancer cells which are responsible for its initiation, progression and metastasis. CSCs are resistant to conventional chemo- and radio-therapies and therefore therapeutic strategies targeting CSCs hold great potential for novel advances in cancer treatment. Salinomycin (SAL) is a naturally occurring polyether ionophore antibiotic which was shown to effectively target breast CSCs. A library of 17 novel SAL analogs was synthesized and screened to identify compounds with improved selectivity against breast cancer stem cells. SAL analogs were either single modified esters or amides in the C1 position or double-modified C20-oxo derivatives. Eight single- and two double-modified analogs were more potent ($IC_{50}$ range of 1.13 ± 0.19 to 3.93 ± 0.39 μM) towards the breast cancer cell line MDA-MB-231 compared to parent SAL ($IC_{50}$ of 4.90 ± 1.60 μM). These analogs induced DNA fragmentation suggestive of apoptotic cell death. Compounds 2 (butyl ester analog of SAL) and 17 (double-modified C20-oxosalinomycin with benzhydroxamic acid) have been chosen for follow-up screening due to their improved activity and selectivity versus parent SAL. This included clonogenic assays to assess the ability of the compounds to affect cell renewal, and wound healing assays to assess cell migratory properties. In both assays, compound 17 showed superior properties over SAL. Furthermore, analog 17 showed improved targeting of breast CSCs in both cell monolayer and organoid culture as assessed in assays measuring the $CD44^+/CD24^-$ stem cell sub-population. Analogs and parent compound were further studied examining (ADP-ribose) polymerase (PARP) cleavage and Bcl-2 levels by immunoblotting. All three compounds induced loss of 116 kDa PARP expression within 48h, with the highest effect induced by analog 17. In addition, treatment with compound 17 caused a decrease in Bcl-2 expression as early as 24 h. Select analogs were next screened against the NCI-60 Human Tumor Cell Line Panel. The described above double-modified analog was found to be more potent than SAL towards all 6 breast cancer cell lines in the panel as well as other tumor types. The present findings highlight the therapeutic potential of SAL analogs towards breast stem cells and support further research and clinical development of these compounds.**

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# Pkc agonism restricts immune suppression and promotes antigen cross-presentation in triple negative breast cancer

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**Immunotherapy has revolutionized cancer treatment showing unprecedented long-term antitumor responses. However, most patients do not respond to immunotherapies due at least partly to immune suppression. Immunotherapy non-responders have high levels of circulating myeloid-derived suppressor cells (MDSCs)- an immunosuppressive innate cell population that suppresses both innate and adaptive immunity. Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancers with poor responses to conventional therapies. TNBC patients harbor higher levels of MDSC populations compared to non-TNBC breast cancer patients. Consequently, TNBC and other solid tumor patients who have high levels of circulating MDSCs respond poorly to immunotherapy. On the other hand, cross-presenting dendritic cells (DCs) are essential to generate an antitumor immune response. Breast cancer patients who harbor higher numbers of these DCs have a better prognosis than patients with lower DC numbers. Several strategies aiming at achieving an effective combination with immunotherapy are under active investigation. The central dogma of these strategies consists of inducing T cells into "immunologically cold tumors" which are defined by having low neoantigen burden and a paucity of T cells and DCs. Hence, strategies that enhance cross-presenting DCs and T cell antitumor potential while altering MDSC's suppressive function are likely to be effectively combined with immunotherapy for a maximum therapeutic benefit. Protein Kinase C (PKC) is a family of enzymes that play a critical role in cell signaling controlling the balance between survival and cell death. With the discovery in 1980s that PKC is a receptor for the tumor-promoting phorbol esters, the dogma that PKC is an oncoprotein was fueled. This led to more than three decades of failed clinical trials trying to inhibit PKC in cancer. Recent evidence suggests that PKC isozymes are generally inactivated in cancer and that most mutations affecting PKC isozymes are in fact loss of function mutations. This suggests that PKC is a tumor suppressor rather than an oncoprotein and that strategies in cancer treatment should focus on restoring PKC, rather than inhibiting it. To date, the role of PKC isozymes in antitumor immunity is unknown. Herein, our novel data suggest that PKC agonism using established agonists reduced MDSC generation from bone marrow (BM) progenitors specifically via activation of the PKC delta (PKCδ) isoform. PKC agonism induced MDSC differentiation to cross-presenting CD103+ DCs both *ex-vivo* and *in vivo*. Additionally, PKC agonist-treated purified MDSCs lost their suppressive capacity on CD8+ T cells in both *in vitro* and *in vivo* suppression assays. In contrast, PKC agonism significantly increased the generation of cross-presenting DCs (cDC1) from BM progenitors. Treatment of TNBC-bearing C57BL/6J mice with PKC agonist PEP005 markedly reduced tumor burden by decreasing the frequencies of M-MDSCs in tumor, spleen, and bone marrow while increasing cDC1 frequencies in tumor and spleen. These findings propose PKC as a common pathway in myeloid cells to tip the balance from immune suppression to effective antitumor immunity.**

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# Homologous recombination deficiency score predicts patient characteristics and outcomes of triple negative breast cancer in China

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**Background**Previous studies found homologous recombination deficiency (HRD) score could predict response to platinum-containing neoadjuvant chemotherapy in patients with triple negative breast cancer (TNBC), but its predictive effects of adjuvant chemotherapy is unexplored.

**Methods** We developed the 3DMed-HRD algorithm, which combines loss of heterozygosity score (LOH), telomeric allelic imbalance score (TAI) and large-scale state transition score (LST) to characterize genomic instability using over 10000 SNPs, adjusted by tumor ploidy and purity. HRD positive is defined by deleterious mutation in BRCA1/2 or HRD score above the threshold (cut-off ≥30). Tumor samples were retrospectively obtained from 149 TNBC patients who received platinum-based (paclitaxel and cisplatin, TP) or platinum-free (cyclophosphamide and adriamycin, EC) adjuvant chemotherapy after surgery. All patients underwent the 3DMed-HRD testing.

**Results**In 25.5% (38/149) of TNBC patients deleterious germline or somatic mutation in BRCA 1/2 was detected. HRD results were available for all patients and 81of the 149 patients (54.4%) were defined as HRD positive. HRD-positive patients had younger age at diagnosis (median 46.7 years vs 51.5 years, P=0.002), higher differentiated (59.8% vs 39.5%; p=0.037), lower N-stage (55.7% vs 33.3%; p=0.006) and more common at high expression of Ki67 (64.7% vs 39.0%; p=0.015). In TP treatment group, patients with HRD positive tumors had a lower 5-year recurrence rate although the difference was not statistically significant (8.82% vs 16.1%; p=0.463). Patients in EC treatment cohort, 5-year recurrence rate was comparable between HRD positive and negative subgroups (15.4% vs 13.3%; p=1.0). In the 81 patients in HRD-positive cohort, patients in TP treatment group showed a numerical lower 5-year recurrence rates compared with patients in EC treatment group (8.82% vs 15.4%; p=0.489).

**Conclusions**54.5% patients were characterized as HRD positive in TNBC patients in our cohort. HRD was associated with clinicopathologic characteristics. Our results suggested that HRD status mightguide chemotherapy treatment decisions. Prospective validation with larger sample size is needed.

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# Correlation of Tumor-infiltrating lymphocytes with clinicopathological features and treatment outcomes in non-metastatic breast cancer patients

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Background Breast cancer is the second most common cancer in the world and most frequent among women. Tumor-infiltrating lymphocytes (TILs) can impact tumor progression and response to therapies. Here we aimed to study TILS using the International Immunooncology Biomarkers Working Group guidelines and correlating the TILS with clinicopathological characteristics, disease free and overall survival in non-metastatic breast cancer patients. Methods Non metastatic breast cancer patients (N = 86) who presented to our department between (2013 - 2015) were retrospectively evaluated. The assessment of TILS distribution was based on the TILS International Working Group 2014 recommendations. The eligible patients were reviewed retrospectively regarding the demographic status and clinical parameters and primary treatment information were extracted from the medical records. For all of the available patients, disease-free survival (DFS) and overall survival (OS) were calculated. Results In the study the majority of the patients were 45 years of age or less. The TILS percentage was measured using image analysis. All samples had a range of 1-100%, with a mean 22%. There was 9.3% of the patients having lymphocyte predominant breast cancer (≥50%), while 90.3% had TILS percentage of <50%. Dividing the patients into low (0-20%), intermediate (20-<50%) and high (50-100%). TILS percentage gave us 62.7%, 27.9% and 9.3% of the patients respectively. The distribution of TILS according to age showed a trend towards decreasing TILS with increasing age, and this was not statistically significant. The majority of tumors in the study were T2 (60.5%) followed by T1 (15.1%).. T1 and T2 tumors had significantly higher TILS percentages compared to T3 and T4, mean 24.94% versus mean 13.37% respectively. Using the t-test this showed a p<0.006. The majority of patients in the study were N1 at 62.8% followed by an equal percentage of 17.4% as both N0 and N2. Patients who were N0 had a significantly higher TILS percentage when compared with N1 and N2, mean 33.07% versus mean 20.0% respectively. This was statistically significant using the t-test with a p<0.032 (table 1). Also in this study, there were 74.4% tumors of the luminal subtype, 11.6% of the Her-2 enriched subtype and 12.8% of the triple negative subtype. Although there was no statistically significant correlation between any molecular subtype and TILS, there was a tendency for Her-2 enriched tumors and triple negative tumors to have a higher percentage of TILS in comparison with luminal subtypes as seen in table 1. Table (1): )

| Final | N | Tumor infiltrating lymphocytes (TILS %) | | |
|---|---|---|---|---|
| Min. - Max. | Mean ± SD. | Median | | |
| ER | | | | |
| Negative (0) | 21 | 2.0 - 100.0 | 27.33 ± 28.93 | 18.0 |
| Weak (1+) | 6 | 3.0 - 40.0 | 19.67 ± 16.29 | 17.0 |
| Moderate (2++) | 13 | 5.0 - 62.0 | 24.38± 20.63 | 17.0 |
| Strong (3+++) | 45 | 1.0 - 87.0 | 19.78 ± 17.92 | 17.0 |
| N/A | 1 | | 5.0 | |
| PR | | | | |
| Negative (0) | 28 | 2.0 - 100.0 | 24.86 ± 26.19 | 16.50 |
| Weak (1+) | 3 | 6.0 - 12.0 | 8.33 ± 3.21 | 7.0 |
| Moderate (2++) | 17 | 1.0 - 87.0 | 22.12 ± 22.10 | 17.0 |
| Strong (3+++) | 37 | 1.0 - 62.0 | 21.68 ± 17.55 | 18.0 |
| N/A | 1 | | 5.0 | |
| HER-2 | | | | |
| Negative (0) | 44 | 1.0 - 100.0 | 22.84 ± 22.97 | 17.50 |
| Weak (1+) | 1 | | 6.0 | |
| Moderate (2++) | 11 | 4.0 - 87.0 | 25.09 ± 23.76 | 25.0 |
| Strong (3+++) | 23 | 2.0 - 65.0 | 18.70 ± 17.13 | 12.0 |
| N/A | 7 | 4.0 - 53.0 | 26.71 ± 22.12 | 25.0 |
| BC subtypes | | | | |
| Luminal A | 40 | 1.0 - 62.0 | 21.28 ± 17.92 | 17.50 |
| Luminal B | 24 | 2.0 - 87.0 | 19.75 ± 18.90 | 13.50 |
| Her2 Enriched | 10 | 4.0 - 65.0 | 23.20 ± 21.36 | 16.50 |
| Triple -ve | 11 | 2.0 - 100.0 | 31.09 ± 35.08 | 19.0 |
| N/A | 1 | | 5.0 | |

We noticed that there is a subgroup of patients with exceptionally high TILS, (called LPBC with TILS ≥50%) had a beneficial response to treatment and confers additional survival benefit; every incremental increase of 10% also resulted in benefit to treatment and delayed relapse. High level of TILS associated with delayed relapse and a survival benefit. Conclusions We demonstrated that increasing TILS confer a relapse free benefit of breast cancer patient, regardless of the tumor subtype, indicating that TILS represent an breast cancer the patients. Keywords Tumor-infiltrating lymphocyte, Breast cancer, outcome of management

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# Pre-diagnosis major life stressors and breast cancer outcomes

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**Background: Multiple studies have identified an association between diagnosis of breast cancer and post-diagnosis psychological distress. Some have taken a step further, identifying predictive markers of distress in diagnosed patients and interventions to minimize post-diagnosis distress. Data regarding pre-diagnosis psychological distress and its impact on surgical decision making and clinical outcomes in the breast cancer population are limited. Here, we assessed pre-diagnosis major life stressors and breast cancer outcomes in a single-center population.**

**Methods: Patients with newly diagnosed stage 0-3 breast cancer seen at Mayo Clinic Florida between June 11, 2018, and October 7, 2019, were included. Prior to their initial visit, patients were administered a voluntary telephone survey regarding the incidence of major life events and stressors during the 18 months preceding their diagnosis. Demographic data including age and ethnicity were also included. Subsequent clinical outcomes were obtained through retrospective chart review. Clinical outcomes were assessed with descriptive statistics. Chi-square tests were used to compare subgroups, with $p < 0.05$ considered statistically significant.**

**Results: Of 469 patients seen for a new breast cancer diagnosis, 222 patients completed the intake survey and met inclusion criteria. Median age was 60 (27-84) years. 80.6% of patients were white, 7.7% were black, 5.4% were Asian/Pacific Islander, and 2.3% were Latino. Over 95% endorsed having some form of social support. 51.3% reported experiencing a major life event prior to breast cancer diagnosis. Of these patients ($n$ = 114), 43.9% denoted this stressor as family-related, as compared to 20.2% citing non-breast cancer illness, 14.9% claiming relationship stress, and 14% describing employment-related stress. Only 1.8% endorsed stress caused by financial concerns. Multiple major life events were reported by 10.8% of all included patients. Subgroup analysis of the patients with pre-diagnosis stress revealed a similar demographic distribution to the overall sample. Compared to the subgroup without pre-diagnosis stress ($n$ = 108), there were more patients with carcinoma in situ and stage T3/T4 disease (21.1% versus 13.0%, $p$ = 0.11) and 11.4% versus 10.2%, $p$ = 0.77), respectively) in the subgroup with pre-diagnosis stress, although these differences were not statistically significant. More patients with pre-diagnosis stress elected to undergo mastectomy (34.2% versus 22.2%, $p$ = 0.048) as compared to the group without stress.**

**Conclusions:**

**With over half of sample patients reporting pre-diagnosis major life stressors, psychological distress is prevalent prior to breast cancer diagnosis and should be considered as a factor for early intervention, such as psychological and financial counseling, during breast cancer evaluation. The sample population was predominantly white and resource-rich in terms of financial and social support, highlighting a need for characterization of pre-diagnosis psychological distress in more ethnically diverse and/or resource-limited settings. Although additional study is recommended, current data suggest possible associations between pre-diagnosis psychological distress and treatment decision making, particularly the decision to pursue mastectomy.**

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# Local recurrence and aesthetic outcome following conventional breast conserving surgery and oncoplastic breast surgery: A randomized controlled trial

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**Oncoplastic breast surgery (OPBS) is offered to patients with early breast cancer. Local (LR) recurrence following OPBS reported only in case series till date. There is no RCT comparing the incidence of local recurrence (LR) following conventional BCS & OPBS. Aim: Evaluation of incidence of LR & cosmesis following conventional BCS & OPBS Methods: After obtaining IRB approval, over a 2 year period, 94 consenting Women with breast tumors ≤ 4cm were randomised to BCS (group 1: 47 patients) or OPBS (group 2: 47 patients). Patients with no suspicious axillary nodes underwent SLNB & those with nodal metastasis underwent ALND. All surgeries were performed under general anaesthesia. Patients in group 1 underwent 'standard' wide local excision with 1 cm tumor free margin following which wound was closed with absorbable sub cuticular sutures. Patients in group 2 underwent level 1 or level 2 oncoplastic breast surgery using volume displacement techniques wherein breast parenchymal plates were mobilized on either sides from underlying pectoral fascia and overlying skin. The cut edges were approximated by absorbable interrupted sutures so as to obliterate the cavity following which skin was closed with absorbable sub cuticular sutures. Cavity margins were marked with titanium clips to facilitate planning of radiotherapy. All patients were discharged on postoperative day 1 & were followed up as per standard protocol. At follow up patients were assessed for surgical site infection, seroma etc. Cosmetic & aesthetic outcome were evaluated by patient herself, a female nurse & surgeon 3 & 6 months after surgery. Aesthetic score was assessed individually using the predetermined criteria viz. shape with brasserie, shape without brasserie, symmetry to the opposite breast, mobility, consistency, position of inframammary fold & NAC and overall appearance. All patients received whole breast RT with boost to cavity site followed by systemic treatment. Statistical Analysis: Qualitative & quantitative data was expressed as frequency , mean +SD, and median (min-max). Categorical & continuous variables were compared among the groups by chi-square, Fischer exact test, independent t test or Wilcoxon rank sum test . P value <0.05 was considered as significant. Results: Mean age of patients was 48.78 years (range 23-76 years SD: 12.29). Tumor size ranged from 1-4 cm ( mean: 2.9 cm; median 3 cm in group 1 & mean 3.14 cm; median 3 cm in group 2). Primary tumor was T1 in 17 (18 %) & T2 in 77 (82%). Node status was N0 in 79 (81%) patients and N1 in 15 (19%). 66 (69.6%) tumors were ER and PR +ve, 21 (22.3%) were triple negative and 8 (8.5%) were Her2 neu positive. 91 (93.61%) were invasive carcinoma and 3 (6.39%) were DCIS. Seven patients (7.4%) received NACT. 79 (81.4%) underwent SLNB and rest underwent ALND. Patient & tumor characteristics were similar in both groups. Local Recurrence: At a mean follow up of 28.02±8.82 ( range 13-47) months, 5 patients (5.3%) developed LR ( 1 in group 1 (2.1%) and 4 in group 2 (8.5%). However, this difference was not statistically significant. Three (3.19%) of these patients ( 1 in group 1 and 2 in group 2) developed systemic metastasis and died. Patients' satisfaction with surgery and comfort with brassiere were significantly higher in group 2. However, there was no difference in sexual and social life among the two groups. Shape of the breast with & without brassiere, and over all appearance were rated to be significantly better in group 2 by both the surgeon and nurse. Conclusions: Contrary to published literature, in this RCT, LRR following OPBS is slightly higher as compared to conventional BCS. But the difference is not statistically significant. Larger trials with longer follow up are needed to confirm this observation. Cosmetic satisfaction and aesthetic outcome were significantly better with OPBS**

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**Introduction and clinical validation of metrology standards for immunohistochemistry (IHC); New tool for standardization of estrogen receptor (ER) IHC assay in breast cancer**

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**Traceability of measurement to a higher order reference standard is a foundation of laboratory testing. There is as yet no method for creating reference standards for cellular proteins in situ in an analogous fashion as for soluble analytes. At present, IHC laboratories produce results for breast cancer hormone receptors without connection to a reference standard. Not surprisingly, high rates of testing variation as well as discrepancies among IHC laboratories have been reported. To address this need, we developed a system of measurement traceability using a linked fluorescein tag for creating reference standards for any cellular analyte and, as a first test, validate it for estrogen receptor (ER) testing. In this study, the newly developed ER standard defines and compares the thresholds separating "high positive", "low positive", and "negative" tests according to updated ASCO/CAP guidelines as detected by clinical IHC laboratories in a national external quality assessment survey. This reference standard utilizes NIST Standard Reference Material (SRM) 1934 as a universal IHC standard. We calculated ER concentration based on a linked fluorescence measurement traceable to NIST SRM 1934 as each ER is linked to a single fluorescein, and fluorescein concentration equals ER concentration. Each laboratory's lowest detected ER concentration (i.e. "limit of detection", LOD) was compared to their results with 80 tumor samples enriched for triple negative breast cases. For the Canadian Immunohistochemistry Quality Control (CIQC) ER proficiency testing run, calibrator sets with peptides for the SP1, EP1, and 6F11 epitopes were created. The various concentrations were pipetted onto histology slides used by CIQC to place its 80-case breast cancer tissue microarray. These slides were stained by participating laboratories using their routine ER IHC protocols and returned to the CIQC. For the purpose of this study, Histology Score and ASCO/CAP categorical scoring recommendation was used for the readout. Results with SP1 clone are reported here because it was employed by overwhelming majority of laboratories. A total of 3,038 readouts were included in the analysis. Most IHC laboratories had a LOD between 10,000 – 25,000 molecules ER per microbead. Highly sensitive ER assays (low LODs) detected more positive cases while those with poorly sensitive assay detected fewer. The LOD correlated with the percent positive cases ($R^2$= -.767, $p < 0.0001$, Spearman Correlation) as well as with cumulative individual laboratory Histology Score ($R^2$= -.612, $p < 0.0001$, Spearman Correlation). The tumor samples accounting for this difference were principally "low positive" (ASCO/CAP classification) while ER-high positive tumors were less affected. Although the concept of a non-quantitative IHC LOD has been introduced with critical assay performance controls (iCAPCs, e.g. germinal center cells in the tonsil for ER), there were no tools until now to actually measure LOD for ER IHC testing. With the calibrators introduced here, it is now possible to measure the LOD for ER IHC assays. Furthermore, our data show that ER low positive and some cases of ER high positive breast cancers are highly affected by the variability of analytic sensitivity between clinical IHC laboratories. These data argue for the urgent need to standardize testing to a defined analytic sensitivity range, which is now possible for the first time. Beyond inter-laboratory standardization, known measured LOD also enables: i) methodology transfer from clinical trials to clinical laboratories; ii) determination of optimal analytical sensitivity to produce assays with highest clinical and analytical validity, and iii) daily monitoring of analytical sensitivity for each tested IHC slide.**

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# Enrollment of older metastatic breast cancer patients in clinical trials

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Background : About 40% of breast cancer cases occur in women 65 years old (yo) or older and 20% in women over 75 yo. These numbers are expected to increase in the near future. Ironically, older patients remain underrepresented in clinical trials with no improvement in the past decade, although they may present different efficacy/toxicity profiles compared with younger adults. In this context, real life cohorts may bring valuable insight to identify potential barriers to recruitment of older patients with metastatic breast cancer (MBC) in clinical trials. Methods : We used the national Epidemio-Strategy and Medical Economics (ESME) MBC Data Platform, a multi-center real life database using a retrospective data collection process in 18 French Cancer Centers. Cases selected were adult patients with MBC whose first metastasis was treated between January 1st, 2008 and December 31st, 2016. We selected MBC women over 70 yo at the time of MBC diagnosis, with at least one line of systemic treatment and no other cancer in the 5 years before MBC. The primary objective was to describe factors associated with enrollment in clinical trials in older patients, using a multivariable Cox model. Factors included in this model were age (continuous, and by class), period (2008-2011 vs 2012-2016), phenotype (ER+, HER2+, or ER- HER2-), ECOG Performance Status (PS), treatment, metastatic sites (brain, visceral, nodes/bone only) and number, and volume of hospital activity. No geriatric description could be extracted from the database. Results : There were 5846 patients ≥70yo (median age 77) and 15892 patients < 70 yo. Of the older ones, 245 (4.2%) were enrolled in a clinical trial in first line compared with 1602 (10%) for younger ones. Most of the older patients in this cohort (66%) had ER+ HER2+ disease, half had visceral metastases (< 3 metastatic sites in 82%). Median follow-up of older patients was 46.3 months; 95%CI 44.8-49.0. Cause of death was related to disease in 1155 (33.9%) older patients, and related to another cause or unknown in 2156 (63.3%), data were missing for 2441 patients. Median overall survival (OS) was 34.1 months in the older population, 95%CI 32.9-35.4, and specific overall survival was 70.8 months, 95%CI 66.3-80.0. Significant factors identified in the multivariable analysis for enrollment in 1st line treatment clinical trial ≥70 are shown in table. Volume of activity was not identified as one.

| Variable | OR | 95%CI |
|---|---|---|
| Age vs 70-75 75-80 80-85 85+ | 0.74 0.47 0.17 | 0.54-1 0.31-0.71 0.06-0.37 |
| MBC diagnosis period vs 2008-2011 2012-2016 | 1.67 | 1.23-2.27 |
| Phenotype vs Others HER2+ | 1.76 | 1.26-2.45 |
| PS vs 0 1 2-4 | 0.71 0.15 | 0.5-1 0.08-0.26 |
| Treatment | 4.88 5.25 | 3.08-7.9 3.48-8.14 |
| Chemotherapy vs others | 4.88 | 3.08-7.9 |
| Targeted treatment vs others | 5.25 | 3.48-8.14 |

By multivariate analysis, participation of older patients to a clinical trial was associated with an increased OS (HR 0.7; 95% CI 0.6-0.8) but not with a better breast cancer specific survival (HR 0.94; 95%CI 0.68-1.29). Conclusions : In this large real-life database, few older MBC patients were enrolled in a trial compared with younger ones. Factors associated with such participation to clinical research were younger age (< 80 yo), good PS, HER2+ disease, and investigational treatment consisting of chemotherapy or targeted therapy. There was a small improvement in accruing older patients between 2007-2011 and 2012-2016 (2.6% versus 5.5%). Most of these factors raise questions on drug availability and perceived potential benefits by investigators and medical teams. Accrual of older patients with cancer in other disease types should be more encouraged.

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# Immunomodulation with dexamethasone in neoadjuvant chemotherapy for triple negative breast cancer

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**Introduction: The immunomodulatory effects of dexamethasone and prednisone have been a staple of chemotherapy regimens since Mustargen, Oncovin, procarbazine, prednisone (MOPP) was used to treat lymphomas in 1963. Since then steroids have become ubiquitous in chemotherapy and were transitioned to an anti-nausea medication in solid tumor therapies and now anti-inflammatory therapies for common side effects of immune checkpoint inhibitors. While some modern immunomodulator therapies like rituximab and mycophenolate mofetil work through specific mechanisms, steroids have a much more non-specific effect working through a wide variety of pathways. Traditionally, chemotherapies such as paclitaxel, doxorubicin, and cyclophosphamide have been thought to induce cell death purely through cell-autonomous mechanisms such as DNA damage or interference with accurate chromosome segregation during mitosis. More recently, the strong correlation between tumor-infiltrating lymphocytes (TILs) and pathological complete response (pCR) to chemotherapy has been demonstrated. We hypothesized that dexamethasone use may adversely affect the efficacy of chemotherapy due to down-regulation of TILs. Therefore, we investigated the effects of dexamethasone exposure levels on response rates to neoadjuvant therapy of triple negative breast cancer (TNBC) with doxorubicin, cyclophosphamide and paclitaxel. We evaluated TNBC due to its high sensitivity to chemotherapeutic agents in the neoadjuvant setting and because pCR following neoadjuvant chemotherapy is an indicator of better long-term outcomes in TNBC patients. Dexamethasone use as an anti-emetic in the neo-adjuvant setting is highly variable, often being substituted for with olanzapine.**

**Methods: All patients with TNBC who received neo-adjuvant chemotherapy with doxorubicin and cyclophosphamide (AC) between January 1st, 2012 and November 31st, 2018 at The James Comprehensive Cancer Center at The Ohio State University were included in this retrospective study, which totaled 174 patients. We omitted patients who received carboplatin with the paclitaxel, or received other experimental therapies during the neoadjuvant period. The primary exposure was dexamethasone dose by chemotherapy cycle, and the primary outcome was pCR. We used logistic regression to perform an intent-to-treat analysis, and defined $P<0.05$ as the significant level. We adjusted for diabetes status, age, and metformin prescription.**

**Results: We have found that there is no statistical or apparent difference in pCR by average dexamethasone dose per neoadjuvant chemotherapy cycle ($P = 0.51$), including when adjusting for diabetes status, metformin prescription and age ($P=0.85$). We found that there was sufficient variation in dexamethasone dose per cycle with the main mass of observations between 10 and 60 mg/cycle.**

**Conclusions: We did not detect a difference in dexamethasone dose per neoadjuvant chemotherapy cycle between patients who did or did not achieve pCR. Thus, based on this retrospective analysis, the use of dexamethasone as an anti-emetic for triple negative breast cancer may not be harmful or beneficial in terms of the pathologic response to chemotherapy. This suggests that its use as an agent to mitigate side effects from chemotherapy is reasonable.**

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# Multi-country clinical validation of can assist breast in Europe indicates robustness of the test

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**Background: CanAssist Breast (CAB) is a prognostic test for early stage hormone receptor positive breast cancer patients, that predicts risk of distant recurrence in five years post-diagnosis. Its support vector machine-based algorithm utilizes immunohistochemistry profiles of five biomarkers involved in tumor biology (CD44, ABCC4, ABCC11, N-Cadherin and pan-Cadherin) and three clinical parameters (tumor size, grade, and node status) to categorize patients into low- or high-risk of distant recurrence. CAB was developed on Indian patients, and has been validated in Indian and US patients. The current study presents first ever multi-country, blinded, retrospective validation of CAB. Methods: A total of 669 patients' breast tumors from Austria (n=327), Spain (n=292) and Italy (n=50) diagnosed 5-10 years ago along with known clinical parameters were included. CAB was performed on the formalin fixed tumor samples using Roche's automated immunohistochemistry platform at OncoStem's CAP accredited reference laboratory in India. CAB risk predictions were matched with the clinical outcomes by the respective hospitals. Distant Metastasis Free Survival (DMFS), negative predictive value (NPV) and Hazard Ratio (HR) were computed from Kaplan-Meier survival curves using MedCalc software. Results: The median age of the cohort was 60 years (range: 28-92 years), with only 28% of patients aged < 50 years. The cohort had equal proportions of stage I and stage II patients and 19% of patients with poorly differentiated tumors (G3). Amongst stage II patients 57% had three nodes positive (N1) disease. Total cohort had of 72% N0 patients and 28% N1 patients. The DMFS of this cohort was 95% in low-risk versus 82% in high-risk category ($p < 0.0001$). The recurrence rate was 5% in low-risk category as against 18% in high-risk category. The risk stratification of patients treated with endocrine therapy alone (68%) was similar to chemo-endocrine therapy (32%) treated patients, both had 95% DMFS in low-risk category. Subtle differences in the NPV was observed across different European patient cohorts: Spain-96%, Italy-100%, Austria-93%. The performance of CAB in European cohort was comparable to the mixed validation cohort of ~1100 patients from India and US, with identical DMFS of 95% in the low-risk category. In a sub-cohort of T1N0 patients (50%),**

**the DMFS in low-risk group was still higher at 97%. In the multivariate Cox proportional hazards model, CanAssist Breast risk score had the highest and significant hazard ratio of 2.9 (p=0.0013, CI: 1.5-5.5) over clinical parameters (node, grade, tumor size), age and type of therapy (endocrine vs. chemo-endocrine). Conclusion: The current study demonstrates the robustness of risk prediction by CAB in an European cohort of diverse nationalities and ethnicities. Similar accuracy of CAB in the Indian and European cohort emphasizes that CAB based risk predictions are driven by tumor biology and are independent of conventional prognostic factors.**

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**Factors influencing choice of contralateral prophylactic mastectomy in patients with unilateral breast cancer**

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**Background: Rates of contralateral prophylactic mastectomy (CPM) have more than doubled in the past decade irrespective of inherited predisposition related to high penetrance genes. Increasing numbers of women with unilateral breast cancer are opting for removal of both the affected ipsilateral and contralateral 'normal' breast when otherwise suitable for breast conserving surgery. Reasons for this surge in women choosing maximal surgery are poorly understood but trends in CPM are most evident for younger patients (<40 years) and those with non-invasive and stage I disease. Patient decision-making and surgeon interaction may be dominated by 'fear of recurrence' and 'avoidance of decisional regret' with healthcare professionals feeling pressurized to accede to demands in the wider context of patient-centered care. Methods: A retrospective analysis examined breast cancer patients undergoing unilateral mastectomy with or without CPM between January 2014 and December 2018. Patient information was extracted from an electronic database with documentation of demographic/clinico-pathological details for each group. A cross-sectional survey was undertaken that was compiled and based on validated questionnaires and responses to defined statements generated using a 5-point Likert scale. This questionnaire was posted to patients and contained specific sections relating to reasons for requesting CPM or not. The questionnaire contained a section on pre-surgical discussion and whether the surgeon's opinion influenced decisions not only for CPM but also immediate breast reconstruction. Results: A total of 403 unilateral therapeutic mastectomy procedures were performed during the study period. The annual number of CPM cases increased by 50% from 14 in 2014 to 20 in 2018. The total number of CPM cases over this period of 5 years was 78 - mean rate of 16.2% per annum. Amongst those CPM patients who were sent questionnaires (n=75), response rate was almost two-thirds (47/75=63%); more than half of respondents (n=46) had simultaneous CPM with immediate breast reconstruction (IBR) whilst 13 patients had immediate CPM without reconstruction. A total of 16 patients had delayed CPM with (n=10) or without (n=6) IBR. The most common reason for seeking CPM was prevention of recurrent breast cancer (mean score 4.5) followed by a desire for "peace of mind" (mean score 4.4). The third most cited reason was to enable patients to move on with their lives as soon as possible (mean score 4.2). Interestingly, patients undergoing CPM were more likely to have no regrets about their decision than patients who chose not to undergo CPM either as a delayed or immediate procedure (mean score 3.0). The least popular reasons for requesting CPM were to avoid regular check ups (mean score 2.7) and to be balanced and minimize chances of back pain (mean score 2.6).Conclusion: This study revealed a relatively high rate of CPM attributable primarily to patient-driven factors including perceived risk of contralateral recurrence, desire for 'peace of mind' and resumption of a normal lifestyle. Patients did not sense surgeons being against patient-led proposals for CPM. Patient education is crucial in promoting psychological comfort without the necessity for surgical risk reduction and is consonant with a patient-centric approach that addresses issues of surgical safety and quality of life.**

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# Treatment naïve patient-derived xenograft model compared to the post-neoadjuvant model from the same patient diagnosed with triple negative breast cancer

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**Triple negative breast cancer (TNBC) is an aggressive and difficult-to-treat subtype of breast cancer that typically exhibits rapid growth rates, high rates of metastasis, and resistance to commonly used oncological drugs. Historically, cell lines have been utilized in order to study TNBC; recently, however, patient derived xenografts (PDX) models have evolved as the new standard that offers a translational approach to the research and subsequent treatment of breast cancer. Here, we characterize two novel PDX models for TNBC: TU-BcX-4QA and TU-BcX-4QAN. The former derived from a biopsy specimen prior to any therapies, and the latter derived from a mastectomy of the same patient after three rounds of AC-T therapy (doxorubicin and cyclophosphamide followed by paclitaxel). In establishing a treatment naïve and post-neoadjuvant therapy PDX model pair, we created a prime model that examines the effects of chemotherapy on tumor heterogeneity, clonal selection, and the overall characteristics of a tumor. Furthermore, we examined the evolution of the characteristics of the post-neoadjuvant therapy PDX model after continual passaging within the SCID/Beige murine models. Through serial implantation in SCID/Beige murine models for tissue propagation, we observed that TU-BcX-4QAN consistently had a higher tumor growth rate and a smaller number of metastatic lesions that developed on the lungs and liver in comparison to the TU-BcX-4QA model. In treating the tumor derived cell lines with NCI-approved oncological drugs, we distinguished the variations in their responses to various, commonly used therapies, and determined that TU-BcX-4QAN had a more resistant profile. Using qRT-PCR, we further discovered the differences between the two models in their contrasting gene expression; preliminary data indicates an increase in certain mesenchymal genes (CDH2, VIM, and ZEB2), a decrease in cell cycle genes (p21, p53), and an increase in proliferation genes (MK167) in TU-BcX-4QAN compared to TU-BcX-4QA. Additionally, serial passages are correlated with a decrease trend in human gene expression within TU-BcX-4QAN. This suggest that treatment can select for certain cancer cells within the primary tumor that allows for the growth of a different tumor altogether and illustrates both the advantages and limitations of the TU-BcX-4QA andTU-BcX-4QAN model pair in translational research.**

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# A phase II trial with safety run-in of neoadjuvant therapy with an aromatase inhibitor in combination with durvalumab (MEDI4736) in postmenopausal patients with hormone-receptor-positive (HR+) breast cancer

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**Background: HR+ breast cancer has a long dormancy and steady rate of recurrence over decades from initial diagnosis. It is a misconception to think that HR+ disease has good prognosis since long term PFS and OS are only a few percent better for HR+ disease compared with HR- disease over a follow up of 20 years. Neoadjuvant endocrine therapy has been shown to be equivalent to chemotherapy but less toxicity. Aromatase inhibitors have also been shown to have immunomodulatory activity. In order to improve short term and long term outcomes, we started an investigator-initiated study using anastrozole plus the anti-PD-L1 antibody durvalumab in the neoadjuvant treatment of HR+/HER2- breast cancer. Methods: This is an open label, phase II with safety run-in trial conducted at Moffitt Cancer Center. The primary objective is modified Preoperative Endocrine Prognostic Index (mPEPI) score of 0. Secondary objectives are clinical response rate, pathologic response rate, recurrence free survival. Correlative objectives include phenotypic changes in immune cells and cytokine patterns pre-, during- and post-treatment. Inclusion criteria include postmenopausal females, ECOG 0-1, HR+ with Allred score of 6 to 8, HER2-, cT2-cT4, any N, M0, appropriate lab values, agreeing to research biopsies. Exclusion criteria include multicentric disease, bilateral disease, autoimmunity or inflammatory disease, use of immunosuppressant, known HIV, Hep B/C infection, history of TB, h/o interstitial lung disease or pneumonitis, clinically significant cardiovascular disease, mean QTcF > 470 ms. Patients will receive anastrozole 1 mg PO daily for 6 months concurrently with durvalumab 1500 mg IV every 4 weeks for 6 cycles, followed by definitive surgery. Results: This is a trial in progress. However, limited preliminary results will be presented. Conclusion: The combination of anastrozole and durvalumab may lead to improved mPEPI score in the short term and improved RFS in the long term.**

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# Breast cancer and COVID-19: Impact of active treatment on severe outcomes

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**Background: Several reports have observed that cancer patients who recently underwent chemotherapy or surgery had a higher risk of severe events compared with patients without cancer. Limited data is available on outcomes in specific cancer types, as well as the impact of non-cytotoxic systemic treatment, such as targeted therapy and hormonal therapy on severe outcomes. We aim to identify whether active treatment impacts severe outcomes (rate of hospitalization, ICU admission, intubation, and death) in breast cancer patients. Methods: We conducted a multicenter study in the state of Louisiana, throughout the Ochsner Health System, in both tertiary and non-tertiary centers. Patients must carry a diagnosis of breast cancer, and have a completed SARS-CoV-2 test between March 1st and April 30th, 2020. Chi-squared and Fisher's exact tests were performed to compare the proportion of patients experiencing severe outcomes between treatment groups. Results: As of April 30, 2020, a total of 70 patients with breast cancer who had a positive SARS-COV-2 test were identified. Median age 64.5, median BMI 30.8, 62.9% (n=44) black, 27.1% (n=19) current/former smokers, HTN (n=52) and DM2 (n=22) were the most common comorbidities, and 12.9% (n=9) of patients had stage IV disease. Of these patients, 58.6% (n=41) were on hormonal treatment, and another 12.9% (n=9) were receiving other forms of systemic therapy (cytotoxic chemotherapy or targeted therapy). In terms of severe outcomes, 32.9% (n=23) of patients required hospitalization, 8.6% (n=6) required ICU admission with 7.1% (n=5) patients requiring intubation, 11.4% (n=8) of patients died. There was not a statistical difference in rate of severe outcomes (rate of hospitalization, ICU admission, intubation, and death) among breast cancer patients receiving active treatment (chemotherapy, targeted therapy, or hormonal therapy) vs those receiving no active treatment. There was also no difference in terms of severe outcomes by race. Conclusion: With an ongoing global COVID-19 pandemic, it is important to identify how the treatment and management of cancer impacts COVID-19 outcomes. This small cohort does not identify active treatment as a risk factor for increased rate of severe outcomes in patients with breast cancer. Further analyses describing impact of specific hormonal and chemotherapy regimens on risk of hospitalization and death will be completed by time of presentation.**

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# A scoping review characterizing “choosing wisely” recommendations for breast cancer management

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Background: Choosing Wisely (CW) ® was created by the American Board of Internal Medicine (ABIM) to promote patient-physician conversations about unnecessary medical tests and treatment. It is estimated that 20% of healthcare cost is wasted on ineffective interventions. National societies such as American Society of Clinical Oncology, Americal Society of Breast Surgeons, and American Society for Radiation Oncology have developed lists of recommendations within the Choosing Wisely initiative to to eliminate non-evidence based practices and improve patient outcomes. Similarly, other countries outside of the US have created their own national panels of experts called “CW® campaigns” which typically review recommendations submitted by that country’s oncology societies. We performed a scoping review to consolidate CW® recommendations from different groups with respect to breast cancer care.

Methods: A systematic search of Medline and Embase for English language publications presenting CW® recommendations for breast cancer care practices was conducted from Jan 1, 2011 - May 11, 2020. The search was designed and peer reviewed by information specialists. We also reviewed the CW® websites of ABIM and associated international CW® campaigns. Two reviewers independently screened studies for inclusion and performed data extraction, and findings were summarized narratively.

Results: Review of ABIM CW® recommendations showed 26 breast cancer-related recommendations. These pertained to: screening (n=5), radiological staging (n=2), treatment (n=15), surveillance (n=2), and miscellaneous (genetic testing and pathology; n=2). Treatment recommendations were sub-classified into surgery (n= 9), chemotherapy (n= 2), radiation therapy (n= 2), and supportive therapy (n= 2). Of 20 countries which have a CW® campaign and endorse recommendations for a range of diseases, 13 have published recommendations for breast cancer. While most international campaigns published recommendations on the same topics as the ABIM campaign, 6 campaigns developed recommendations on new topics. These included: follow-up visits (Canada), involvement of multi-disciplinary teams and imaging in palliative care setting (India) and comparison of screening imaging modalities (Portugal). There was concordance in screening, treatment, and surveillance recommendations between the CW® campaigns.

Conclusion: CW® recommendations focus on reducing overutilization of investigations and treatments. Breast cancer screening and treatment were most frequently addressed by CW® recommendations. There was a high rate of consensus between international CW® recommendations with respect to breast cancer care. As health care systems globally move attention to reduce low value care, further studies are required to address adherence to these current recommendations and develop new recommendations addressing topics not currently included in the US CW campaigns.

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# Real world study on the efficacy and tolerability of ixabepilone monotherapy vs. combination therapy with capecitabine in metastatic breast cancer patients (MBC)

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BACKGROUND: Ixabepilone is a microtubule stabilizing agent that was approved as monotherapy and in combination with capecitabine for the treatment of refractory metastatic or locally advanced breast cancer resistant to anthracyclines, taxanes. With limited options for refractory MBC, especially in triple negative breast cancer (TNBC), ixabepilone plus capecitabine has demonstrated an increase in progression free survival (PFS) compared to patients treated with capecitabine alone. We assess the effectiveness and safety of the drug in a real-world setting. METHOD: REDCAPS is a large, ongoing clinical database of over 1800 women (1999 to present) was used to identify 91 patients who had received ixabepilone monotherapy and in combination with capecitabine during their treatment course at the Magee Women's Hospital, Women's Cancer Center. Clinical outcomes were retrospectively analyzed utilizing descriptive and comparative statistics. RESULTS: Patients were heavily pretreated: 41.8% had received at least 6 lines of prior chemotherapy in the metastatic setting. Treatment was late in the disease course; median line of treatment was 5.3. At the time of receiving ixabepilone, the patients had multiple metastases (64.8% have ≥ 3) and widespread disease (57% had both visceral and non-visceral disease). PFS was 3.5 months with n=4 patients attaining a PFS ≥ 12 months. Overall survival (OS) was 11.3 months. A subset of patients that had triple negative breast cancer (N=37) had similar PFS, 3.6 months, and OS, 10.2 months, as the total population of patients that received the medication. Another subset analysis was conducted looking at patients who had received ixabepilone monotherapy (82 patients) vs those who had received combination therapy with ixabepilone and capecitabine (9 patients). The PFS and OS was not statistically significant between the two groups. Most common adverse events of any grade were fatigue (37%), nausea (32%), and peripheral sensory neuropathy (28%). Grade 3 or higher anemia was present in 10% of the patients. CONCLUSION: Ixabepilone monotherapy and in combination with capecitabine has demonstrated efficacy in the treatment of heavily pretreated patients with MBC, including the challenging population of TNBC patients in this real-world example. While the number of patients receiving the combination therapy was low (n=9), PFS and OS were still demonstrated to be comparable to monotherapy. It is also well tolerated. These findings make ixabepilone a reasonable chemotherapeutic agent for refractory MBC and TNBC patients with visceral metastases, more than 3 metastatic disease sites, poor prognosis and who have limited treatment options after having failed anthracycline or taxane treatment.

**Ixabepilone Treatment in TNBC Patients**

| | All patients (N=91) | TNBC (N=37) |
|---|---|---|
| Age, yearsMedian (Range)<50>=50 | 48.1 (32.6-85.1)56 (61.5)35 (38.5) | 49.4 (28.8-85.1)20 (54.1)17 (45.9) |
| Number of metastatic sites< 3≥ 3 | 32 (35.2)59 (64.8) | 14 (37.8)23 (62.2) |
| Type of metastatic disease sitesVisceralNot visceralCombined | 21 (23.1)13 (14.3)57 (62.6) | 11 (29.7)7 (18.9)19 (51.4) |
| Anthracycline or taxane received prior to ixabepilone in neoadjuvant/adjuvant settingYes No | 71 (78.0)20 (22.0) | 32 (78.0)5 (5.0) |
| Anthracycline or taxane received prior to ixabepilone in metastatic settingYesNo | 67 (23.1)24 (76.9) | 26 (70.3)11 (29.7) |
| Number of prior regimens prior to ixabepilone in metastatic setting Median 12345=> 6 | 5.3 5 (5.5)2 (2.2)14 (15.4)15 (16.5)17 (18.7)38 (41.8) | 4.2 4 (10.8)1 (2.7)9 (24.3)9 (24.3) 6 (16.2)8 (21.6) |
| Progression free survival, monthsMedian (Range)95% CI | 3.53 (0.33-22.73)2.68-4.38 | 3.56 (0.33-22.73)1.92-5.20 |
| Overall survival, monthsMedian (Range)95% CI | 11.34 (0.33-67.73)8.52-14.26 | 10.10 (0.33-54.03)6.09-14.13 |

**Treatment with Ixabepilone Monotherapy vs. Combined with Capecitabine**

| All Patients | Ixabepilone monotherapy (n=82) | Ixabepilone+capecitabine(n=9) | |
|---|---|---|---|
| Progression free survival (PFS), months Median 95% confidence interval | 3.58(2.63-4.52) | 3.11(0.83-5.41) | P=0.74 |
| Overall Survival (OS), months Median 95% confidence interval | 11.21(8.18-14.23) | 13.11(0.64-25.59) | P=0.70 |
| PFS by line of previous therapy, months <4 (n=21) >=4 (n=70) | 2.403.81 | 3.013.28 | P=0.64P=0.84 |
| OS by line of previous therapy, months <4 (n=21) >=4 (n= 70) | 9.8411.51 | 15.737.88 | P=0.41P=0.67 |

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# Physician and patient satisfaction with poly(ADP-ribose) polymerase inhibitors (PARPi) versus chemotherapy in adult patients with germline BRCA1/2 mutated (gBRCA1/2mut) HER2- advanced breast cancer (ABC): Results from a multi-country real-world (RW) study

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**Background: Within the past 3 years, PARPi have demonstrated improved progression-free survival and favorable PROs compared with chemotherapy in randomized clinical trials in patients with *gBRCA1/2*mut HER2- ABC. These agents are now available in multiple countries for the treatment of *gBRCA1/2*mut HER2- locally advanced and/or metastatic breast cancer. Limited information is available on physician/patient satisfaction with PARPi from the RW. We assessed RW physician/patient treatment satisfaction among adult patients with *gBRCA1/2*mut HER2- ABC in Germany, France, Italy, Spain (EU4), US, and Israel.**
**Methods: Oncologist were recruited to abstract data from medical records (2019/2020) for patients with *gBRCA1/2mut* HER2- ABC. Physicians were asked to rank (1=very dissatisfied to 5=very satisfied) their satisfaction with their patient's current ABC treatment. The scores were dichotomized to a 0/1 variable (0=very dissatisfied/ dissatisfied/moderately satisfied; 1=satisfied/very satisfied). A subset of patients completed the Cancer Treatment Satisfaction Questionnaire, a validated instrument that was used to measure patient's satisfaction with their current therapy. The physician and patient sample were matched. Physician/patient satisfaction scores were compared between chemotherapy and PARPi monotherapy utilizing inverse probability weighted regression adjustment controlling for age at therapy initiation, Charlson Comorbidity Index at time of data collection, baseline symptoms, hormone receptor (HR) status, ECOG score at therapy initiation, stage of therapy initiation (locally advanced breast cancer or metastatic breast cancer) and number of lines of ABC treatment.**
**Results: Overall 96 adult female patients participated; mean age was 51 years. Tumor characteristics were: 34.4% HR+/HER2-, 65.6% triple negative breast cancer. Chemotherapy (n=58) was received among 60.4% of pts [n=29 (50.0%) platinum based, n=29 (50.0%) non-platinum based], and PARPi monotherapy (n=38) was received among 39.6% of pts. Physicians were significantly more likely to be satisfied or very satisfied with PARPi in comparison with chemotherapy (95.4% vs. 40.8%, p<0.001). Mean patient satisfactions scores were numerically higher with PARPi vs. chemotherapy: expectation of therapy 81.3 vs. 72.0 (p=0.13), feelings about side effects 55.7 vs. 51.4 (p=0.30), satisfaction with therapy 74.0 vs. 68.5 (p=0.13).**
**Conclusions: PARPi have demonstrated superior efficacy and favorable PROs vs. chemotherapy in randomized controlled trials. In this RW study, physicians reported significantly higher satisfaction with PARPi vs. chemotherapy; patients reported numerically higher satisfaction scores with PARPi vs. chemotherapy across all domains. These findings further support the value of PARPi in patients with *gBRCA1/2*mut HER2- ABC. Additional studies to validate these findings are planned.**
**Funding: Pfizer**

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# Real-world treatment patterns in older patients with stage I-III breast cancer: A population-based study

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**Background: The number of older patients is increasing globally. However, older patients are less likely to be offered participation in clinical trials. We aimed to assess the real-world treatment patterns in older patients with breast cancer and to examine the associations of advancing age with cancer specific survival (CSS) and overall survival (OS).**
**Methods: Patients aged > 65 years and diagnosed with stage I-III breast cancer in a large Canadian province from 2004 to 2017 were identified. Data from administrative sources were linked with the provincial cancer registry. Patients were categorized based on their age at diagnosis: old (65-74 years), older (75-84 years) and oldest (> 85 years). Logistic regression analyses were performed to determine the associations of age with receipt of surgery, chemotherapy, radiotherapy, and hormone treatment. Kaplan-Meier survival curves were plotted to estimate the 5-year CSS and OS. Cox proportional hazards models were constructed to examine the associations of age with CSS and OS, adjusting for stage and treatment.**
**Results: A total of 10,719 older patients were eligible. The median age was 73 (interquartile range, 68-79) years and 99.2% were women. There were 6,057 (56.5%) old, 3,438 (32.1%) older, and 1,224 (11.4%) oldest patients. The oldest patients were more likely to have a higher Charlson comorbidity index (CCI) score (<.001) and present with stage III disease (P<.001). Further, the oldest patients were least likely to be treated with surgery (80.2% vs 98.2%, P<.001), chemotherapy (0.8% vs 24.7%, P<.001), radiotherapy (14.6% vs 56.8%, P<.001) and hormone therapy (41.8% vs 66.8%, P<.001) compared with old women with breast cancer. In multivariable logistic regression analyses, the older and oldest patients had a lower likelihood of surgery (odds ratio [OR], 0.42; 95% confidence interval [CI],0.33-0.53; P<.001 and OR, 0.10; 95% CI, 0.08-0.13; P<.001), chemotherapy (OR, 0.08; 95% CI, 0.06-0.09; P<.001 and OR, 0.01; 95% CI, 0.01-0.02; P<.001), radiotherapy (OR, 0.50; 95% CI, 0.46-0.55; P<.001 and OR, 0.13; 95% CI, 0.11-0.15; P<.001) and hormone treatment (OR, 0.61; 95% CI, 0.56-0.67; P<.001 and OR, 0.31; 95% CI, 0.27-0.35; P<.001). There were 1,504 breast cancer**
**related deaths and 1,845 deaths due to other causes. At a median follow-up of 4.9 years, the 5-year CSS rates were 90.7%, 84.1% and 74.9% (P<.001), while 5-year OS rates were 86.2%, 71.3% and 43.2% (P<.001) for the old, the older and the oldest patients. After adjusting for stage and treatment, advancing age predicted for worse CSS (older; hazards ratio [HR], 1.33; 95% CI, 1.17-1.50; P<.001, oldest; HR, 1.49; 95% CI, 1.26-1.76; P<.001) and worse OS (older; HR, 1.82; 95% CI, 1.67-1.98; P<.001, oldest; HR, 3.13; 95% CI, 2.82-3.48; P<.001).**
**Conclusions: Although all treatment modalities were administered less frequently with advancing age, a more significant decline was noted for adjuvant therapy than surgery. The worse CSS observed in the advanced age groups suggest a potential role for cancer-directed therapy in improving outcomes. Further research should focus on the development of less toxic treatment strategies in geriatric patients with breast cancer.**

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# Use of the published kinase inhibitor set to identify therapeutic targets in TNBC

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**Breast cancer (BC) is the second leading cause of cancer associated deaths in women globally [1]. Broadcategorization of BC is based on protein receptor expression: triple negative breast cancer (TNBC) lacksexpression of estrogen receptors, progesterone receptors, and exhibits non-amplification of HER2/Neu. Due tothe receptor status in TNBC, hormone-based targeted therapies are not effective; systemic chemotherapy is theprimary treatment which results in significant adverse effects for patients [2]. TNBC would benefit significantlyfrom the development of novel targeted therapeutics and in this study, we describe a small molecule inhibitor-based approach to identify candidate targets.We screened TNBC cells using the Published Kinase Inhibitor Set (PKIS), a highly annotated set of kinaseinhibitors [6] and demonstrated the utility of screening chemogenomic sets for target vulnerability identification. Ahigher rate of metastasis is a defining characteristic of the TNBC subtype; a proposed mechanism for acquisitionof a metastatic phenotype is a cellular process known as epithelial-mesenchymal transition (EMT). In an initialadherent cell culture screen of the PKIS library using established TNBC cell lines (MDA-MB-231, BT-549) andprimary patient-derived TNBC cells (TU-BCX-4IC, TU-BCX-49S), we identified three compounds that had themost dramatic effects on reversing the mesenchymal cell phenotype such as an increase in cell size and cellularproliferation/death: GSK907232A, GSK1440913, and GW494601. Following cell culture studies, molecular andbiochemical assays were performed to analyze known EMT-related cancer pathways. Results showed an overalldecrease in mesenchymal gene expression (Vimentin, FOXC2, SNAIL, SMAD2, TGF- β) and an increase inepithelial expression (E-Cadherin) in all four tested cell lines. In addition to EMT analysis, we investigated therole of our three hits in breast cancer stem cell populations. These inhibitors showed a reduction in breast cancerstem cell marker ganglioside GD2, a population that is strongly associated with tumorigenesis, metastasis, anddrug resistance. These data suggest these inhibitors reverse EMT and inhibit the cancer stem cell effects,attributes linked to poor prognoses in cancer [3,4,7].Because these three PKIS compounds are non-selective and affect diverse kinases, we then examined kinomewide activity of the selected inhibitors using the KINOME*scan*â assay to discover candidate kinase targets topursue. Some kinases identified as targets of these inhibitors, such as NEK5 and MAP3K19 [5] are understudiedboth in and out of the field of breast oncology and warrant further exploration in TNBC. In conclusion, our primaryobjective was to demonstrate the utility of the PKIS library as a primary screening tool for target discoveryapplications. Ongoing work focuses on validation of the identified understudied kinases as druggable therapeutictargets for TNBC.**

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# Depression, sexual dysfunction and quality of life among breast cancer patients with ovarian function suppression: A cross sectional study between ovarian ablation verse GnRH agonists

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**Background: Ovarian function suppression is being widely utilized as endocrine therapy to reduce estrogen release in premenopausal breast cancer patients and was achieved either by medical treatment with the Gonadotropin releasing hormone (GnRH) agonist or bilateral oophorectomy. This study aimed to examine the difference between GnRHa and ovarian ablation on depression, sexual dysfunction and quality of life.Methods: The premenopausal breast cancer patients who received ovarian function suppression were enrolled from seven hospital between June 2019 and February 2020. Our independent variable was the type of ovarian suppression, categorized as Ovarian Ablation (OA cohort, n=62) and medical GnRH agonist (GnRHa cohort, n=260). The self-administered questionnaire (OFS-Q5) developed and used in this study aimed to assess the depression (PHQ-9), sexual dysfunction (FSFI) and quality of life (EORTC QLQ-BR23), as well as the contributing factors.Results: In this cross-sectional study, 322 patients with ovarian function suppression completed surveys were collected. The mean sum score of the PHQ-9 in GnRHa cohort tend to be lower than that in ovarian ablation (OA) cohort (9.6 ±5.2 vs. 11.0 ±5.8, OR=1.495, *P*=0.080). Patients with major depression (PHQ-9≧15) was indicated significantly fewer in GnRHa cohort. Less patients met the criteria for sexual dysfunction (66.1%, FSFI< 26.55) in OA cohort compared with 81.5% of patients with GnRHa (P = 0.008). The ratio of sexual dysfunction remained lower for ovarian ablation women in long-term ovarian suppression (duration of ovarian suppression > 2 years: OA vs GnRHa, 36.7% vs 78.4%, P=2.4E-05). The differences of most subscales of QLQ-BR23 were insignificant in both cohorts.Conclusions: Our finding demonstrate here for the first time that ovarian ablation resulted in worse depression, favour sexual function than those with medical GnRHa, with similar quality of life. More attention need to paid on adverse effect in patients with diverse ovarian function suppression.**

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# A phase 1 study of abemaciclib and niraparib as neoadjuvant therapy in hormone receptor positive (HR+) HER2 negative (HER2-) breast cancer

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Background: Achieving a pathologic complete response (pCR) to neoadjuvant therapy correlates with excellent outcome in early stage breast cancer, including HR+ breast cancer (HRBC). Unfortunately, less than 10% of HRBC patients achieve pCR to neoadjuvant therapy; indicating a need for novel HRBC therapies, especially in the neoadjuvant setting. This study evaluates the novel combination of the cyclin dependent kinase inhibitor (CDKi), abemaciclib, in combination with the poly-ADP ribose polymerase inhibitor (PARPi), niraparib, as a neoadjuvant therapy for HRBC.

Niraparib is an orally bioavailable PARPi indicated for the maintenance treatment of platinum-responsive, ovarian cancer, both 1st line and 2nd line. Abemaciclib is approved as a monotherapy or in combination with endocrine therapy in metastatic HRBC. In addition to targeting CDK4/6, abemaciclib also inhibits CDK1, CDK2, and Aurora A/B kinases, which are involved in DNA damage repair. Targeting kinases with abemaciclib sensitizes tumors to DNA-damaging agents, including PARPi. Preclinical data justifies the combination of abemaciclib and niraparib as a novel combination for the treatment of HRBC.

Trial Design: This is a phase I dose-finding study evaluating the combination of abemaciclib and niraparib as a neoadjuvant therapy in patients with early stage HRBC. All eligible participants with biopsy-proven HRBC will undergo a pre-treatment biopsy and start on-study treatment with the combination of abemaciclib and niraparib using a traditional 3+3 dose-escalation algorithm to determine maximum-tolerated dose (MTD). Dose levels are outlined in Table 1. Each cycle is 28 days. After 2 cycles, participants will undergo repeat imaging and biopsy: those with stable or responding disease will continue to receive an additional 2 cycles of abemaciclib and niraparib, followed by surgical resection. Participants with progressive disease will be switched to standard of care chemotherapy. Once the MTD is determined, additional participants up to a sample size maximum of 25 will be enrolled into an expansion cohort (including those from the dosing finding phase) and treated at the established MTD.

Eligibility Criteria: Key Inclusion Criteria: Age ≥ 18 years, biopsy-proven HR+ Her2 non-amplified breast cancer planned for neoadjuvant chemotherapy, ECOG PS ≤1, disease amenable to curative surgical resection. Key Exclusion Criteria: Evidence of metastatic disease, prior PARPi or CDK 4/6i exposure

Specific Aims: Primary Endpoints: Incidence of dose-limiting toxicities (DLTs), incidence of adverse events (AEs) and serious AEs (per CTCAE 5.0). Secondary Endpoints: overall objective response rate, clinical benefit rate, pCR rate, and rate of residual cancer burden 0-1

Statistical Methods: This phase I dose-escalation study for the proposed combination will follow traditional 3+3 escalation rules. The sample size maximum of 25 (including both those from the dosing finding and expansion portions) allows for a greater than 80% chance that the incidence of any AE as rare as 6.4% or greater will be observed in the cohort. For assessments of preliminary efficacy, the sample size provides a two-sided 95% confidence interval with a half width equal to 0.140 when the targeted pCR is 0.15.

Planned Activation Date: Target Accrual: n=25 participants

Table 1. Study Regimen Dose Levels

| *Dose Levels (DL* | Abemaciclib (PO) | Niraparib (PO) |
|---|---|---|
| DL -1 | 100 mg BID | 100 mg QD |
| DL 1 starting | 150 mg BID | 100 mg QD |
| DL 2 | 150 mg BID | 200 mg QD |

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# The effect of oncoplastic reduction on the incidence of post-operative breast lymphedema in breast cancer patients undergoing lumpectomy

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**Purpose / Objectives: In patients with macromastia, breast conservation surgery (BCS) followed by radiation therapy (RT) for the treatment of breast cancer may be associated with a different complication profile than those without macromastia. General complications of BCS followed by RT includes seroma, infection, wound complications, cosmetic deformity, asymmetry, acute versus long term arm and/or breast lymphedema. Oncoplastic reduction mammoplasty (ORM) aims to reduce breast volume while excising the tumor bed and its margins. Since breast volume was found to be a risk factor for chronic breast lymphedema, this study was performed to determine the impact of ORM on chronic breast lymphedema as well as other complications compared to BCS without ORM. Materials / Methods: We performed a retrospective chart review on patients who underwent lumpectomy with RT from 2014 to 2018. Chronic breast lymphedema (CBL) was defined as swelling that persisted >1 year post-RT. Breast volumes (BV) were determined by contoured breast volumes or, if unavailable, estimated by the 95% isodose volumes from the RT treatment planning system. Univariate analysis was used to evaluate various patient factors and treatment outcomes in women with BV ≥1300 cc compared to <1300 cc. These same factors were compared in women who underwent ORM vs. BCS alone. Multivariate regression analysis was used to evaluate factors associated with ≥1 complication. Logistic regression was performed to identify factors associated with the development of CBL. Results: The total population included 1173 patients, of which 51 (4.3%) underwent ORM and 1122 (95.7%) underwent BCS. 440 (37.5%) patients had BV ≥1300 cc and 733 (62.5%) patients had a BV <1300 cc. Multivariate regression analysis demonstrated that patients with BV ≥1300 cc had a higher BMI (OR=1.200, P<0.001), decreased risk of grade 2 radiation dermatitis (OR=0.457, P=0.002), and increased risk of CBL (OR=2.127, P=0.024) compared to patients with BV <1300 cc. However, oncoplastic reduction was associated with an increased risk of hematoma (OR=5.934, P<0.001), increased risk of wound dehiscence (OR=12.433, P<0.001), and decreased risk of seroma (OR=0.201, P<0.001) compared to BCS patients. Conclusions: Our data demonstrates that patients with breast volume > 1300 cc are at increased risk for developing several complications regardless of the presence of ORM. Those who had ORM experienced an increase in wound complications but having undergone ORM appeared to eliminate the increased risk of CBL associated with macromastia. This suggests that ORM should be considered at the time of BCS to reduce their future risk of CBL as there is no cure for this disease.**

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# I'm willing to be that woman: Exploring Black women's decisions to participate in breast cancer clinical trials

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**Black women die of breast cancer (BC) at a higher rate than any other racial group. Researchers' scientific understanding about this racial disparity, as well as the ability to develop targeted BC treatments for this racial group, is hampered by Black women's well-documented hesitancy to participate in medical research. In this study, we conducted interviews with 14 participants who were Black BC survivors/patients who had participated in a BC clinical trial (CT).**

**In this Integrated Behavioral Model-guided study, we explored participants' attitudes, perceived norms, and personal agency in relation to their decision to participate in a BC CT. Findings about the women's attitudes revealed that despite their often-demonstrated reluctance to be involved in medical research, Black women's strong, altruistic desires to serve others and their communities made them prime candidates for CT participation. In other words, their instrumental attitudes reveal a desire to participate as a way to help themselves and are greatly influenced by the need to leave a "legacy" of better treatment for other Black women. At the same time, while a few participants demonstrated some hesitancy to take unknown or new drugs, most expressed experiential attitudes of feeling safe in their choices.**

**Study results concerning norms showed that despite the Black population's instilled community values, decisions about BC CT participation do not seem to be motivated by a strong injunctive normative influence from friends or family. Most women reported sharing their decision to participate in a CT after the fact. The two strongest normative influences were oncologists and/or their staff members, and patient support groups. From a descriptive normative perspective, most Black women realized their decision to participate in a CT was an unusual one but overestimated how many Black women they believed did participate in BC CTs.**

**These women expressed strong personal agency when they made independent, informed decisions to participate. Most were proactive in seeking out CTs; in cases where they were recruited into a trial by a medical professional, they expressed clear details about how they independently thought through their decision before agreeing to participate, also suggesting perceived control. This study concluded that Black women actively involved in BC support groups, who have developed trusting relationships with their doctors, may feel more motivated and have higher perceived personal agency about participation in a BC CT. Through CT participation, Black women not only potentially help themselves but also demonstrate care about their racial group and the legacy of helping others, suggesting that altruistic messaging may be particularly salient for this group. Finally, these participants, despite their higher education levels and involvement with BC support groups, were quite inaccurate in their reporting of descriptive norms about Black women's participation in CTs, suggesting that social norms messaging may be one way to alert other Black women about the continuing disparity in CT participation. Future work needs to explore these findings in the context of CT recruitment messaging and continue to involve and include Black women's voices to improve BC outcomes in research and medicine.**

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# Impact of oncologists' beliefs and habits on treatment decisions in hormone receptor positive (HR+)/ HER2 negative advanced breast cancer (ABC)

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**Background Current international expert guidelines in the 1st line setting for HR+/HER2- ABC recommend endocrine therapy plus a CDK4/6 inhibitor unless there is a visceral crisis. However, due to a lack of sequencing data, recommendations for further treatment lines are not clear-cut. In this context, treatment decisions are often based on response to first line treatment, aggressiveness of the disease and clinical expertise. Evidence-based medicine should inform decisions. This study aims to estimate the weight of beliefs and habits in therapeutic strategy choices. Methods This observational survey « Chemotherapy : beliefs and habits » was conducted among a representative sample of French oncologists with a breast cancer activity in private and public hospitals. The survey was conducted between November 2019 and January 2020. Oncologists were asked about their knowledge, perception and practice regarding the treatment of HR+/HER2- ABC patients. A focus was made on their perception of best available external clinical evidence leading to guidelines. Results 119 physicians answered the survey. They agreed that in absence of visceral crisis the first line treatment of HR+/HER2- metastatic breast cancer should be endocrine therapy plus a CDK4/6 inhibitor (98,3%). First line endocrine therapy was believed to be associated with a higher progression-free survival benefit (79%) and overall survival benefit (75%) compared to chemotherapy. Even in case of primary or secondary endocrine resistance, oncologists remained in favor of using an endocrine-based therapy at first line in 82% and 66% of cases respectively. The visceral crisis concept was presented through clinical cases. In a life-threatening situation, 10% of physicians maintained their choice of 1rst line endocrine therapy plus a CDK4/6 inhibitor. The oncologists were asked to choose the determinants of treatment choices (patient's preferences, efficacy, safety, quality of life). Oncologists valued patients' preference and quality of life with increasing treatment lines while clinical efficacy as measured by survival data were less and less guiding in their choice of treatment. Conclusion Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values. It is a useful framework held as a standard in therapeutic strategy. However, beliefs and habits play an important role in the choice of treatment for HR+/HER2- ABC beyond the first treatment line. Clinical trials are needed in this setting to determine the best sequence of treatments. A comprehensive analysis of the survey results will be presented at the meeting.**

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# Potential role of activated leukocyte cell adhesion molecule (ALCAM) in hepatocyte growth factor (HGF) signalling in vascular endothelial cells and implications in breast cancer

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**Background. Activated Leukocyte Cell Adhesion Molecule, ALCAM (also known as CD166) is a member of the immunoglobulin superfamily and a cell surface adhesion molecule involved in heterophilic and homophilic interactions during cell-cell adhesion in epithelial cells, cancer cells and endothelial cells. ALCAM appears to be linked to tumour progression in a number of cancers including breast cancer, though there are conflicting reports as to its precise prognostic implications and significance. We have previously reported that ALCAM has a tumour suppressive role in breast cancer and is inversely correlated with clinical outcome (1) and interestingly bone metastasis of breast cancer (2). We have also reported that ALCAM has a diverse role in other cell types including keratinocytes and endothelial cells. In the present study, we investigated the association between ALCAM and hepatocyte growth factor (HGF)/cMET, a signalling pathway established as a key promoter of cancer progression, influencing both the aggressive nature of cancer cells and acting as an angiogenic and lymphangiogenic factor, in breast cancer and endothelial cells.**

**Methods. The expression pattern and correlation of ALCAM, HGF and cMET in human breast cancer were deduced from a clinical breast cancer cohort. ALCAM manipulated HECV cell lines, previously established in our laboratories, were used in conjunction with recombinant human HGF and cMET inhibitors to assess cellular functions and the implications of this relationship at a cellular level.**

**Results. We compared the expression of ALCAM with that of HGF and cMET within the breast cancer cohort and found that ALCAM/CD166 showed a highly significant negative correlation with the HGF receptor cMET ($r=-0.17$, $p<0.0001$) and a weak negative correlation with HGF, although this was not significant. ALCAM was not found to correlate with its heterophilic partner CD6. In previously generated HECV models, ALCAM manipulation showed a marked influence on cellular function and responsiveness to HGF treatment.**

**Discussion. ALCAM's role in breast cancer progression and related mechanisms is complex. Our current data suggests this may involve an interaction with the cMET/HGF signalling pathway and may also impact the endothelial component within the tumour microenvironment to influence disease progression.**

**Reference1 King JA, Ofori-Acquah SF, Stevens T, et al. Activated leukocyte cell adhesion molecule in breast cancer: prognostic indicator. Breast Cancer Res. 2004;6:R478-87.**

**Reference2 Davies SR, Dent C, Watkins G et al. Expression of the cell to cell adhesion molecule, ALCAM, in breast cancer patients and the potential link with skeletal metastasis. Oncol Rep. 2008;19:555-61.**

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# Comprehensive analysis of solute carriers to characterise differential expression in breast cancer cell lines and human tissue

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**Essential nutrient uptake required for cell growth and survival is mediated by Solute Carrier (SLC) transporters both physiologically and in cancers. The SLC super-family encompasses sub-families of transport proteins including organic anion transporters (OAT), organic cation transporters (OCT) and organic anion transporting polypeptides (OATP). SLCs transport a vast array of endogenous and exogenous substances, including estrogen, its conjugates, and clinically relevant anti-cancer drugs. Accumulating evidence suggests that SLC transporters are differentially expressed in hormone-responsive and hormone non-responsive breast cancers, which could influence breast cancer pathogenesis, both in disease progression and treatment resistance. We investigated whether SLC transporters are differentially expressed in different breast cancer cell lines and in human breast cancer tissue. First, bulk cells from the breast cancer cell lines MCF-7 (hormone responsive) and MDA-MB-231 (hormone non-responsive) were analysed for differential expression of SLCs using sq-PCR and RT-PCR. 8 of 11 SLCO and 10 of 14 SLC22 transporters were expressed in at least one cell line. Transporter expression was either similar or lower in MCF-7 cells compared to MDA-MB-231 cells, with the exception of SLCO2A1, SLCO4C1, SLCO5A1 and SLC22A5 which were higher in MCF-7 cells. mRNA expression of SLCs was then compared between both cell lines and human breast cancer tissue. The latter showed an expression pattern largely reminiscent of the MCF-7 cells. Because these techniques measure the average level of expression shown by a pooled cell population, there is the potential disadvantage that cell heterogeneity is masked. To help address this, Single Cell RNA Sequencing (scRNA-Seq) was performed using the 10x Genomics Chromium Single Cell 3' platform and NovaSeq Technologies to compare SLC transporter expression between the cell lines. Together these results provide evidence for differences in SLC transporter expression between cell lines and cancer tissues that may contribute to cancer progression.**

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# Clinicopathologic features and follow-up outcomes of breast cancers with HER2 FISH group 3 Results: A single institution experience

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INTRODUCTION: There is dearth information on the long-term outcome and role of HER2 targeted therapy in breast cancer patients in the HER2 FISH group 3 category, which is defined as breast cancer with a HER2/CEP17 ratio < 2 and HER2 copy number ≥ 6 signals/cell. In this study, we report the clinicopathologic features and outcomes of breast cancer patients in the HER2 FISH group 3 category at our institution. METHODS: We identified 52/2,874 (1.8%) breast cancer patients with HER2 FISH group 3 results between 1/2007 and 3/2020. 28 of these 52 patients had available detailed clinicopathologic and follow-up data, with an average follow-up of 38.5 months. RESULTS: Most of the cases with group 3 FISH results were high grade ductal carcinomas with positive hormonal receptor expressions and equivocal HER2 expression by immunohistochemistry. Among all the clinicopathologic variables, only tumor size (p=0.048) significantly contributed to the poor clinical outcomes. HER2 copy number failed to show any significant association with histologic grade, tumor size, clinical stage, hormonal receptor status or disease outcomes. There was no statistically significant difference in disease outcome between patients who were treated with HER2 targeted therapy and patients who did not receive HER2 targeted therapy, regardless of the HER2 copy number or clinical stage (Table 1). CONCLUSION: Our preliminary findings suggest that certain patients with HER2 FISH group 3 category breast cancer may not need HER-2 targeted therapy. Larger-scale studies are needed to further evaluate which HER2 FISH group 3 results are more likely to benefit from the HER-2 targeted therapy.

Table 1

Response to HER2 targeted therapy in HER2 FISH group 3 breast cancer patients based on HER2 copy numbers and clinical stage

| | HER 2 targeted therapy | | p-value |
|---|---|---|---|
| | Given | Not given | |
| Total population | | | |
| Good outcome (n=21) | 13 | 8 | 0.371 |
| Bad outcome (n=7) | 6 | 1 | |
| HER2 copy number < 10 | | | |
| Good outcome (n=16) | 10 | 6 | 0.366 |
| Bad outcome (n=7) | 6 | 1 | |
| HER2 copy number ≥ 10 | | | |
| Good outcome (n=5) | 3 | 2 | 1.000 |
| Bad outcome (n=0) | 0 | 0 | |
| Stage I-II | | | |
| Good outcome (n=16) | 9 | 7 | 0.737 |
| Bad outcome (n=3) | 2 | 1 | |
| Stage III-IV | | | |
| Good outcome (n=5) | 4 | 1 | 0.343 |
| Bad outcome (n=4) | 4 | 0 | |

*Good outcome = No evidence of disease**Bad outcome = Local recurrence, distant metastasis, and/or died of disease

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# Development of a multiplexed protein panel using a targeted proteomics approach for the study of CDK4/6 inhibitors resistance in hormone receptor positive breast cancer

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**Background Breast cancer is the most common malignancy in woman and hormone receptor positive breast cancer represents approximately 70% of all cases. These patients are treated with endocrine therapies aimed at disrupting hormone receptor signaling and estrogen production which improves survival and allows a cure in early stages. However, recurrent disease, metastatic dissemination and drug resistance limit the survival of patients. The limitations regarding endocrine therapy have prompted the search for new therapeutic targets, such as CDK4/6 Inhibitors. Despite the improved disease control that CDK4/6 Inhibitors offer to patients, not all patients respond to these drugs and some patients whose tumors respond to CDK4/6 Inhibitors eventually develop acquired resistance. No proven biomarkers of CDK4/6 Inhibitors efficacy exist to date, and there is a need for diagnostic tools that could stratify patients to save costs and the burden of unnecessary therapy. Our aim is to perform a quantitative evaluation of marker proteins with a developed multiplexed panel using targeted mass spectrometry (MS)-based proteomics for 25 proteins from the CDK/RB/E2F-pathway which have been shown in the literature to be central to CDK4/6I resistance. Material and Methods We developed Multiple Reaction Monitoring (MRM) MS methods for the 25 target proteins from the CDK/RB/E2F-pathway using synthetic heavy-isotope-labeled standards with the aim of creating MRM assays to enable specific, sensitive and precise quantitation of these proteins in small amounts of cell line and tissue samples. Moreover, we developed a high resolution peptide fractionation system using high-pH micro-flow liquid chromatography (LC) which is required to overcome the problem of small samples amounts while improving analytical assay sensitivity in the analysis of complex biological matrices such as breast cancer biopsies. The MCF-7 human breast cancer cell line was used as model during method development. Proteins from cell lysates were isolated, reduced, alkylated and digested with trypsin. The resulting tryptic peptides were micro-flow fractionated into 70 fractions and the developed nano-LC-MS MRM assays were used for peptide detection and quantification. Data were analyzed using Skyline. Results Our developed micro-flow fractionation method allowed us to work on limited amounts of samples (60ug), and increased the possibility to detecting low abundance proteins such as cell cycle components. Using the MCF-7 cell model, we are able to identify and quantify 17 proteins out of the 25 from our panel: CDK1, CDK2, CDK4, Cyclin B1, Cyclin D1, Cyclin D3, Cyclin E1, RB1, E2F-3, E2F-4, E2F-5, ESR1, TOP2A, TYMS, EZH2, MKI67, BIRC5. Conclusion We have developed a highly specific MS-based multiplexed assay with peptide standards targeting 25 proteins relevant to CDK4/6 Inhibitors breast cancer treatment. Our micro-flow fractionation method increased assay sensitivity and allows for the analysis of small sample amounts. In the future we will apply this workflow to samples such as Patient Derived Xenografts models, breast cancer tissues and FFPE samples in order to identify the predictive value of these potential biomarkers for responsiveness to CDK4/6 Inhibitors.**

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# Cardiovascular (CV) risk profile in patients with estrogen receptor (ER) positive HER2 negative advanced breast cancer (ABC): A retrospective cohort study (CAREB)

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Background: CDK 4/6 inhibitors in patients (pts) with HR+/HER2- ABC has led to significant improvements in clinical outcomes, however our understanding of the impact of these treatments on CV health is unknown. Gains in overall survival should not be offset by increased CV morbidity and mortality; a particular concern given the shared risk factors for both breast cancer and CV disease. Objective: The aim of this study was to describe patient characteristics, treatment patterns and cardiovascular risk factors and disease in pts with ABC treated with endocrine therapy (ET) or ET + CDK 4/6 inhibitor. Methods: We retrospectively studied pts with HR+/HER2- ABC who were receiving first line endocrine therapy. Post-menopausal (PM) women, pre-menopausal women on ovarian suppression (OS), and men were included. Two cohorts were included: Group A - treated with ET alone (2012-2014; prior to US approval of CDK 4/6 inhibitors) and Group B - treated with ET+ CDK 4/6 inhibitor (2015-2017). The following data was extracted from Duke University Health System's electronic medical record (EPIC) and entered into a REDCap database: demographics, baseline cardiovascular risk factors, and co-morbidities. Pt characteristics are summarized using medians and interquartile ranges for continuous variables and categorical descriptions are summarized using frequencies and percentages. Results: In total 103 patients were included with 57 in Group A (ET alone) and 46 in Group B (ET + CDK 4/6 inhibitor). Median age was 62.0 and 63.5 years in Group A and B, respectively. Fifty-three (93%) of pts in Group A were PM women compared to 37 (80%) PM women and 1 (3%) male in Group B. The groups seemed to be similar in terms of race (white 70% vs 72%), baseline body mass index (28.2 vs 27.6), baseline systolic blood pressure (132.0 vs 135.5) and diastolic blood pressure (79.0 vs 77.5). Similarly, the groups seemed to be similar in baseline hypertension (68% vs 62%); diabetes (23% vs 24%); Hemoglobin A1c (7.2% vs 6.4%) or family history of CV disease (56% vs 55%), Group A versus Group B, respectively. There were slightly more current/past smokers in Group B than Group A (48% vs 35%) and more pts in Group A with a history of hyperlipidemia relative to Group B (52% vs 31%). Conclusions: In this retrospective descriptive cohort study there seemed to be no differences in demographics or baseline CV risk factors between the ET and ET + CDK 4/6 inhibitor cohorts with the exception of more baseline hyperlipidemia in the ET cohort. This might suggest that baseline CV risk factors did not dissuade practioners from prescribing ET + CDK 4/6 inhibitor therapy. We plan to expand our cohort to collect information on type and duration of ET and CDK 4/6 inhibitors, reason for treatment discontinuation, and CV events (eg heart failure, arrhythmias, stroke, myocardial infarction), to better understand the impact that cardiovascular risk factors have on outcomes in breast cancer patients taking ET+ CDk 4/6 inhibitor. Table 1: Demographics and CV risk factors in ABC patients treated with ET or ET + CDK4/6 inhibitor

| Median (IQR) unless otherwise indicated | Group A ET (n=57) | Group B ET+ CDK 4/6 inhibitor (n=46) |
|---|---|---|
| Age median (range) | 62.0 (27-84) | 63.5 (30-82) |
| Menopausal status, n (%) Post menopausal Premenopausal + OS Male | 53 (93) 4 (7) 0 | 37 (80) 8 (17) 1 (3) |
| Race, n (%) White Other | 40 (70) 17 (30) | 33 (72) 13 (28) |
| Type of Insurance, n (%) Private Medicare Medicare and Private Medicaid Medicaid and Medicare Vererans Sponsored Self-Pay Unknown | 19 (33) 14 (25) 16 (28) 1 (2) 4 (7) 0 3 (5) 0 | 19 (41) 4 (9) 15 (33) 1 (2) 4 (9) 1 (2) 0 2 (4) |
| BMI (kg/m2) | 28.2 (24.9, 30.6) | 27.6 (24.4, 34.5) |
| Baseline BP (mmHg) Systolic Diastolic | 132.0 (118.0, 145.0) 79.0 (73.0, 84.0) | 135.5 (124.0, 149.0) 77.5 (72.0, 84.0) |
| HgbA1c (%) | 7.2 (6.4, 7.4) | 6.4 (5.4, 6.4) |
| CVRF, n (%) Hypertension Diabetes FH CVD Current/past smokers Hyperlipidemia | 36 (68) 13 (23) 28 (56) 20 (35) 29 (52) | 28 (62) 11 (24) 22 (55) 22 (48) 14 (31) |

OS = ovarian suppression; BMI = body mass index; BP = blood pressure; HgbA1c = hemoglobin A1c; CVRF = cardiovascular risk factors; FH = family history; CVD = cardiovascular disease; IQR = Interquartile range

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# Investigating CDK4/6 inhibition in triple negative breast cancer

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**The purpose of our study is to evaluate the immunological effects of CDK4/6 inhibitors in pre-clinical models of triple negative breast cancer (TNBC). CDK4/6 inhibitors, including abemaciclib, are currently approved to treat patients with metastatic hormone receptor-positive (HR+), Her2-negative breast cancer. We previously reported in our Her2+ model that CDK4/6 inhibitors promote anti-tumor immunity through inducing tumor cell antigen presentation via activating tumor endogenous retroviral elements, which induce type III interferon production and MHC-I upregulation (Goel, DeCristo, et al., Nature, 2017). We also uncovered important anti-tumor effects on the immune system: CDK4/6 inhibitors decrease T regulatory cell proliferation without affecting cytotoxic CD8 T cell numbers. TNBC has been considered a poor candidate for CDK4/6 inhibitor therapy, as tumors often lose retinoblastoma (Rb) protein expression/function, which is critical for CDK4/6 inhibitor-induced cell cycle arrest. However, Rb mutation or loss occurs in only ~20% of TNBC cases and we found Rb expressing murine and human TNBC cell lines decreased proliferation *in vitro* in response to abemaciclib. In our preclinical model of TNBC, abemaciclib induced tumor regression. Consistent with previous findings, TNBC tumor cells upregulated MHC-I upon abemaciclib treatment, suggesting increased antigen presentation. Tumor cell-surface PD-L1 was also increased with abemaciclib both *in vitro* and *in vivo,* as assessed by flow cytometry and RT-qPCR. These results are encouraging, given that αPD-L1 therapy (Atezolizumab) in combination with chemotherapy (nab-paclitaxel) has recently been approved as standard care for metastatic TNBC and the IMpassion130 trial reported enhanced progression-free and overall survival in patients with PD-L1+ tumors. We also found that abemaciclib increased CD8+ and CD4+ T cells and decreased PD1+ CD8 and CD4 cells in the spleen. Furthermore, total numbers of naïve CD8+ and CD4+ T cells increased with abemaciclib treatment, suggesting a favorable anti-tumor systemic immunological effect. Our data suggest the potential efficacy of CDK4/6 inhibitors in combination with αPD-L1 in the treatment of Rb+ TNBC. Deeper analysis of the mechanisms involved in regulating PD-L1 and enhancing naïve T cells should enable us to evaluate combination therapies using CDK4/6 inhibitors for this particularly deadly breast cancer subtype.**

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# Solti-1903 hope: Real-world clinical practice study to assess the impact of using comprehensive genomic data on the next treatment decision making-choice in patients with locally advanced or metastatic breast cancer in Spain

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BACKGROUND: Metastatic breast cancer (mBC) remains an incurable disease and is the cause of nearly all deaths from breast cancer. Targeted molecular therapies and the evolving role of next-generation sequencing (NGS) technologies are increasing and may improve outcomes in breast cancer patients. However, they are not being routinely used in the clinic. One strategy to overcome the barriers of implementing NGS in the clinic is to promote the active participation of mBC patients in the management of their disease. With this in mind, we designed HOPE (SOLTI-1903), a national real-world study where patients lead their inclusion, participation and follow-up in the study through a digital tool that will guide them in every step of the journey. Our objective is empowering mBC patients and gather real-world data about the utilization of molecular information in the management of mBC. TRIAL DESIGN: Patients diagnosed with mBC who are receiving, have just received, or will receive standard treatment or treatment in a clinical trial (CT) can be included. Demographic data, disease characteristics, treatment history and quality of life data will be collected through a digital tool (DT) by the patient. Patients are encouraged to involve their physician`s in the study journey. The study is complemented by a patient empowerment program including informative workshops and precision medicine video-tutorials. A total of 600 patients will be included in Spain. Patient Journey Once patients request to participate in HOPE through the DT, a dedicated team from SOLTI will assist them in the following steps while validating that eligibility criteria are met according to data introduced by themselves. Then, patients will receive instructions via DT to go to the nearest partner local laboratory, where they will sign the study consent form. A metastatic (preferably) or primary archival tumor sample will be requested to the patient’s reference hospital and analyzed by FoundationOne®CDx. Also, a blood sample will be collected and analyzed by Guardant360. For all patients, two NGS tests will be offered (If no tissue available, only blood test will be performed). Both molecular analyses results will be reviewed during regular meetings by a Molecular Advisory Board (MAB). The MAB, based on their joint experience in clinical oncology, genomics, molecular biology, bioethics and pathology, may add some advice to these reports via DT, making comments about detected molecular alterations and adding further recommendations for specific treatment options or available CT with targeted therapies. From that moment, patients will record their disease evolution in the DT each 3 months for 2 years. The primary objective is to assess the real-world clinical practice integrating molecular profiling in the Standard of Care management of mBC patients connected through a DT. Secondary objectives include to describe genetic mutational profile of mBC, to evaluate the enrollment rate in CT of patients engaged in a patient-centered strategy for molecular tumor assessment, to asses Progression Free Survival, Overall Survival and Quality of life status among patients enrolled in CT according to the tumor’s genomic profile and those receiving standard treatment and to describe logistic feasibility of the study. This study is sponsored by SOLTI and financially supported by Novartis and two non-profit organizations: Asociación Cáncer de Mama Metastásico y Fundación Actitud frente al Cáncer. Roche and Guardant Health provide their test for all patients.

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# Assessment of patient out-of-pocket cost for palbociclib therapy in advanced breast cancer

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**Assessment of patient out-of-pocket cost for palbociclib therapy in advanced breast cancer*Background*:Palbociclib has demonstrated improved outcomes in patients with advanced hormone receptor positive (HR+)/human epidermal growth factor 2 (HER2) negative breast cancer when used in combination with endocrine therapy [1,2]. The current average wholesale price of therapy with this medication class exceeds $190,000 per year (at full dose). Financial toxicity is a major concern in the oncology population and can decrease patient quality of life and may result in non-adherence [3,4]. Our objective was to describe the out-of-pocket cost burden for patients treated with palbociclib.**

***Methods*:A retrospective review of patients newly initiated on palbociclib therapy between May 5, 2018 and May 30, 2019 was completed at our institution. Patients were included if they were 18 years of age and older, newly starting palbociclib for advanced or metastatic HR+/HER2- breast cancer, had US-based insurance, and received palbociclib from our internal specialty pharmacy. Cost information was collected utilizing dispensing reports and additional patient-specific information was obtained from the EHR. Descriptive statistics were performed on the collected data.**

***Results*:A total of 44 patients were included in the cost analysis. Primary sources of coverage for these patients included commercial insurance (n=13), Medicare (n=25), and state/federal insurance (n=6). We first assessed costs with primary insurance coverage alone. The sum of all the initial cycle out-of-pocket copays after primary insurance totaled $49,108. The median individual copay was $291, the range was $0 to $2,943, and 9 of the 44 patients had no copay after the primary insurance was applied.**

**The impact of assistance programs, which include independent grant funding, copay cards, vouchers, and secondary Medicaid plans, was significant. After applying primary insurance and aid from assistance programs, the sum of all initial cycle out-of-pocket copays reduced from $49,108 to $3,172. After assistance, 33 of the 44 patients had an initial copay cost of $0. Over 90% of the out-of-pocket total was from two patients (one each with a copay of $2,467 and $497). Ultimately, Mayo Clinic Specialty Pharmacy helped patients avoid $45,851 in first cycle out-of-pocket copays, of which $41,079 and $4,772 were for Medicare and commercially-insured patients, respectively.**

**Copay cost by type of insurance was assessed. All patients with commercial insurance (n=13) had no actual copay for the first cycle. Medicare patients (n=25) are not eligible for copay cards and had larger pre-assistance copays compared to commercial patients (median $2,454 vs. $45). Vouchers or grants were utilized by 16 out of 25 Medicare covered patients. State/Federal insurance included 2 Tricare and 4 Medicaid patients. While ineligible for copay card assistance, the copays for these patients were low, ranging from $0-$28.**

**Standard Medicare D plans do not have an out of pocket maximum for the year. The catastrophic phase requires an ongoing copay of 5% of the total claim cost, resulting in approximately a $600 per month copay for the remainder of the calendar year during the study period. When combined with the first cycle cost of approximately $2500, the yearly out-of-pocket cost for a patient with a standard Medicare D plan is roughly $10,000.**

***Conclusion*:Patients initiating therapy with palbociclib are commonly faced with high out-of-pocket costs. The availability, eligibility, and use of financial assistance programs are imperative in decreasing the financial toxicity. Specialty pharmacies play an important role in obtaining financial assistance which leads to decreased out-of-pocket expenses for patients.**

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# Effectiveness of platinum-based chemotherapy for hormone receptor-positive HER2-negative metastatic breast cancer

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**Background: Platinum-based chemotherapy (CT) regimens have activity in triple-negative breast cancer (TNBC), with overall response rates around 50%. The evidence for activity of these regimens for hormone receptor (HR)-positive breast cancer is scarce. We aimed to evaluate the effectiveness of platinum-based CT for HR-positive HER2-negative metastatic breast cancer. Methods: We evaluated, retrospectively, electronic medical records of patients with HR-positive HER2-negative metastatic breast cancer who have received, at least, 1 dose of platinum-based CT in the metastatic setting from Jan/2015 to May/2020 in a single cancer center. Data on clinical and demographic features, treatment, and outcomes were collected. The primary study endpoint was the clinical benefit rate at 3 months. Secondary endpoints were overall response rate, progression-free survival (PFS), overall survival (OS), and prognostic factors. Results: 244 patients were included. All patients were female, with a median age of 51.5 years, 59% were premenopause, 32.8% were metastatic at diagnosis, and 63.5% had ECOG-PS 0-1 by the time of platinum-based CT initiation. Although tests for hereditary breast and ovarian cancer were not available, 41% of patients met criteria for hereditary cancer testing. Most patients had invasive ductal carcinoma (90.2%), estrogen receptor >10% positive (92.2%), and progesterone receptor >10% positive (69.7%). Main sites of metastatic disease were bone (76.2%), lymph nodes (59.4%), lung (52.9%), and liver (62.7%). The majority of patients had received previous palliative systemic therapy before platinum-based CT; 36.5% had not received previous palliative endocrine therapy (ET), and 30.7% had not received previous palliative chemotherapy. The preferred platinum-based CT regimen was cisplatin plus gemcitabine (68.8%), and a small proportion received single-agent platinum-based CT (14.3%). Forty-three patients (17.7%) started platinum-based CT during hospitalization. Grade 3-4 treatment-related toxicities occurred in 40.9% of the patients. The clinical benefit rate at 3 months was 41.2% in the overall population, 46.7% when platinum-based CT was used as first-line CT, and 38.6% when used as subsequent CT line. Overall response rate was 26.7% in first-line platinum-based CT and 18.1% in subsequent CT line. Median PFS and OS were 3.2 months (95% CI 2.8 - 3.8) and 8.6 months (95% CI 6.8 - 9.9), respectively. One-year OS rate was 37.1% (95% CI 30.5 - 43.7%). Factors associated with worse OS were ECOG-PS 3-4 (HR 1.85, 95% CI 1.21-2.82, P=0.004), presence of liver metastases (HR 1.61, 95% CI 1.16-2.23, P=0.004), and platinum-based CT initiation during hospitalization (HR 1.74, 95% CI 1.18-2.56, P=0.005). Conclusion: Despite some activity of platinum-based CT for HR-positive HER2-negative metastatic breast cancer, especially as first-line CT, response rates were lower than historically observed in TNBC. Platinum-based CT was associated with poor PFS and OS outcomes. Negative prognostic factors for OS were ECOG-PS 3-4, presence of liver metastases, and initiation of the platinum-based CT during hospitalization.**

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# Comparison of the quality of life (QOL) of patients with an arm vein port (TIVAD) versus a peripherally inserted central catheter (PICC)

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**Introduction: Venous access is a crucial element in systemic therapy delivery. PICCs are usually more easily and quickly inserted. It remains unclear whether cancer patients prefer a port to a PICC. Our study aimed to assess cancer patients' satisfaction with their venous access device and to compare the QOL of subjects with a PICC to those with a port. Methods: In this prospective cohort study, EORTC QLQ-C30 and a locally developed QOL survey, designed to assess satisfaction with venous access devices, were administered to breast cancer (BC) or colorectal cancer patients up to four times over a 1-year period. Mixed effects models were used controlling for other covariates to assess changes on mean scores at different time points. Results: A total of 101 patients were recruited, 50 (BC, 29) in PICC and 51 (BC, 35) in port group. Survey response rates for months 1 and 3 were, 72% and 48%, respectively. Overall, no significant differences were noted between the two groups in relation to EORTC QOL constructs. Mixed effect model showed that patients with a PICC had significantly lower pain score estimate compared to patients with a port (β= -1.98, 95% CI: -0.92 - -3.05, p<0.001). Conversely, patients with a port had a psychosocial score estimate significantly higher than patients with a PICC (β= 2.18, 95% CI: 0.83 - 3.53, p=0.002). As survey time variable was not significant, there was no change in the mean pain or psychological scores for both devices at 3 months. Results for the QLC-30 survey did not reveal any statistically significant changes in mean scores for the different constructs between the surveys conducted at baseline and 3 months for the devices investigated. At 3 months 66.7% patients with a PICC vs. 33.3% with a port felt they had changed the way they dressed due to their device (OR=4.0, 95% CI:1.2-13.3, p=0.02). 88.2% patients with PICC vs.18.3% with port reported difficulties with showering, bathing or performing personal hygiene activities due to their device (OR=18.3, 95% CI: 3.5-97.1, p<0.0001). 41.7% patients with a PICC vs. 12.5% with a port experienced comments from people about their device (OR=5.0, 95% CI: 1.2-21.5, p=0.02). 45.8% patients with a PICC worried that their device may become infected vs. 8.3% with a port (OR= 9.3, 95% CI: 1.8-48.7, p=0.003). No significant differences were noted between the two group regarding sports, exercise, social activities, or the degree of discomfort in between treatments. The 3-month mean satisfaction score between two groups showed no difference (25.0 ±6.6 vs 25.2 ±5.9, p=0.87). Complications rates were 38% in PICC vs. 41% with a port (p>0.24). Overall, 8% patients with a PICC vs. 12% with a port developed DVT (p=NS). Conclusions: Although patients with a port experience more pain, it had a smaller negative impact on psychosocial scores than the PICC. No significant difference in device satisfaction or complications rates was observed between the two devices.**

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# Locoregional therapy in de novo metastatic breast cancer: Systemic review and meta-analysis

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**Background: De novo metastatic breast cancer represents around 6% of breast cancer diagnoses. Retrospective data suggest that locoregional therapy (LRT) for the primary breast cancer in metastatic disease may improve outcomes. Randomized control trials (RCTs) have evaluated the role of LRT in this setting with inconsistent results. Methods: We searched PubMed to identify RCTs that compared LRT and standard systemic therapy to standard therapy alone in de novo metastatic breast cancer. The search was supplemented by a review of abstracts from key conferences. Hazard ratios (HRs) and their associated 95% confidence intervals (CIs) were computed and pooled in a meta-analysis using generic inverse variance. Overall survival (OS) data were extracted for the intention to treat (ITT) population and for pre-specified subgroups defined by tumor subtype and by site of metastases. Subgroup analysis evaluated the effect of systemic treatment prior randomization to LRT. Results: Analyses included 4 trials comprising 970 patients. LRT included standard surgery to the primary breast tumor in all studies, and adjuvant radiation per standard of care was mandatory in 3 studies. Systemic treatment prior randomization showed similar results (HR=0.92 and HR=1.06 for upfront LRT and LRT following systemic treatment, respectively, p for the subgroup difference=0.72). LRT was not associated with improved OS in the ITT population (HR 0.97, 95% CI 0.72-1.29, p=0.81). LRT was not associated with improved OS in any tumor subtypes, including hormone receptor positive (HR for OS= 0.96, 95% CI 0.65-1.43, p=0.85), triple negative (HR 1.4, 95% CI 0.50-3.91, p=0.52) and human epidermal growth factor receptor 2 (HER2) positive disease (HR 0.93, 95% CI 0.68-1.28, p=0.67). Additionally, LRT did not improve OS in bone only disease (HR 0.97, 95% CI 0.58-1.62, p=0.92) and in visceral disease (HR=1.02, 95% CI 0.77-1.35, p=0.90). Conclusions: LRT in de novo metastatic breast cancer is not associated with improved OS. Results are consistent among different breast cancer subgroups.**

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# A transcriptome approach to reveal CTDP1 knockdown induced G1 cell cycle arrest in triple negative breast cancer cells

**Henry Chun Hin Law and Nicholas Woods. University of Nebraska Medical Center, Omaha, NE**

**CTDP1 (C-terminal domain phosphatase 1) is the only phosphatase domain with a BRCT-domain and known to be associated with transcription and mitosis in eukaryotic systems. Our previous research showed that CTDP1 participates in the DNA damage response by mediating interstrand DNA repair through the Fanconi anemia pathway. This study also revealed that CTDP1 is an essential gene in breast cancer cell lines but not in normal breast derived epithelial MCF10A cells. This project aims to identify the changes in transcripts, kinases and interactors leading to the cell death induced by CTDP1 knockdown in the triple-negative breast cancer cell lines. Since RNA Pol II is one of the major targets of CTDP1 phosphatase activity, we initially hypothesized that the cellular changes were mediated by transcriptional regulation. The global transcriptomic profiling of shCTDP1 MDA-MB-231 cells detected more than 29000 gene products, where 1000 and 616 genes were found consistently up- and down-regulated, respectively. The downregulation of cell cycle-associated genes CCNA2, TOP2A and POLA1 in the MDA-MB-231 cells were confirmed with q-RT-PCR. While the upregulated genes did not show enrichment in the Reactome pathway database, the downregulated genes were significantly associated with DNA damage response, mitosis and transcription, which is consistent with the known functions of CTDP1. The transcription factor binding motifs analysis with iRegulon reveals that the E2F1 transcription activity decreased as CTDP1 was knocked down in MDA-MB-231. The subsequent cell cycle analysis supports this prediction and showed G1 arrest as CTDP1 is knocked down in MDA-MB-231 and MDA-MB-453, but not in MCF10A. A kinase array analysis was also conducted to further identify kinases activated or deactivated as CTDP1 is knocked down. A nested network analysis of the predicted transcription factors, kinases and CTDP1 interactors is used to identify potential pathways contributing to cell death of the triple-negative breast cancer cells upon loss of CTDP1 expression.**

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# Phase 3b CompLEEment-1 study of ribociclib plus letrozole in the treatment of HR+/HER2- advanced breast cancer: Final results from the UK cohort

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**Background: Ribociclib is an oral selective CDK4/6 inhibitor approved for use in combination with an aromatase inhibitor (AI) or fulvestrant, in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) in several countries, including the UK. Ribociclib plus endocrine therapy (ET) significantly improved PFS outcomes in phase III registration studies (MONALEESA-2, -3, and-7) compared with placebo plus ET; and significantly increased OS in combination with AI in premenopausal women (MONALEESA-7), and in combination with fulvestrant in postmenopausal women (MONALEESA-3). This analysis aims to report the final efficacy and safety results for the UK cohort of CompLEEment-1, a phase 3b trial evaluating ribociclib plus letrozole in an expanded patient population.Methods: Patients with HR+, HER2- ABC, ≤1 line of prior chemotherapy (CT), and no prior ET in the advanced setting, received ribociclib + letrozole. Baseline characteristics and interim results of the UK cohort have been reported previously (Ring et al. SABCS 2019. Poster 443).Results: A total of 139 UK patients received ≥1 dose of study treatment at UK sites. At the cut-off date, November 8th 2019, 53 patients (38.1%) had completed treatment and 86 discontinued due to disease progression (30.9%), adverse events (24.5%), physician or subject/guardian decision (2.9% each), and protocol deviation (0.7%). The mean age of patients was 61.3 (SD10.67). 138 (99.3%) patients were female, 125 (89.9%) were post-menopausal and 50 (35.9%) had an ECOG status of ≥1. 85 (61.1%) patients had received prior chemotherapy in any setting.89 (64.0%) patients had measurable disease at baseline. 80 (60.4%) patients presented with visceral disease, 35 (25.2%) with bone-only metastases and 4 (2.9%) had CNS metastases. 59 (42.5%) of patients had ≥3 metastatic sites. The median duration of exposure to study treatment was 18.4 months with a median time to progression of 27.6 months. The overall response rate was 25.9% (95% CI: 18.8, 34.0) and clinical benefit rate was 74.1% (95% CI: 66.0, 81.2). Overall, the adverse event (AE) profile was consistent with previous phase III trials. Neutropenia (68.3%), nausea (59.7%), and fatigue (54%) and neutropenia (48.9%) were the most common adverse events (all grades). Neutropenia was the most common AE leading to dose reduction (12.2%) or interruption (33.8%), with ALT increase the most common cause for treatment discontinuation (10.1%). QT prolongation (all grades) led to 3 (2.2%) dose interruptions and 2 (1.4%) dose reductions, but no treatment discontinuations. Conclusions: This subgroup analysis of the COMPLEEMENT-1 study provides further clinically meaningful outcomes on first-line ribociclib and letrozole treatment in a UK cohort. This treatment combination showed consistent efficacy and side effect profile in UK HR+, HER2- ABC patients, consistent with the overall ITT population as well as results observed in the other pivotal ribociclib registration studies. NCT02941926.**

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# Intratumoral cytotoxic t-lymphocyte numbers and chemokine predict long-term survival of triple-negative breast cancer independently of tumor mutational burden

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**Background: Cytotoxic T-lymphocyte (CTL) infiltration into tumor is a positive prognostic factor in breast cancer. While high tumor mutation burden (TMB) is also considered as a predictor of tumor immunogenicity and response to immunotherapy. Triple-negative breast cancer (TNBC) has a higher TMB and accumulates more CTLs compared to other breast cancer subtypes. CTLs are identified by CD8 surface marker, which is encoded by CD8A gene. Granzyme B (GZMB) is a serine protease that is secreted by activated CTLs to induce apoptosis of the target cells. Chemokines, such as CXCL10 and CCL5 are key to the selective attraction of activated CTLs into tumors, as shown in multiple cancers. However, it remains unknown whether tumor infiltrating functional CTLs levels correlate with improved patient survival and are independent of TMB. In order to investigate it, we developed Functional Hotness Score (FHS) combining gene expressions of markers and attractants of activated CTL. Methods: Utilizing publicly available breast cancer cohorts, we established Functional Hotness Score (FHS), based on gene expression levels of CTL and chemokine markers in bulk tumors. The associations of FHS and breast cancer patient prognosis as well as distinct immunity markers were analyzed. Results: CD8, GZMB and CXCL10 combination resulted in the best prediction of the breas cancer patient prognosis. Thus, we established FHS based on the expression levels of these three genes. Breast cancer patients with the high-FHS tumors showed significantly better survival. FHS was lower in the metastatic breast cancers. Among breast cancer subtypes, triple-negative breast cancer (TNBC) showed the highest FHS. FHS predicted patient survival in hormone receptor (HR)-negative, especially TNBC, but not in HR-positive breast cancer. The high-FHS TNBCs showed not only higher CD8+ T cell infiltration, but also enhanced broader type-1 anti-cancer immunity. The patients with the high-FHS tumors showed better prognosis not only in high-TMB tumors but also in low-TMB TNBCs. The combination of high-TMB with high-FHS identified a unique subset of patients who do not recur over time. Conclusions: TNBCs with high-FHS based on the expression levels of CD8A, GZMB and CXCL10 showed improved prognosis with higher anti-cancer immunity regardless of TMB. FHS constitutes an independent prognostic marker of survival, particularly robust when combined with TMB in TNBCs.**

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# A nomogram for predicting three or more axillary lymph node involvement before breast cancer surgery

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**Introduction Focus has moved to de-escalate of axillary surgery in the management of early breast cancer. Based on the American College of Surgeons Oncology Group-Z0011, our team created the nomogram to be useful for identifying patients who do not require intraoperative analysis of the sentinel lymph node. The nomogram could identify as patients likely to three or more positive axillary lymph nodes by preoperative imaging. But the nomogram had several limitations. This study investigated a developed nomogram by excluding the chest computed tomography (CT) and adding $^{18}$F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT as a modality. Material and Methods Patients underwent preoperative ultrasonography (US) and PET/CT. The training set consisted of 1030 patients with clinical T1-2 and node-negative invasive breast cancer. Factors associated with ≥ 3 involved axillary lymph nodes (ALNs) were evaluated by logistic regression analysis. The validation set consisted of 781 independent patients. The nomogram was applied to 1,067 patients who met the selection criteria of the ACOSOG-Z0011. Results Of the 1,030 patients, 89 (8.6%) had ≥ 3 positive nodes. Multivariate analysis according to be used for making a new nomogram to predict the probability of involvement ≥ 3 nodes, there was significantly associated with larger tumor size, higher grade ultrasonographic ALN classification, and findings suspicious of positive ALN on PET/CT. The areas under the receiver operating characteristic curve of the nomogram were 0.856 (95% confidence interval [CI], 0.815 to 0.897) for the training set and 0.866 (95% CI, 0.799 to 0.934) for the validation set. Application of the nomogram to the patients who met the ACOSOG-Z0011 showed that 90/1067 (8.4%) had scores above the cut-off and the false-negative rate was 37/977 (3.8%). And the specificity was 93.8%, and the negative predictive value was 96.4%. Conclusion The upgraded nomogram improved predictive accuracy, and that was possible using only US and PET/CT. It reduced operation time and cost, with a very low re-operation rate. This nomogram is useful for identifying patients who do not require intraoperative analysis of sentinel lymph nodes.**

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# Patterns of use of a trastuzumab biosimilar (ABP 980) in patients with HER2+ breast cancer treated in clinical practice in Europe: An interim analysis from an observational chart review study (GARDENIA)

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Background: Over recent years, therapeutic biosimilars have started to be licensed as oncology treatments in both palliative and potentially curative settings, but little is known about their uptake and usage in routine clinical practice. ABP 980 is a trastuzumab biosimilar that is licensed in Europe and the USA for the treatment of HER2+ early or metastatic breast cancer and metastatic gastric cancer. This European real-world study aimed to describe patterns of ABP 980 usage in clinical practice in patients with breast cancer. Methods: This descriptive observational chart review study included consecutive patients aged ≥18 years with HER2+ breast cancer (any disease stage or treatment phase) who were receiving or had previously received ABP 980 and had medical charts available for data extraction. Patients were followed up from ABP 980 initiation to withdrawal of consent, death, loss to follow up, entry into an interventional trial, or study end (12 months after last patient enrolled). Follow-up data from ABP 980 initiation to enrolment were retrospectively collected; data after enrolment were prospectively collected. Data were extracted into electronic case report forms quarterly. The primary objective is to describe patient demographics and disease characteristics by treatment phase and prior trastuzumab exposure and communication with patients about biosimilar use is an exploratory objective. Other exploratory endpoints are ABP 980 safety (including cardiac dysfunction, infusion-related reactions and other adverse events of interest) and efficacy (both to be assessed in the final analysis). This planned interim analysis was performed approximately 6 months after the first patient enrolled and provides baseline data on patient characteristics. Results: At the time of analysis, 135 women were included from five countries (Poland n=42; Italy n=38; the Netherlands n=32; France n=21; Spain n=2). Patients were mostly recruited from hospital-based sites (61%), including a mixture of academic/non-academic and publicly/privately funded centers. A policy on biosimilar use was documented in 28% of sites and 36% of patients were informed they were starting a biosimilar, with the brand mentioned to 34% of patients. Mean (standard deviation [SD]) age at ABP 980 initiation was 58.3 (11.5) years and mean (SD) time from ABP 980 initiation to enrolment was 7.3 (4.8) months. At ABP 980 initiation, 22%, 27%, 13% and 28% of patients had Stage I, II, III or IV disease, respectively. Overall, 68% of patients had estrogen/progesterone receptor-positive tumors and all patients with known ECOG performance status (n=73) had a score of 0 or 1. ABP 980 usage was approximately equally distributed across neoadjuvant (39%), adjuvant (30%), and metastatic settings (30%). Of the patients receiving treatment for metastatic disease (n=41), most received ABP 980 as their 1$^{st}$- (56%) or 2$^{nd}$- (20%) line treatment. Overall, 40% of patients had switched to ABP 980 from another trastuzumab product. Of these 54 patients, 44% switched from the intravenous form of originator trastuzumab and 15% switched from the subcutaneous form. Most of those switching from subcutaneous originator trastuzumab to ABP 980 were being treated for metastatic disease (7/8 patients). Conclusions: These interim results report usage patterns of the trastuzumab biosimilar ABP 980 in Europe. There was uptake across a mixture of institution types and breast cancer treatment settings, including those with curative potential, and 40% of patients switched to ABP 980 from another trastuzumab product. Recruitment to this study is ongoing.

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# Single-cell transcriptomic analysis reveals tumor microenvironment in male breast cancer

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Objectives: Male breast cancer (MBC) is a rare aggressive malignant tumor that accounts for only 1% of all breast cancers and has a worse prognosis compared with female breast cancer (FBC). However, little is unveiled regarding the mechanisms of MBC occurrence and development, and there is a lack of relevant basic research and clinical studies at a global scale. The rapid development of single-cell transcriptomic technologies has helped uncover the heterogeneity within cell populations and tumor microenvironment, as well as the clonal evolution of breast cancer cells. This study aims to explore: (1) the tumor microenvironment of MBC; (2) the heterogeneity of male/female breast cancer cells and cell subgroup differences; (3) the potential specific therapeutic targets and biological characteristics differences between MBC and FBC.
Methods: Single-cell transcriptome sequencing (scRNA-seq) and single cell sequencing of T cell receptors (scTCR-seq) combined with whole genome sequencing (WGS) and immunohistochemical staining were performed to deeply analysis the heterogeneity and clonal evolution of MBC, reveal the tumor microenvironment, especially the composition and function of tumor infiltrating immune cells. We performed scRNA-seq using fresh samples from three luminal type MBC patients and two post-menopausal luminal type FBC patients. Firstly, t-SNE dimensionality reduction analysis was conducted according to different genders, different patients and subpopulation of cells, and gene expression profiles were processed and visualized using heatmap. Moreover, through comprehensive analysis of scRNA-seq and scTCR-seq results of MBC and FBC, we further explored the characteristics, interrelation and dynamic changes of various types of cells in the tumor interior, and then mined novel specific therapeutic targets.
Results: Based on the single cell sequencing results, we observed a striking difference in cell subsets distribution and gene expression profiles between MBC and FBC. The cell subsets were then sorted by the proportion of MBC tumor cells, and 7 subsets were selected as potential MBC specific cellular subpopulation. Further comparative analysis with Luminal type of post-menopausal FBC samples suggested that fatty acid synthase (FASN) expression was remarkably elevated in MBC, and the overall survival was significantly decreased in MBC patients with high FASN expression. Meanwhile, MBC tumors were found to have lower rates of immune cell infiltration and higher proportion of exhausted T cells, which were also validated by immunohistochemical staining of 160 cases of pathological sections. Surprisingly, we also observed the presence of some “intermediate cells”only in MBC specimens, which exhibited simultaneous expression of cancer epithelial cell marker KRT8 and T cell marker CD3E. These “intermediate cells”showed immunosuppressive status.
Conclusion: In this study, we found that the high expression of FASN and the lipid metabolism pathway may play important roles in the MBC development, providing theoretical foundation and experimental basis for further clinical trials of FASN inhibitors, as well as precision therapy and prognostic evaluation for MBC. Meanwhile, further study of the “intermediate cells” may facilitate the discovery of novel tumor immune escape strategies. Our findings also played a role in promoting the comprehensive description of tumor microenvironment of MBC and the mechanism study of its occurrence and development.
Key words: male breast cancer, single-cell sequencing, tumor microenvironment, intermediate cells, fatty acid synthase

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**Nuclear expression of acetyl-CoA producing enzymes and their roles in epigenetic reprogramming in breast cancer cells**

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**Metabolic and epigenetic reprogramming are two key hallmarks of cancer. Rapidly proliferating cancer cells often exhibit a higher and differentially reprogrammed transcriptional activity than normal cells of the same tissue. To support transcriptional reprogramming and increased transcriptional load, sustained chromatin acetylation is required to loosen the chromatin and enable RNA transcription. Histone acetylation also requires a constant supply of acetyl-CoA, a labile, membrane impermeable metabolite that is the obligatory donor of the acetyl groups for histone acetylation. However, the pathways responsible for increased synthesis of acetyl-CoA inside the nucleus remain largely elusive. Using estrogen-responsive (MCF7) and their matched endocrine therapy resistant breast cancer cells (LCC9 and MCF7:5C), we show that blocking p300-mediated acetyltransferase activity is crucial for proliferation of endocrine therapy-resistant breast cancer cells. Furthermore, we found nuclear expression of two acetyl-CoA producing enzymes, *i.e.,* pyruvate dehydrogenase complex (PDC), and ATP citrate lyase (ACLY), which implies their functional role inside the nucleus. PDC is a multimeric protein complex enzyme made up of five different subunits. Canonically, PDC is found in mitochondria and is responsible for the conversion of pyruvate to acetyl-CoA, linking glycolysis to the tricarboxylic acid (TCA) cycle. Our results show that multiple PDC enzyme subunits, *e.g.,* pyruvate dehydrogenase (PDH) E1 alpha (E1 alpha), dihydrolipoal dehydrogenase (DLD), and PDHX (also known as E3BP) are expressed in the nucleus of MCF7, LCC9 and MCF7:5C cells. Moreover, expression of nuclear DLD and PDHX subunit is higher in endocrine resistant cells (LCC9 and MCF7:5C) than in their parental MCF7 cells, strongly suggesting a possible role in endocrine resistance. Notably, high expression of PDHX is correlated with poor relapse-free survival in estrogen-receptor positive breast cancer patients in four independent publicly available datasets. ACLY is a tetramer of identical subunits catalyzes conversion of citric acid and co-enzyme A to acetyl-CoA. ACLY is also overexpressed in the nucleus of endocrine-resistant breast cancer cells (LCC9 and MCF7:5C) when compared with their endocrine sensitive MCF7 controls. This study investigates the role of nuclear PDC and ACLY mediated acetyl-CoA synthesis and its impact on histone acetylation enabling reprogrammed transcriptional activity supporting proliferation of endocrine therapy-resistant breast cancer cells.**

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# The metastatic breast cancer project: Generating the clinical and genomic landscape of metastatic breast cancer through patient-partnered research

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The Metastatic Breast Cancer Project (MBCproject) is an ongoing research study that directly engages patients (pts) through social media and advocacy groups, and empowers them to share their samples, clinical information, and experiences. The goal is to create a publicly available dataset of linked genomic, clinical, and pt-reported data to enable research. In collaboration with pts, advocates, and advocacy groups, a website (MBCproject.org) was developed that allows pts with metastatic breast cancer (MBC) anywhere in the US or Canada to register. From 10/20/15-3/31/20, 5708 women and men with MBC registered for the MBCproject. Registered pts are sent an online consent form that asks for permission to obtain and analyze their medical records and samples. Consented pts are sent a saliva and/or blood kit and asked to mail back a saliva sample, which is used to extract germline DNA, and/or a blood sample, which is used to extract germline DNA and cell free DNA (cfDNA). We contact participants' medical providers to obtain medical records and a portion of their stored tumor biopsies. 3245 pts receiving care at over 1700 different institutions have consented to share medical records and tumor/saliva/blood samples and to have genomic analysis performed. Whole exome sequencing (WES) is performed on tumor DNA, germline DNA, and cfDNA; transcriptome sequencing (RNA-seq) is performed on tumor RNA. Medical records and pt-reported data are abstracted to create a detailed clinical record for each pt. Table 1 highlights clinical data collection, biospecimen acquisition, and genomic data generation to date. Examples of clinicogenomic analyses are shown in Table 2. De-identified linked genomic, clinical, and pt-reported data is shared regularly via public and semi-public databases (mbcproject.org, cBioPortal, dbGaP, NCI Genomic Data Commons). To date, this data has been cited in over 20 published journal articles. Study updates are shared with participants regularly. The MBCproject continues to enroll new patients, generate additional data, and perform integrated clinical and genomic analyses with the goal of building a dataset that is representative of patients with MBC. We have partnered with over 30 non-profit breast cancer advocacy groups. We also have several community engagement efforts underway to more directly reach patients in underrepresented communities, including partnerships with faith-based organizations and colleges/universities, as well as targeted engagement with the African American community. In addition, in partnership with Latinx patients, advocates, and researchers, the project has been translated into Spanish and is expected to launch in late 2020. Partnering directly with pts rapidly enables thousands of pts to remotely share tumors, blood, saliva, and medical records to accelerate research. The resulting publicly shared clinically annotated database is a resource that allows researchers to identify patients with specific phenotypes, who have often been challenging to identify with traditional approaches.

| Clinical data collection, biospecimen acquisition, and genomic data generation: | Number |
|---|---|
| Consent signed (US & CA) | 3245 pts |
| Survey #1 submitted(demographics, diagnosis details, receptor status, clinical experiences) | 3245 pts |
| Survey #2 submitted(pathology details, sites of metastasis, treatments with start and stop dates) | 1638 pts |
| Medical record received | 1352 pts |
| Saliva sample received | 2004 pts |
| Blood sample received | 1121 pts |
| Tumor samples received | 585 tumor samples from 424 pts |
| Digital image of tumor slide H&E generated | 585 tumor samples |
| WES from germline complete | 458 germline samples |
| WES from tumor (primary and metastatic) samples complete | 343 tumor samples |
| RNA-seq from tumor (primary and metastatic) samples complete | 228 tumor samples |
| ULP-WGS from cfDNA (taken in metastatic setting) complete | 993 blood samples |
| WES from circulating tumor DNA (taken in metastatic setting) complete | 143 blood samples |

| Cohort | Consented (US & CA) | Tumor WES complete | Tumor RNA-seq complete |
|---|---|---|---|
| Pts diagnosed < 40 yrs of age | 1073 | 120 | 71 |
| De novo MBC | 1127 | 121 | 83 |
| Late recurrence (>5 years after dx) | 830 | 77 | 52 |
| Long term survivors (MBC > 10yrs) | 158 | 11 | 5 |
| Resistance to CDK4/6 inhibitors | 709 | 148 | 39 |
| NED at time of f/u survey | 423 | 89 | 39 |
| Triple Negative Breast Cancer | 310 | 75 | 31 |
| Patients with 2 or more tumor biopsies / cfDNA samples collected by the MBCproject | 287 | 61 | 38 |

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# A multicenter, prospective, observational study to determine the incidence of febrile neutropenia (FN), persistence and G-CSF utilization among cancer patients at high risk for FN receiving pegfilgrastim by an on-body injector (OBI) versus other FN prophylaxis strategies: An interim analysis

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Background Pegfilgrastim is a long-acting granulocyte colony-stimulating factor (G-CSF) shown to effectively reduce the risk of chemotherapy-induced FN. Pegfilgrastim should be administered on the day after chemotherapy completion (Lyman, *Cancer*, 2017). For patient convenience, an OBI was developed to deliver pegfilgrastim 27 hours after OBI application on the day of chemotherapy. Real-world data on whether OBI improves patient persistence, compliance, and outcomes are limited. To address this, a multicenter, prospective, observational study was conducted to describe the incidence of FN, persistence, and G-CSF utilization among patients treated with myelosuppressive chemotherapy for non-myeloid malignancies who received pegfilgrastim by OBI or other physician choice options for FN prophylaxis. Here, we report the interim results of the study. Methods Adult patients with breast, prostate, lung cancer, or non-Hodgkin's lymphoma were stratified into 2 groups, curative or palliative intent, and classified into subgroups of FN prophylaxis based on the first chemotherapy cycle: receiving pegfilgrastim OBI (OBI group) vs other options (Other group; options: pegfilgrastim or biosimilar pegfilgrastim prefilled syringe [PFS], daily filgrastim, no G-CSF) up to 4 planned chemotherapy cycles. Additional eligibility criteria included a life expectancy of >6 months, chemotherapy with high (>20%) FN risk or intermediate (10%-20%) FN risk with ≥1 risk factor administered once every 3 or 4 weeks, and no radiation <2 weeks before enrollment. The prespecified analysis was based on the first 2,000 enrolled patients who completed up to 4 chemotherapy cycles. The primary endpoint is the incidence of FN (defined as absolute neutrophil count [ANC] <1,000 x $10^6$/L and one of the following occurring within 24 hours of decreased ANC: temperature >38$^o$C, use of intravenous antibiotics, or use of oral antibiotics). The clinical study team was blinded to FN per group at the time of analysis. Secondary endpoints include persistence (defined as G-CSF support for all chemotherapy cycles regardless of the timing of administration). G-CSF utilization was included as an exploratory endpoint. Results For the analysis, 1,930 patients were eligible (OBI, 1208; Other, 722). Patients were characterized in table 1 regarding sex, age, tumor type, and FN risk of chemotherapy regimens administered. Most patients were female (OBI, 82.0%; Other, 71.7%). The most common tumor type was breast (OBI, 72.4%; Other, 57.5%). The proportion of patients undergoing chemotherapy regimens with high FN risk was higher in the OBI group than in the Other group. The overall incidence of FN was 7.3% (95% confidence interval [CI], 6.1%-8.4%). In the Other group, 60.5% of patients received pegfilgrastim PFS, 7.6% received a short-acting G-CSF, and 30.6% did not receive G-CSF support in the first cycle. Persistence to G-CSF support was 93.5% (95% CI, 92.2%-94.9%) for the OBI group and 56.9% (53.3%-60.5%) for the Other group. Updated data will be presented at the meeting. Conclusions The OBI improved adherence to clinically appropriate G-CSF support across all chemotherapy cycles. However, approximately a third of patients did not receive primary prophylaxis with G-CSF despite being considered as a high risk for FN.

| Characteristic | On-Body Injector (N=1,208) | Other Physician Choice Options (N=722) |
|---|---|---|
| Sex, n (%) | | |
| Male | 218 (18.0) | 204 (28.3) |
| Female | 990 (82.0) | 518 (71.7) |
| Age | | |
| <65 years, n (%) | 679 (56.2) | 397 (55.0) |
| Median, years | 63.0 | 62.0 |
| Tumor type,[a] n (%) | | |
| Breast | 874 (72.4) | 415 (57.5) |
| Non-Hodgkin's lymphoma | 178 (14.7) | 142 (19.7) |
| Lung | 107 (8.9) | 104 (14.4) |
| Prostate | 49 (4.1) | 51 (7.1) |
| FN risk of chemotherapy, n (%) | | |
| High | 777 (64.3) | 330 (45.7) |
| Intermediate | 376 (31.1) | 326 (45.2) |
| Unknown | 55 (4.6) | 66 (9.1) |
| [a]Ten patients were missing a tumor type in the Other Physician Choice Options group. FN, febrile neutropenia | | |

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# Relationship of dedicated breast PET and MRI features in breast cancer patients receiving neoadjuvant chemotherapy

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**Introduction:** Dedicated breast positron emission tomography (dbPET) is an emerging imaging technique with the spatial resolution needed to assess functionality and intra-tumor heterogeneity in primary breast lesions. Breast cancer patients may benefit from dbPET imaging combined with molecularly targeted agents to non-invasively assess and predict response to targeted therapy in the neoadjuvant treatment setting. We have previously observed that [$^{18}$F]-fluorodeoxyglucose (FDG) PET provides tumor metabolic information complementary to the angiogenic properties reflected by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for characterizing triple-negative breast cancers (TNBC) (1). In this study, we examined the relationship between FDG-dbPET and MRI features in a cohort of breast cancer patients receiving neoadjuvant chemotherapy (NAC).

**Methods:** With institutional review board approval, patients with biopsy-proven locally-advanced breast cancer were imaged with breast MRI and dbPET before (T0) and after three weeks (T1) of NAC. Standard DCE-MRI was obtained using a dedicated breast coil. Patients also underwent dbPET with 5 mCi of FDG at 45 minutes post-injection. Functional tumor volumes (FTV) were calculated from DCE-MRI by summing all voxels with an early percent enhancement (PE) exceeding 70% within a manually defined volume of interest (VOI). Maximum and mean PE ($PE_{Max}$, $PE_{Mean}$) values within the VOI were also computed for analyses. Tumors were segmented in dbPET images using semi-automated threshold-driven methods. Body weight-corrected maximum and mean standardized uptake values ($SUV_{Max}$, $SUV_{Mean}$), total lesion glycolysis (TLG), and metabolic tumor volume (MTV) were calculated for FDG-dbPET. Percent change relative to T0 (Δ = 100*(T1 - T0)/T0) was calculated for each feature. Spearman's correlation coefficient was used to evaluate the relationship between MRI and dbPET features.

**Results:** Of the 16 patients enrolled in this study, 13 patients (N = 15 unique tumors) with MRI and dbPET at T0 and T1 were included in the analysis. 46% (6/13) of the patients had TNBC. Our initial findings indicated that $\Delta PE_{Max}$ and $\Delta SUV_{Max}$ had the highest correlation ($\rho = 0.59$, $p = 0.022$). FTV and TLG at T1 were also correlated ($\rho = 0.56$, $p = 0.032$). Among all imaging features, ΔMTV showed the largest post-treatment difference between TNBC (-54.5%) and non-TNBC (-6.06%) groups. Among MRI features, ΔFTV exhibited the largest difference between the groups: -70.4% in TNBC and -43.1% in non-TNBC. $\Delta SUV_{Max}$ and ΔTLG were additional dbPET features with large differences between TNBC and non-TNBC patients (Table 1).

**Conclusion:** This exploratory study suggests that post-treatment $\Delta SUV_{Max}$ and TLG provide complementary metabolic information to angiogenic properties ($\Delta PE_{Max}$ and FTV, respectively) reflected by MRI. Other dbPET features may provide independent information adjunct to MRI for describing primary breast tumors. Patients with TNBC exhibited larger reductions in FDG uptake values and metabolic volume than non-TNBC patients. These observed reductions may improve early treatment response in patients with TNBC, enabling more precise treatment guidance. Further studies in larger cohorts are needed to validate these initial observations.

1. Bolouri MS*, et al.* Triple-Negative and Non-Triple-Negative Invasive Breast Cancer: Association between MR and Fluorine 18 Fluorodeoxyglucose PET Imaging. Radiology 2013;269:354-61

**Comparison of ΔMRI and ΔFDG-dbPET in TNBC vs non-TNBC patients**

| | All Tumors (N = 15 tumors) Median(IQR) | TNBC (N = 6 tumors) Median(IQR) | non-TNBC (N = 9 tumors) Median(IQR) |
|---|---|---|---|
| DCE-MRI | | | |
| ΔFTV (%) | -66.1 (-77.6, -19.1) | -70.4 (-79.0, -62.1) | -43.1 (-72.5, -2.95) |
| $\Delta PE_{Max}$ (%) | -9.91 (-31.5, 19.5) | -10.3 (-26.3, 24.2) | -9.91 (-31.8, 8.42) |
| $\Delta PE_{Mean}$ (%) | -10.7 (-22.4, 2.77) | -9.57 (-12.8, 0.29) | -17.0 (-26.0, 2.33) |
| FDG-dbPET | | | |
| $\Delta SUV_{Max}$ (%) | -31.6 (-53.9, -20.6) | -47.3 (-55.7, -41.1) | -23.1 (-31.6, 1.13) |
| $\Delta SUV_{Mean}$ (%) | -34.1 (-65.4, -14.2) | -48.5 (-74.6, -9.74) | -34.1 (-44.5, -14.8) |
| ΔMTV (%) | -6.18 (-57.0, 38.5) | -54.5 (-75.4, 15.3) | -6.06 (-47.2, 38.9) |
| ΔTLG (%) | -64.9 (-75.2, 23.3) | -75.2 (-84.0, -60.0) | -47.9 (-65.2, 31.1) |

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# Identification of a low-risk luminal breast cancer cohort that may not benefit from multi-gene testing

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**Purpose: Dutch clinical risk criteria (low-risk definition: age > 35 years and (grade 1 with tumor ≤3cm, grade 2 with tumor ≤2cm, or grade 3 with tumor ≤1cm) have been used to stratify the benefit of MammaPrint and Oncotype DX for the decision-making regarding adjuvant chemotherapy for early-stage luminal breast cancer. We propose that the criteria could help to identify low-risk patients who could barely benefit from multi-gene testing. Materials and methods: Breast cancer patients from Taiwan Cancer Database initially treated with primary surgeries between 2008 and 2012 who met the following criteria: (1) pathologic node-negative, (2) hormone receptor-positive, (3) HER2-negative, (4) undergone hormonal therapy, and (5) a minimum follow-up time of 5-year if free from any event, were enrolled in this study. Out of the total 2679 eligible patients, 1074 (40.1%) patients received adjuvant chemotherapy in addition to endocrine therapy. The study endpoints included breast cancer-specific survival (BCSS) and overall survival (OS). Kaplan-Meier statistics estimated the difference between clinical outcomes in low- and high-risk groups. Results: The median follow-up time of BSCC and OS was 5.9 years (range, 0-7 years) and 5.8 years (range, 0-7 years), respectively. There were statistical significances of 5-year BCSS (n=2679) and 5-year OS (n=2636) between low-risk and high-risk groups (in both endpoints, P < 0.0001). According to the Dutch criteria, low-risk patients with and without adjuvant chemotherapy had a 5-year BCSS of 99.0% vs. 99.2% and a 5-year OS of 98.4% vs. 97.4%, respectively. High-risk patients with and without adjuvant chemotherapy had a 5-year BCSS of 97.7% vs. 98.1% and a 5-year OS of 96.4% vs. 95.3%, respectively. Conclusion: The benefit of chemotherapy in low-risk patients classified by Dutch criteria might be very small since the breast cancer mortality was less than 1% with a minimum of 5-year follow-up. Dutch criteria cannot identify high-risk patients who would benefit from chemotherapy. We assumed that multi-gene testing in low-risk patients would not be cost-effective.**

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# Angiogenesis in a bulk tumor is associated with cancer immunity and metastasis

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**Angiogenesis is included in one of the hallmarks of cancer because it not only provides conduit to supply oxygen and nutrients to the cancer cells, but also deliver molecules that confer immune resistance, cell adhesion proteins, and other various growth factors. We hypothesized that angiogenetic score that accumulate 200-related genes will accurately grasp angiogenesis in bulk tumor that enable as to assess clinical relevance of angiogenesis in breast cancer. Angiogenesis pathway score was defined using the molecular Signatures Database Hallmark angiogenesis gene set. Median was used to divide into high and low score groups within each cohort. High angiogenesis score is associated with high expression of Vascular endothelial growth factor (VEGF)- (VEGFA/B, VEGFR1/2/3; p = 0.094, < 0.001, < 0.001, < 0.001, < 0.001, respectively), Endothelial cell surface marker- (CD31 and VWF; all p < 0.001), Vascular stability- (TIE1/2, ANGPT1/2, VE-Cadherin, Claudin 5 and JAM2; all p < 0.001), Hypoxia- (HIF1A/1B; p < 0.001 and 0.004), and Shlingosine-1-phosphate (S1P)- (SphK1/2, S1PR1, SPNS2; all p < 0.001) related genes in TCGA cohort. These results were validated by METABRIC cohort. Even though none of the angiogenesis-related genes analyzed were included in the angiogenesis pathway score except for VEGFA. Although angiogenesis score was not associated with aggressive clinical features nor response to neoadjuvant chemotherapy, high angiogenesis score tumors were associated with both favorable and unfavorable immune cell infiltrations including CD4 memory (p < 0.001 and 0.03), T helper 1 (Th1) (p < 0.001 in both cohorts), B cell (p < 0.001 in both cohorts), T helper 2 (p < 0.001 in both cohorts) and regulatory T cell (p < 0.001 and 0.037) in both cohorts. On the other hand, Dendritic cell and M2 macrophage were highly infiltrated in high angiogenesis score tumors in both cohorts (p < 0.001 in both cohorts). TIL regional fraction was higher in the low angiogenesis score group (p < 0.001), while Leukocyte fraction and lymphocyte infiltration signature showed higher values in the high angiogenesis score tumors (both p < 0.001). High angiogenesis pathway score significantly enriched immune response-related Hallmark gene sets; interferon (IFN)-γ response, IL2-STAT5 signaling, and IFN-α response. Furthermore, high angiogenesis score significantly enriched unfavorable inflammation-related Hallmark gene sets; inflammatory response, IL6-JAK-STAT3 signaling, TNF-α signaling via NFkB, and TGF-β signaling and hypoxia. Furthermore, we found that metastasis-related genes sets; including epithelial mesenchymal transition (EMT), HEDGEHOG signaling, NOTCH signaling and WNT-β catenin signaling were also enriched in high angiogenesis score group in both cohorts (all FDR < 0.25). In particular, EMT pathway score was strongly correlated with angiogenesis pathway score in both cohorts (spearman r = 0.894 [*p* < 0.01] and 0.868 [*p* < 0.868] respectively). High angiogenesis pathway scores were significantly associated with site-specific metastasis-free survival especially brain and bone metastasis (p = 0.029 and 0.043 respectively). In conclusion, the angiogenesis score covers many of the angiogenesis-related genes, and it show the correlation between the amount of angiogenesis with inflammation and metastasis in breast cancer.**

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# A prospective comparison of skin staining after sentinel lymph node biopsy, using blue ink (PB) and superparamagnetic iron oxide nanoparticles (SPIO) tracers

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**Background: Superparamagnetic iron oxide (SPIO) nanoparticles is a magnetic sentinel lymph node (SN) tracer. Since no radioisotope (technetium, $Tc^{99}$) is used, there is no need for a nuclear medicine department. Compared to the use of Patent Blue V® (PB), no allergic reactions have been reported so far. However, a long lasting skin staining has been observed. We compared skin staining in women who were injected with both SPIO (MagTrace®) and PB. Methods: SPIO, $Tc^{99}$ and PB were injected in all women in the SentiDose study (2017-2019), a SPIO dose optimizing trial, including six Swedish hospitals. For PB, a 1.0ml sub/intradermal, peri-areolar injection was administred. For SPIO either a 1.5ml retro-areolar (*Cohort 1.5*, n=163) or a 1.0ml peri-tumoral (*Cohort 1.0*, n=164) interstitial injection was administred. Staining was assessed by telephone interviews at 6, 12 and 24 months post surgery, and mean size calculations only included women with a stain. Mastectomy cases (n=63) were excluded from the analysis. SN detection rates will be reported elsewhere. Results: In *Cohort 1.5*, 27.7% (33/119) of the women had a SPIO stain and 25.2% (30/119) a PB stain at 6 months (p=0.66). The mean stain sizes were 13.4 and 9.1cm$^2$ (p=0.16), respectively. At 12 months, 20.8% still had a SPIO stain and 17.6% a PB stain (p=0.91), with mean sizes of 4.1 and 3.7 cm$^2$ (p=0.73), respectively. At 24 months, from the 11 women followed so far, all 3 with an earlier SPIO stain and 7 of 8 with an earlier PB stain are now stain free. In *Cohort 1.0*, 16.5% (25/145) had a SPIO stain and 16.9% (24/139) had a PB stain at 6 months (p=0.94). The mean stain sizes were 11.8 and 8.4 cm$^2$ (p=0.42), respectively. Nine women were not injected with PB. After 12 months, 15.9% still had a SPIO stain and 12.4% a PB stain (p=0.42). The mean sizes were 5.1 and 2.6 cm$^2$ (p=0.99), respectively. Comparing all women at 6 months, 22.0% had a SPIO stain and 20.5% a PB stain (p=0.12) with mean sizes 12.5 and 8.6 cm$^2$ (p=0.83), respectively. At 12 months, 17.8% had a residual SPIO stain and 14.9% a PB stain (p=0.37) with mean sizes 4.6 and 3.3 cm$^2$ (p=0.16), respectively. The difference in incidence of SPIO staining between *Cohort 1.5* and *Cohort 1.0* was statistically significant at 6 months, but not at 12 months, 27.7% vs. 16.5%, (p=0.04) and 20.8% vs 15.9% (p=0.28), respectively. The difference in SPIO stain sizes between the cohorts was neither significant at 6 months, 13.4 vs 11.8 cm$^2$(p=0.61) nor at 12 months, 4.1 vs 5.1 cm$^2$ (p=0.30). Conclusion: No statistically significant differences in incidence or stain size were observed between SPIO and PB. The 2-year follow up will be completed during 2021. The 1.0ml compared to 1.5ml SPIO dose, resulted in fewer but equally large stains at 6 months, but there was no difference at 1 year.**

**Table 1. Skin staining after SPIO and Patent Blue (PB) for sentinel lymph node detection**

| Tracer | Staining/Size | Staining/Size |
|---|---|---|
| | 6 months | 12 months |
| SPIO 1.5ml, n=119 | 27.7%/13.4cm$^2$ | 20.8%/4.1cm$^2$ |
| SPIO 1.0ml, n=145 | 16.5%/11.8 cm$^2$ | 15.9%/5.1 cm$^2$ |
| PB, n=258 | 20.5%/8.6 cm$^2$ | 14.9%/3.3 cm$^2$ |

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# Phase I study to evaluate the safety and feasibility of preoperative ablative radiotherapy (SABER) for selected early stage breast cancer

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Background: Breast conserving therapy is an established option for early stage breast cancer. Shorter postoperative radiotherapy (RT) regimens have similar efficacy in lower risk breast cancer, including hypofractionated whole breast RT and Accelerated Partial Breast Irradiation (APBI). Despite similar efficacy results for APBI, RAPID trial showed worse cosmetic outcomes for patients receiving APBI compared to whole breast RT. Larger postoperative lumpectomy cavity volumes and the used dose regimen could have had an impact on cosmesis. There are only few published preoperative APBI pilot studies with different dosimetric schemes treating smaller RT target volumes that would potentially translate into less toxicity. Our study is designed to evaluate the safety and feasibility of preoperative ablative RT in patients with early stage breast cancer. An array of ancillary imaging, blood and tissue biomarker collection is also planned in order to study the radiation response in breast cancer. Trial Design: This phase I study uses a modification of the standard 3+3 Phase I design to identify the recommended phase 2 dose of preoperative SABER for treatment of selected breast cancer patients. Participants will be treated with assigned dose level of preoperative SABER, once a day, for 5 fractions given on non-consecutive days, over a period of 2 weeks. The tested dose levels are: Level I=35 Gy (7 Gy x 5), Level II (starting dose)= 40 Gy (8 Gy x 5), Level III=45 Gy (9 Gy x 5), Level IV=50 Gy (10 Gy x 5). Standard partial mastectomy and axillary surgery will be performed 4-6 weeks after preoperative SABER. Adjuvant systemic therapy will be per standard of care. Exploratory studies will be performed pre/post RT and postoperative, including multiparametric breast MRI, biomarkers in blood (CTC's, SNPs, cytokines, CRP) and tissue (assessment of radiation response, expression of PD-L1, PD1, TILs). Cosmesis and QoL assessment will be performed at scheduled 1, 6, 12, 24 months follow-up. Eligibility criteria: Women, 50 or older, clinical stage T1 unifocal, N0, ER/PR+/HER2 negative, ECOG 0-1, able to undergo MRI with contrast are eligible. Specific Aims: Aim 1. To identify the recommended phase II dose of preoperative SABER; Aims 2.a) to determine the safety, tolerability, Dose Limiting Toxicity (DLT) and toxicity profile of delivering SABER; b) to determine the rate of complete pathological response after preoperative SABER; c) To assess cosmetic results (by MD and patient's assessment) and QoL after SABER and standard partial mastectomy/axillary surgery. Exploratory aims: a) to determine biomarkers in blood and tissue, and multiparametric MRI radiographic changes and associate them with toxicity and radiation tumor response; b) to assess locoregional recurrence, disease-free survival, and overall survival; c) to assess sentinel lymph node biopsy identification rates after SABER. Statistical Methods: In this novel phase I study, escalation to the next higher dose level will occur only if 0 or only 1 out of 6 patients has DLT. Present accrual and target accrual: A total of 12 to 18 evaluable patients will be enrolled. Expected enrollment period is 3 years and time to complete the study is about 5 years. Open for accrual in 06/2020. Clinical trial information: NCT04360330

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# TAA013 a trastuzumab antibody drug conjugate phase I dose escalation study in recurrent her2 positive breast cancer

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**Background: A phase 1 dose escalation study of TAA013, an antibody drug conjugate linking trastuzumab to a cytotoxic small molecule, DM1, through an SMCC linker, in previously treated recurrent Her2 positive breast cancer patients. Material and Methods: This phase I study follows the traditional 3+3 design, dosing started at 0.6mg/kg, followed by 1.2, 2.4, 3.6, 4.8mg/kg, one intravenous infusion was given every 3 weeks, the initial infusion had to be over 90 minutes, infusion times were later shortened if treatment was well tolerated. The subsequent recommended dose would be expanded to include at least 10 patients. Patients were observed for dose-limiting toxicity (DLT) during a 21-day DLT observation period. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Maximum-tolerated dose (MTD) was defined as the highest dose level that resulted in a DLT in no more than 1 of 6 patients. Study endpoints included safety and tolerability, pharmacokinetic and immunogenicity parameter evaluation, with preliminary evaluation of efficacy. Results: The study enrolled 22 female patients with histologically confirmed Her-2 positive metastatic breast cancer, median age of 50yrs (25-67), median time from initial diagnosis to TAA013 dosing was 39 months (5-99), median prior treatment regimen was 4 (2-10), all had received trastuzumab for a mean of 8.2 months (2-10), alone or in combination with chemotherapy, other prior Her2 targeting drugs given included pertuzumab (2), lapatinib (7), and pyrotinib (8). All patients received at least 2 (median of 6 infusions, range of 1-15) infusions, except for the last 4.8mg/kg patient, but all patients passed the dose limiting toxicity (DLT) observation period of 21 days. There were no dose limiting toxicities, no serious adverse events, nor that resulting in mortality, the maximum tolerated dose was not reached. The most common treatment emergent adverse events (TEAE) included 9 (40.9%) grade 1-2 infusion reactions associated with fever(5) and/or chills(1), the reaction often abated in subsequent cycles. There were no grade 4 TEAE, but there were 3 grade 3 thrombocytopenia, one grade 3 neutropenia, and one grade 3 hyperbilirubinemia which all recovered for the patients to continue treatment, there was also one grade 3 dermatitis in a patient with a history of chronic dermatitis. Antibody drug antibodies were not detected emanating from the TAA013 therapy. Pharmacokinetic studies included evaluation of TAA013, trastuzumab and DM1. Preliminary efficacy evaluation in the 2.4-4.8mg/kg dosing group of heavily pretreated patients resulted in 2 partial responses, including patients who had previously received pyrotinib therapy. Conclusion: TAA013 is a Her2 targeting antibody drug conjugate that is safe and tolerable, with efficacy demonstrated in heavily pretreated Her2 positive breast cancer patients.** **Keywords: breast cancer, antibody drug conjugates, TAA013.**

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# Secondary outcomes in a randomized controlled trial of acupuncture versus sham acupuncture and usual care in solid tumor survivors with chemotherapy-induced peripheral neuropathy

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) is the most common and debilitating long-term adverse effect of neurotoxic chemotherapy and it significantly worsens cancer survivors' quality of life. In a previously reported randomized controlled trial, we showed that real acupuncture is more effective in reducing persistent CIPN symptoms compared to usual care, with a trend of greater CIPN pain reduction compared to sham acupuncture (Bao et al, JAMA Netw Open, 2020). Here, we report secondary outcomes in this trial. Patients and Methods: Solid tumor survivors with persistent moderate to severe CIPN (symptoms of numbness, tingling, or pain rated ≥4 on a numeric rating scale [NRS]) were randomized to three arms: 1) Eight weeks of real acupuncture (RA); 2) eight weeks of sham acupuncture (SA); and 3) usual care (UC). The secondary endpoints were Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx), Hospital Anxiety and Depression Score (HADS), and Insomnia Severity Index (ISI). For each endpoint, the mean changes from baseline and 95% confidence intervals (CI) were estimated within each arm and compared between arms using linear mixed models.Results: We enrolled and randomized 75 solid tumor survivors (53% breast cancer) with moderate to severe CIPN to the study. Compared to baseline, at week 8, FACT/GOG-Ntx, HADS anxiety, and ISI scores significantly improved in both RA and SA arms, but not in the UC arm (Table 1). At week 8, FACT/GOG-Ntx scores significantly increased in both RA and SA arms when compared with UC (p=0.001 and 0.007), indicating improved CIPN related symptoms and quality of life. There was no statistically significant difference between RA and SA arms, p=0.498. When comparing RA and SA with UC, we found no statistically significant difference in changes from baseline in HADS anxiety and ISI.Conclusions: Our study showed acupuncture may be effective in improving CIPN symptoms and reducing anxiety and insomnia in cancer survivors with persistent CIPN. Further large sample size studies are needed to delineate possible placebo effects from SA.

Table 1. Secondary Outcomes in RA, SA, and UC Arms and Changes From Baseline

| | | Real Acupuncture(n=27) | | Sham Acupuncture (n=24) | | Usual Care (n=24) | |
|---|---|---|---|---|---|---|---|
| Outcome | Week | Mean (95% CI) | Change from Baseline,Mean (95% CI) | Mean (95% CI) | Change from Baseline,Mean (95% CI) | Mean (95% CI) | Change from Baseline,Mean (95% CI) |
| FACT/GOG-Ntx | 0 | 24.41 (21.38, 27.44) | NA | 25.13 (21.91, 28.34) | NA | 27.01 (23.80, 30.22) | NA |
| | 8 | 28.60 (25.52, 31.67) | 4.19 (2.39, 5.99)*** | 28.42 (25.19, 31.66) | 3.30 (1.45, 5.15)*** | 26.61 (23.32, 29.89) | -0.40 (-2.35, 1.54) |
| HADS Anxiety | 0 | 6.61 (4.98, 8.25) | NA | 7.66 (5.93, 9.39) | NA | 6.52 (4.79, 8.25) | NA |
| | 8 | 5.61 (3.95, 7.27) | -1.00 (-1.99, -0.01)* | 6.64 (4.89, 8.38) | -1.02 (-2.03, -0.01)* | 6.76 (4.99, 8.53) | 0.24 (-0.81, 1.29) |
| ISI | 0 | 12.93 (10.24, 15.61) | NA | 12.46 (9.61, 15.31) | NA | 10.17 (7.32, 13.02) | NA |
| | 8 | 10.63 (7.88, 13.37) | -2.30 (-3.99, -0.61)** | 10.20 (7.33, 13.07) | -2.26 (-3.99, -0.53)* | 8.96 (6.05, 11.87) | -1.21 (-3.01, 0.60) |

Table Symbols: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

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# The impact of SSRI use on overall survival in breast cancer patients in northern Israel

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**Background: It is estimated that 12.7% of the US population had been prescribed an antidepressant in the past month and that women are twice as likely to be on an antidepressant than men. Therefore, it is especially important to understand how SSRIs interact with female hormones and influence risk and progression of female cancers, especially breast cancer, being the most common. Up to a third of women use selective serotonin reuptake inhibitors (SSRIs) after breast cancer diagnosis. Recent investigation has demonstrated serotonin receptor (5-HTR2B) expression in the breast and identified serotonin production in breast tumor cells as an indicator of poor prognosis. This paper presents a unique comparative assessment between the influence of prior SSRI use, continuous and after use relative to breast cancer diagnosis on overall mortality among breast cancer patients. This analysis is expected to provide a clearer understanding of the influence of SSRIs based on period of use relative to time of diagnosis on overall mortality. Methods: The present study includes a population-based sample of consecutively diagnosed breast cancer cases identified as part of the Breast Cancer in Northern Israel study. Patients were recruited and followed from January 1st, 2000 to July, 2019. Participants completed risk factor questionnaires regarding medical, reproductive, family and personal history of cancer, medication use and health habits. Additionally full prescription data was available through the Israeli national CLALIT medical database. An analysis of 5976 newly diagnosed women with breast cancer was performed. K-M survival analysis and time-dependent and time-independent COX proportional hazard models were performed to determine overall survival based on interval of SSRI use. Results: Use of SSRIs in the 5 years prior to breast cancer diagnosis was associated with a 66% increase in overall mortality ($HR_{adj.}$=1.66; CI: 1.05-2.63). Use of SSRIs with use that initiated after breast cancer diagnosis was associated with an 81% increase in mortality ($HR_{adj.}$=1.81; CI: 1.58-2.06). Use of SSRIs in the 5 years post-diagnosis was associated with a significant (*P*<0.001) dose-response increase in long-term mortality (>5 years). For 24 months of SSRI use after diagnosis, there was a 99% increase in mortality (HR=1.99; CI: 1.39-2.83). Conclusion: SSRIs used both prior to and after breast cancer diagnosis are associated with reduced overall survival in breast cancer patients. The effect of SSRIs on mortality persisted even after adjustment for tamoxifen and factors thought to mediate the relationship behind depression and increased mortality including increased age at diagnosis, comorbidities and stage at diagnosis pointing toward other mechanisms mediating the association between SSRIs and impaired survival in breast cancer patients. Additional research is needed to better understand who is susceptible to the adverse effects of SSRIs on breast cancer overall mortality. Treating depressive symptomatology is of high importance. The results presented here indicate that risks and benefits of SSRI use after breast cancer diagnosis should be weighed when initiating pharmachotherapy and additional research is needed to better understand why SSRIs are associated with worse outcomes in breast cancer patients.**

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# A phase II study of neoadjuvant weekly carboplatin/paclitaxel followed by dose-dense doxorubicin/cyclophosphamide (DD AC)in patients with triple negative breast cancer (TNBC): Wisconsin oncology network (WON) study

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**Background: The CALGB 40603 and BrighTNess studies found that adding high dose carboplatin every 3 weeks to the standard neoadjuvant DD AC - paclitaxel regimen in TNBC increased the pathologic complete response (pCR) rate to 54-58% but with the cost of increased treatment related toxicities resulting in decreased completion of the full course of treatment. Our hypothesis is by changing the high dose carboplatin every 3 weeks to low dose weekly carboplatin, it will retain the same benefit in pathologic response rate and minimize the treatment related toxicities, which in turn permits the full course of neoadjuvant treatment given to patients. Patients and Methods: This multi-center study was conducted through the WON (NCT03301350). Eligible TNBC patients for neoadjuvant chemotherapy received weekly carboplatin (AUC=2) and paclitaxel 80 mg/m2 for 12 doses, followed by dose dense doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 2 weeks with granulocyte growth factor support for 4 cycles. A one-week break was added before DD AC after the first 22 patients in order to minimize prolonged cytopenia. Primary end point was pCR. Secondary endpoints were frequency of dose modification and treatment related toxicities. Results: Accrual target was 50 with 80% power to detect a 20% difference using a one-sided binomial test at an alpha significance level of 0.025, but study was terminated earlier. Twenty-nine eligible patients consented for the study from November 2017 to February 2020. Median age was 52 year-old (range, 33-80). Twenty-eight patients received the study regimen. Three were removed due to early study termination and one (3.8%) died from grade 5 neutropenic sepsis after the last cycle of DD AC before surgery. Thus, 24 patients were evaluable for the primary outcome and 26 were evaluable for dose modification and toxicity outcomes. Eight patients (33%) achieved pCR and another 4 patients (17%) had minimal (ypT1aN0) residual disease. Of 26 patients, 24 (92%) were able to receive the full course of treatment +/- dose modification. One patient required the discontinuation of weekly carboplatin/paclitaxel completely due to severe infusion reaction and one did not finish the treatment before the study was terminated. Eight patients (31%) required dose delay with 5 of them during the weekly carboplatin/paclitaxel treatment. Seven patients (27%) also required dose reduction with 5 of them during the weekly carboplatin/paclitaxel treatment. Seventeen patients (65%) experienced severe adverse event (grade 3 or 4) with the majority of events (12/17) relating to grade 3-4 neutropenia or neutropenic fever. Conclusion: Although our study showed a lower pCR rate of 33% in compare to the previous CALGB 40603 (54%) and BrighTNess (58%) studies, we demonstrated that the majority of patients (92%) were able to receive the full course of study treatment. This weekly carboplatin with paclitaxel - AC regimen was used in the recent Keynote 522 study as the backbone chemotherapy to combine with check-point inhibitor immunotherapy in TNBC. However, any dosing schedules of carboplatin, weekly or every 3 weeks, add substantially to grade 3 or 4 toxicity of paclitaxel - AC. Aggressive supportive care management is needed when carboplatin is used.**

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**Leptin receptor expression in breast tumors and chromatin modulators: A comparative study**

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**Metabolic dysregulation and carcinogenesis are strongly linked. Leptin signaling acts as a metabolic switch that maintains body weight and energy homeostasis and gets impacted during metabolic dysregulation. Leptin signaling mediates its effect on breast cancer cells through downstream effectors like JAK-STAT, MAPK and PI3K pathways. At the molecular level, leptin exerts its effects through its receptor, LEPR, encoded by *LEPR* gene. Leptin signaling has been shown to contribute towards progression of breast cancer. Obese post-menopausal women are considered to be a high-risk category for breast cancer and dysregulated leptin signaling contributes towards it. We in this study focused on comparative molecular analysis of Leptin high (LEPR$^{hi}$) and low (LEPR$^{low}$) expressing breast tumors.Breast cancer data from METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) study was used through the cBioPortal (http://cbioportal.org) platform for cancer genomics. The METABRIC study includes clinical and molecular data from over 2500 breast cancer cases. The LEPR$^{hi}$ and LEPR$^{low}$ expressing breast tumors in RNA-seq dataset were queried using cBioPortal embedded SQL feature as LEPR: EXP>1 and LEPR: EXP<-1 respectively. This query enabled us to create LEPR$^{hi}$ and LEPR$^{low}$ expressing breast tumor cohorts from 243 and 234 patients respectively. Comparative analysis of LEPR$^{hi}$ and LEPR$^{low}$ expressing breast tumors was performed for mRNA expression profiles. The mRNA data was further analyzed for integrated networks using GSEA pathway enrichment and CR2-cancer algorithms.The analysis indicated unique mRNA expression signature for LEPR$^{hi}$ and LEPR$^{low}$ breast tumors. CR2-Cancer analysis of the mRNA dataset revealed chromatin modulators like- EZH2 (Enhancer of Zeste homolog 2), MEN1 (Menin), UHRF1 (Ubiquitin Like with PHD And Ring Finger Domains 1), TTF2 (Transcription termination factor 2), LMNB2 (Lamin B2), and RUVBL2 (RuvB Like AAA ATPase 2) had significantly higher mRNA expression in LEPR$^{low}$ compared to LEPR$^{hi}$ tumor group. GSEA pathway enrichment analysis indicated PLK1 and Aurora A signaling as the most significant signaling pathways with an FDR q-value of less than 0.05.This preliminary study provides us with mechanistic insight into the unique molecular signatures of LEPR$^{hi}$ and LEPR$^{low}$ expressing breast tumors. The results of this study leads to the basis of our hypothesis that leptin receptor signaling in breast cancer mediates epigenetic modifications of key genes that impact promotion and progression of breast cancer through chromatin modulators.**

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# Adjuvant treatment with paclitaxel plus trastuzumab for node negative human epidermal growth factor receptor 2-positive breast cancer: Real life experience

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BackgroundInvasive breast cancers are characterized by overexpression or amplification of the human epidermal growth factor receptor 2 (*HER2*) approximately 15 to 25%. Survival outcomes was improved after introduction of Trastuzumab treatment. Trastuzumab treatment was applied mostly with combination chemotherapy regimens at pivotal trials. There were some efforts to avoid the toxicity of combination chemotherapies and reduce the amount of treatment given especially in stage I HER 2 overexpressed breast cancer patients. Adjuvant paclitaxel plus trastuzumab was shown excellent disease free survival (DFS) and overall survival (OS) in node negative, 3 cm and smaller HER 2 overexpressed breast cancer patients. MethodsAll breast cancer patients that treated in Medical Oncology departments of Hacettepe University (Ankara, Turkey), Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Ankara, Turkey), Nicosia Dr. Burhan Nalbantoglu State Hospital (Nicosia, Cyprus) and Near East University (Nicosia, Cyprus) were retrospectively reviewed from patient files, center's databases and chemotherapy files.ResultsWe retrospectively analyzed 173 patients who treated with adjuvant paclitaxel plus trastuzmab between April 1, 2012 and April 10, 2020. Median age was 52 years (range, 25 to 84 years) and 62.4% had estrogen receptor positive disease. 68.8% of the tumors were high-grade. 14.4% of patients had tumors 1 cm or smaller. 45.0% of patients had tumors larger than 2 cm and 32.3% of patients had tumors larger than 2 cm and up to 3 cm. 12.6% of patients had tumors larger than 3 cm. Mean tumor size was 2.2 cm. 88.4% of patients had N0 disease and 2.9% of patients had microscopic nodal metastasis. 164 of 173 patients completed all 52 weeks of adjuvant treatment. Median follow up of 43 months there were 8 DFS events observed: four distant recurrences (2.3%), three locoregional recurrences (1.7%) and one died without documented recurrence. 3-year DFS rate was 96.6%. There was no recurrences in patients who had tumors 1 cm or smaller. There were 5 DFS events in patients had tumors larger than 2 cm and up to 3 cm subgrup. ConclusionThis real life experience with paclitaxel plus trastuzumab demonstrated few distant recurrences and further supports the APT trial findings.

Table 2. Events Observed for the Disease-free Survival.

| Events | Patients (N=173)no. (%) | Time to Eventmo |
|---|---|---|
| Any recurrence or death | 8 (4.6) | |
| Local or regional recurrence | | |
| Ipsilateral axilla, HER2-positiveIpsilateral breast, HER2-positive | 2 (1.1) 1 (0.6) | 25, 64 48 |
| Distant recurrence | 4 (2.3) | 7, 35, 36, 42 |
| Death | | |
| Not breast-cancer-related | 1 (0.6) | 52 |

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# Identification of Aurora kinase A as a biomarker for prognosis in obesity patients with early breast cancer

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**Background: Obesity is associated both with a higher risk of developing breast cancer, particularly in postmenopausal women, and with worse disease outcome for women of all ages. The molecular mechanisms that link obesity-breast cancer are complex and unclear. We hypothesized that overexpression of Aurora A was associated with poor survival in obesity breast cancer and related axis mechanism were involved.Methods: Fifty hundred and eighteen primary breast cancer specimens were collected from First Affiliated Hospital of China Medical University between January 2011 and November 2016. Our independent variable was BMI at baseline, categorized as overweight (BMI ≥ 25 kg/m$^2$, as Obesity cohort), and normal (18.5 ≤ BMI < 25 kg/m$^2$, as Non-obesity cohort). The Immunohistochemical (IHC) staining was performed with Aurora A, Survivin, MMP11, Cyclin B1 and Cathepsin L. Kaplan-Meier curve was used to analyze overall survival in our cohorts and TCGA-BRCA data (GSE3494). Log-rank test was used to calculate P value. PPI network analysis and MCODE model was used to analysis Aurora- altered signal pathway from GSE78958.Results: We validated Aurora A over expression using an independent cohort with a total of 517 breast carcinoma tissues (319 Non-Obesity patients and 198 Obesity Patients). The expression level of Aurora A-positive was significant higher in obesity breast carcinoma compared with non-obesity cancer carcinoma ($\chi^2$=9.79, *P*=0.002). In the immunohistochemistry assay, the results confirmed that the expression level of Aurora A-positive was significantly associated with hormone receptor status (68.4% vs 77.9%, *P*=0.015) and HER2 status (28.7% vs 17.9%, *P*=0.003). Aurora A-positive tumors had larger tumor size, though not statistically significant (78.1% vs. 71.1%, *P*=0.070). High Aurora A expression was remarkably and significantly associated with OS (8-year OS ratio: 69.5% vs 81.1%, OR=1.76, 95% CI:1.03~3.02, *P*=0.041) in Obesity Cohort. Interesting, higher expression of Aurora A was not associated with a shorter overall survival time among the Non-obesity breast cancer (8-year OS ratio:81.4% vs 85.8%, OR=1.40, 95% CI:0.79~2.45, *P*=0.229). As for RFS, the expression levels of Aurora A expression genes have no significance with RFS statistically in Non-Obesity patients. The in Aurora A low expression group was in high Aurora A expression in Non-Obesity Cohort ( 5-year RFS ratio:82.2% vs 83.2%, OR=1.29, 95% CI: 0.77~2.16, *P*=0.307). While 5-year RFS ratio in high Aurora A expression group of Aurora A were 71.3% was a little shorter than the 5-year RFS ratio in low Aurora A expression group (OR=1.58, 95% CI:0.96~2.57, *P*=0.072). Aurora A and Lymph node metastases were significantly poor prognostic factors for OS, and borderline significance was noted for high BMI. Kaplan-Meier survival analysis from TCGA database confirmed that the high Aurora A expression group had worse prognosis (HR=1.47, 95%CI:1.14-1.90, *P*=0.003). The KEGG pathway enrichment results were consistent with GO biological process term analysis, in which CCNB1 was enriched for upregulated Aurora A. In IHC correlation analyasis, Aurora A level on tumor cytoplasm had broad connections with Cyclin B1 (correlation coefficient = 0.227, *P*=0.001).Conclusions: Our finding demonstrate here for the first time that high expression of Aurora A was notably correlated with early recurrence and poor overall survival in obesity patients with early breast cancer. The Aurora A-Cyclin B1 axis could be a potential promising therapeutic target for cancer intervention and therapy.**

**Keywords: Early breast cancer, obesity, Aurora A, Overall survival, Cyclin B1**

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**Genetic testing for all breast cancer patients (get facts)**

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**Background: There is evidence that increases in germline cancer genetic testing result in higher rates of contralateral prophylactic mastectomy (CPM) in newly diagnosed breast cancer (BC) patients, even among those with negative results. Unlike carriers of BRCA pathogenic variants (PV), the risks of contralateral breast cancer (CBC) and benefits of CPM for women with PV in moderate penetrance genes are not well studied. There is a critical need to determine how to best counsel BC patients about their personal CBC risk and surgical decisions.**
**Trial design: Newly diagnosed BC patients are randomized 1:1 to quantitative or standard post-genetic test cancer risk counseling methods by genetic counselors. Quantitative counseling includes personalized CBC risk estimates. For patients with a PV in a BC risk gene, CBC risk estimates are calculated via the "ASK2ME" decision tool (https://ask2me.org/). For those without a BC-associated PV, CBC risk estimates are calculated via a validated model "CBCRisk" (https://cbc-predictor-utd.shinyapps.io/CBCRisk/).Standard counseling does not typically include specific CBC risk estimates.Eligibility criteria: All patients over 18 with newly diagnosed invasive or in situ unilateral BC considering genetic testing at Dana-Farber/Brigham and Women's Cancer Center are eligible. Exclusion criteria include a diagnosis of previous BC, metastatic or bilateral BC, hematologic malignancy, prior or active other malignancy, prior multi-gene panel testing, known medical or surgical contraindication to surgery and/or CPM.Specific aims: The primary aims are to 1) compare changes in patients' personal CBC risk assessment before/after quantitative versus standard counseling; 2) determine changes in patients' propensity to choose CPM before/after quantitative versus standard counseling. The secondary aims are to: 1) compare CPM rates; 2) determine concordance between patient and surgeon assessment of CBC risk; 3) evaluate patient genetic testing satisfaction via the Genetic Testing Satisfaction Survey administered post-counseling; 4) measure patient anxiety via the PROMIS Anxiety Survey administered pre- and post-counseling, at 6 months and 2 years; and 5) measure patient decisional regret for both undergoing genetic testing and their surgery choices at 6 months and 2 years; all by quantitative versus standard counseling arms.**
**Statistical methods: For aim 1, the difference between patients' reported personal CBC risk and true risk before and after counseling will be determined. True risk will be based on the ASK2ME/CBCRisk estimates. We hypothesize that the difference between the true and estimated risk will be smaller post-counseling, and smaller in the quantitative counseling versus standard arm. Assuming an expected difference of 5% and expected standard deviation of 20%, 199 patients are needed for each arm to achieve 80% power and type I error of 5% (based on a two-sample t-test). For aim 2, to determine propensity to undergo CPM, patient responses will be assigned a numeric value: Very Unlikely (1), Somewhat unlikely (2), Unsure (3), Somewhat likely (4), Very likely (5). For each patient we will then calculate the difference in scores before/after counseling. Our hypothesis is that differences will be greater in the quantitative arm. Assuming an expected difference of 0.8 and expected standard deviation of 3, 175 patients are needed for each arm to achieve 80% power and type I error rate of 5% (based on a two-sample t-test).**
**Accrual: Recruitment began on June 8, 2020; there are currently 9 of the target 450 patients enrolled.**
**Funding Support: Sponsored Research Agreement with Myriad Laboratories, Inc. and a Brigham and Women's Hospital Department of Surgery Robert T. Osteen Junior Fellowship Award.**
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# Preoperative systemic therapy versus upfront surgery in HER2-positive early breast cancer: A prospective nested case-control study in the real world

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Purpose: To comparing the survival in different strategies, preoperative systemic treatment (PST) versus upfront surgery (US) in patients of HER2-positive early breast cancer in real-world.Methods: Eligible patients from 2012 to 2015 were classified as PST or US group prospectively, according to the real upfront treatment. The primary endpoint is disease-free survival (DFS), the second endpoint is overall survival (OS). All the outcomes were examined in unadjusted model, propensity score matching (PSM) model, and inverse probability of treatment weighting (IPTW) model. Results: Finally, 1067 eligible patients (215 in PST group, 852 in US group) were included into analysis (Table 1). In unweighted analysis, the cumulative DFS of PST group was significantly lower than US group (78.1% vs 87.7%, P<0.001), especially for those did not reach pathological complete response after PST. After adjusting the parameters, in PSM model (matching at 1:1 ratio), the DFS of PST group was significantly higher than the DFS of US group (HR, 0.57s2, 95%CI, 0.371~0.881, P, 0.012). In IPTW model, there was no significant difference of DFS between two groups (HR, 0.946, 95%CI, 0.763~1.172, P, 0.609). For OS, there were no significant difference between two groups in all three models. Conclusions: The patients in PST group have worse DFS than those in US group, mainly because of the unbalancing stage and biological risk. By real-world statistic method, after adjusting and making parameters comparable, the DFS of PST group is non-inferiority to the DFS of US group in IPTW model and even superior to US group in PSM model.

Table 1. The clinicopathologic characteristics of two groups in PSM and IPTW models

| Characteristics | | Number of cases | Unweighted primary sample | | | PSM model | | | IPTW model* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | PST group (215) | US group (852) | SMD | PST group (145) | US group (145) | SMD | PST group (765) | US group (1021) | SMD |
| | | | N (%) | N (%) | | N (%) | N (%) | | N (%) | N (%) | |
| Age (years, medium, 95%CI) | | | 50, 39~61 | 50, 33~64 | 0.05 | 50, 40~65 | 49, 34~62 | 0.10 | 49, 39~67 | 50, 31~64 | 0.03 |
| Stage T | 1 | 458 | 8 (3.7) | 450 (52.8) | 0.701 | 8(3.7) | 10 (6.9) | 0.032 | 80 (10.5) | 450 (44.1) | 0.467 |
| | 2 | 529 | 157 (73.0) | 372 (43.7) | | 118 (81.4) | 116 (80.0) | | 635 (83.0) | 458 (44.9) | |
| | 3 | 80 | 50 (23.3) | 30 (3.5) | | 19 (13.1) | 19 (13.1) | | 50 (6.5) | 113 (11.1) | |
| Stage N | 0 | 571 | 37 (17.2) | 534 (62.7) | 1.048 | 37 (17.2) | 32 (22.1) | 0.081 | 310 (40.5) | 538 (52.7) | 0.246 |
| | 1 | 596 | 178 (82.8) | 318 (37.3) | | 108 (81.4) | 113 (77.9) | | 455 (59.5) | 483 (47.3) | |
| Grade | 1 and 2 | 522 | 92 (42.8) | 430 (50.5) | 0.154 | 77 (53.1) | 89 (61.4) | 0.168 | 345 (45.1) | 493 (48.3) | 0.064 |
| | 3 | 545 | 123 (57.2) | 422 (49.5) | | 68 (46.9) | 56 (38.6) | | 420 (54.9) | 528 (51.7) | |
| ER | Negative | 536 | 142 (66.0) | 394 (46.2) | 0.407 | 87 (60.0) | 68 (46.9) | 0.265 | 386 (50.5) | 513 (50.2) | 0.004 |
| | Positive | 531 | 73 (34.0) | 458 (53.8) | | 58 (40.0) | 77 (53.1) | | 379 (49.5) | 508 (49.8) | |
| PR | Negative | 649 | 171 (79.5) | 478 (56.1) | 0.418 | 108 (74.5) | 113 (77.9) | 0.081 | 499 (65.2) | 625 (61.2) | 0.083 |
| | Positive | 418 | 44 (20.5) | 374 (43.9) | | 37 (25.5) | 32 (22.1) | | 266 (34.8) | 396 (38.8) | |

*Proportions and medians are weighted using IPTW, all covariates included in the propensity analysis. Abbreviations: PSM, propensity score matching, IPTW, inverse probability of treatment weighting, PST, preoperative systemic treatment, US, upfront surgery, SMD, standardized mean difference, ER, estrogen receptor, PR, progesterone receptor.In IPTW model, the DFS rate of the PST group was 81.3% versus 80.8% of the US group, and the OS rate of the PST group was 92.1% versus 90.3% (Figure 2E, 2F), both having no significantly differences (Table 4). In further stratified analysis (Figure 3E, 3F), as in PSM model, the DFS and OS rate of the patients without pCR after PST (73.1%, 88.4%) were worse than those with pCR (96.6%, 99.3%) and US group (80.8%, 90.3%), respectively.

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# The upgrade risk to (pre-)invasive breast cancer for B3 lesions diagnosed on core needle or vacuum assisted biopsy. A Belgian retrospective study

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Introduction: Flat epithelial atypia (FEA), classical lobular neoplasia (LN), papillary lesions (PL), radial scars (RS) and atypical ductal hyperplasia (ADH) are lesions of uncertain malignant potential in the breast, which are described as B3 lesions in the B classification system of the European Working Group for Breast Cancer Screening Pathology. Current standard for management of B3 lesions on core needle biopsy (CNB) or vacuum assisted biopsy (VAB), is wide local excision (WE). However, recent consensus-based guidelines no longer recommend WE for all such lesions, but propose surveillance following CNB or VAB to be sufficient in some cases. In the absence of a Belgian guideline on the treatment of B3 lesions, this study was conducted to identify which B3 lesions have the lowest likelihood for breast malignancy and could therefore be spared from WE.

Methods: Using data from the Belgian Cancer Registry (BCR), all patients with a new diagnosis of a B3 lesion on CNB or VAB between 2013-2016 and who had a histological follow up with VAB or WE after CNB or WE after VAB were included. Histological follow-up was retrieved from BCR and limited to 12 months following diagnosis. Histology was compared between the first- and follow-up investigation to determine the upgrade risk to ductal carcinoma in situ (DCIS) or invasive breast cancer (IC) according to the type of B3 lesion. Patients with synchronous (pre-) invasive lesions were excluded.

Results: Between 2013-2016 there were 812 B3 lesions available for upgrade analysis after initial diagnosis. After CNB 551 lesions had WE or VAB as follow up and after VAB 261 lesions had WE. After primary diagnosis on CNB, the total upgrade risk was 19,0%. There was histological agreement in 57,9% and no B3 lesion or upgrade was reported in 21,8%. Per B3 lesion subtype the upgrade risk to DCIS - IC after diagnosis on CNB was : ADH 17,1%-12,4%, FEA 21,1% - 18,4%, LN 18,9% -21,6%, RS 14,3% - 11,4%, and PL 7,2% - 3,2%. After initial diagnosis on VAB the total upgrade risk was 14,9%. There was histological agreement in 52,9% and no B3 lesion or upgrade was found in 31,4%. Per B3 subtype the upgrade risk to DCIS - IC after diagnosis on VAB was: ADH 17,3%- 2,7%, FEA 11,7%- 5,9%, LN 0,0% - 4,3%, PL 10,4% - 2,1%. We found no upgrade for RS. (Table 1).

Conclusions:

In a series of B3 lesions with a histological follow-up, we notice that overall upgrade risk is higher for lesions detected on CNB than on VAB: 19,0% vs. 14,9%. The majority of lesions showed histological agreement between initial B3 diagnosis and histological follow-up: 57,9% after CNB and 53,5% after VAB. More investigation is needed to make a proper risk assessment as to which B3 lesions can be followed with regular surveillance. Also, further prospective research is needed to get a better understanding of associated risk factors for upgrade, upgrade risk and lifetime risk of developing breast cancer after diagnosis of a B3 lesion.

| Subtype | NumberCNB followed by VAB or WE | DCIS | IC | Total Upgrade riskCNB | NumberVAB followed by WE | DCIS | IC | Upgrade riskVAB followed by WE |
|---|---|---|---|---|---|---|---|---|
| ADH | 105 | 17,1% | 12,4% | 29,5% | 110 | 17,3% | 2,7% | 20,0% |
| FEA | 38 | 21,1% | 18,4% | 39,5% | 51 | 11,7% | 5,9% | 17,6% |
| LN | 37 | 18,9% | 21,6% | 40,5% | 46 | 0% | 4,3% | 4,3% |
| PL | 336 | 7,2% | 3,2% | 10,4% | 48 | 10,4% | 2,1% | 12,5% |
| RS | 35 | 14,3% | 11,4% | 25,7% | 6 | 0% | 0% | 0% |
| Total | 551 | | | | 261 | | | |
| Upgrade | 105/55119,0% | | | | 39/26114,9% | | | |
| B3 lesion | 319/55157,9% | | | | 138/26152,9% | | | |
| No B3 lesion | 120/55121,8% | | | | 82/26131,4% | | | |
| Result not available | 7/5511,3% | | | | 2/2610,8% | | | |

Table 1: Upgrade risk per B3 subtype after diagnosis on CNB or VAB

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# A preclinical platform of breast cancer PDX-derived cell lines as a tool for pharmacological screening and functional studies

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**Despite considerable progress in understanding the biology and genetics of breast cancer progression, the development of effective therapies need physiological and predictive preclinical models. In this context, breast cancer patient-derived xenograft (PDX) models has become a standard tool as they reproduce accurately the behavior of tumor of origin, in term of histological and molecular phenotype and response to chemotherapy. Although PDXs in vivo models are indispensable for preclinical studies, they suffer from some limitations due to study costs related to tumor maintenance on mice, variable engraftment rate, growth delay and limited throughput for large-scale drug screening.To address this problem and propose a time and cost effective preclinical screening tool, we developed a panel of breast cancer PDX-derived low-passage 2D cell lines as a convenient *in vitro* pre-screening platform to profile compound activity.30 different breast cancer PDX models including TNBC, HER2+ and ER+ were tested for their capacity to generate cell lines maintaining the characteristics of the parental PDX tumor and usable for *in vitro* assays.Today, we succeeded with a series of 14 PDX models.Tumor cells isolated from PDX tumor tissue were cultured under different media and matrix conditions, allowing at least 5 passages in culture. A Short Tandem Repeat (STR) comparison profile was done with the parental PDX before performing a master bank. We succeeded in establishing a panel of 14 PDX-derived cellular models (14/30 = 46% success rate).We performed short term 2D cytotoxicity assays and long term colony assays to compare cell lines in vitro drug sensitivity with their parental PDX in vivo drug response and overall, the results show that this panel reproduced the drug response profile of the original PDXs with chemotherapies, PARP inhibitors, an ADC (T-DM1) therapies.Moreover, cellular models engrafted back onto mice showed in vivo response to chemotherapies similar to that of the parental PDX confirming the identical behavior of cell line / PDX couples.As the use of cellular models is still considered as a standard for early preclinical test to evaluate drug response before moving to *in vivo* assays, our breast cancer PDX-derived cell line platform appeared to be a robust and relevant tool. Furthermore, since the main concern when using *in vitro* models is the representativeness of the results obtained when transposed to in vivo models, the similarities between cell lines and parental PDX should maximize success of further *in vivo* preclinical drug development.**

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# A randomized phase II trial of interventions with frozen groves and compression stockings to prevent nab-paclitaxel induced chemotherapy-induced peripheral neuropathy (SPOT trial)

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Background: Nab-paclitaxel(nab-PTX) is improved taxane in terms of solubility, alcohol-free and reduced incidence of anaphylaxis. On the other hand, chemotherapy-induced peripheral neuropathy (PN) is known as a major adverse event which was failed to suppress by many medications. Recently, some reports describe about cooling and compression of extremities of patients treated by taxane can reduce the incidence and severity of PN. The efficacies of interventions with frozen groves and compression stockings to prevent nab-PTX-induced PN was examined.Methods: The patients with HER2 negative primary breast cancers treated by four cycles of nab-PTX pre-/post- operative chemotherapies were randomized to two groups (interventions with frozen groves (FG) and compression stockings (CS), and with standard care (SD)). Primary endpoint was frequency and time to onset of >Grade 2 PN by CTCAE ver.4.0, and secondary endpoints are frequency of >Grade2 PN at the end of four cycles of nab-PTX, HRQOL, recovery of PN for 5 years from the end of nab-PTX and safety. Also, we requested to keep diary with several questions for patient reported outcomes (PRO).Results: Of the 124pts enrolled, 123(62 FG/CS, 61 SD) were included in the intent-to-treat analysis. There were no significant differences in clinicopathological findings between two groups. As a primary endpoint, frequency and time to onset of >Grade 2 motor-PN /sensory-NP of hands comparing FG and SD showed p=0.162/0.599, and of foots comparing CS and SD showed p=0.525/0.933 (Log-rank test with one sided significant level of 10%). Conversely, the worst Grade of sensory-PN is statistically significant difference at Cycle 2 (p=0.021; Mann-Whitney's U-test with two-sided significant level of 5%), >Grade3 of motor-PN was statistically significant low in all cycles (p=0.022; Log-rank test with one sided significant level of 10%), >Grade1 of sensory-PN was statistically significant low (p=0.022; Log-rank test with one sided significant level of 10%), and >Grade3 of sensory-PN was statistically significant low in all cycles (p=0.072; Log-rank test with one sided significant level of 10%) with FG in detail. In addition, Grade3 of motor-PN was statistically significant low in all cycles (p=0.022; Log-rank test with one sided significant level of 10%) , >Grade1 of sensory-PN was statistically significant low (p=0.015; Log-rank test with one sided significant level of 10%), and >Grade3 of sensory-PN was statistically significant low in all cycles (p=0.089; Log-rank test with one sided significant level of 10%)in all cycles (p=0.022; Log-rank test with one sided significant level of 10%) with CS in detail. Moreover, PRO indicated by patients' diary showed interesting patterns of increase and decrease in sense of
pain and paralyzed which might be corresponding to efficacy of interventions with FG and CS.Conclusion: Although primary endpoints were not met by the interventions with FG and CS, this trial revealed the detail of PN caused by nab-PTX, and these interventions might delay beginning of sensory and motor PN and reduce the worst grade of PN. The adverse events grading according to CTCAE and PRO indicated by patients' diary seems to be not completely matched, the usefulness of FG and CS are investigating with more questionnaire. (UMIN: UMIN000016902)

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# Does the axilla surgical management for limited sentinel lymph nodes involvement vary between total mastectomy and breast-conserving surgery

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**Purpose: The ACOSOG Z0011 study demonstrated that axillary lymph node dissection (ALND) can be safely omitted in patients with one to two positive sentinel lymph node (SLN) who underwent breast-conserving surgery (BCS) with planned whole-breast irradiation. This study aimed to analysis the surgical management in patients with one to two positive SLNs, and further evaluate the rates of non-sentinel lymph node (non-SLN) metastasis between patients receiving BCS or total mastectomy (TM). Methods: We performed a retrospective analysis of patients with early breast carcinoma from the Shanghai Jiao Tong University-Breast Cancer Database (SJTU-BCDB) between 2011 to 2018. The inclusion criteria were (1) cT1-2N0M0 invasive breast cancer, (2) aged ≥18 years at diagnosis, (3) received surgical treatment for the primary tumor and the axilla, (4) had one to two positive SLNs, (5) no history of previous or concurrent malignant disease, and (6) no neoadjuvant therapy. Patients were classified into the BCS and TM groups. Time trends of ALND rates were analyzed with Chi-square tests. And the rates of non-SLN metastasis between BCS and TM groups were also analyzed with Chi-square tests. Multivariable logistic regression was used to determine factors influencing the completion of ALND and non-SLN metastasis. And Kaplan-Meier estimator and log-rank tests were used to analysis the recurrence-free survival (RFS) between SLNB alone and SLNB+ALND arms. Results: Of the 891 patients enrolled, 586 (65.8%) received TM and 305 (34.2%) received BCS. Between 2011 and 2018, the completion of ALND for 1-2 positive SLN decreased from 100% to 72.7% (P <0.001). And the rate of ALND was significantly higher in the TM group compared with the BCS group (*n* = 541, 92.3% vs *n* = 195, 63.9%; P <0.001).Earlier year of diagnosis (P <0.001), primary mastectomy (P <0.001), SLN positive-total ratio >50% (P =0.001), and SLN macro-metastasis (P <0.001) were all independently associated with a higher probability of completing ALND. Among the 736 patients undergone ALND, the rates of non-SLN metastasis were significantly higher in the TM group, compared to the BCS groups (TM: n = 170, 31.4% vs BCS: n = 46, 23.6%; P =0.044). The multivariable regression analysis indicated that non-SLN metastasis was significantly associated with SLN positive-total ratio >50% (OR=3.43, 95%CI 2.28-5.17; P <0.001), Her-2 positive disease (OR=1.63, 95%CI 1.09-2.46; P =0.019), and pT2-3 disease (OR=1.46, 95%CI 1.01-2.09; P =0.042). However, surgery of the breast was not independently associated with the rate of non-SLN metastasis (P =0.090). After a median follow-up time of 31.9 months (range, 1.0-96.5 months), there were no significant difference in RFS between the SLNB alone and SLNB+ALND arms, regardless of the surgery of the breast (TM group: Log-rank P = 0.910; BCS group: Log-rank P =0.840). Conclusion: There is an increasing trend toward omitting ALND in patients with one to two positive SLNs. Compared with the patients undergone BCS, the rate of non-SLN metastasis was significantly higher in patients undergone TM. However, the omission of ALND had limited influence on disease outcome among those patients received TM.**

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# Modeling breast cancer tissue in vitro using extracted native collagen fibers

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In vitro breast cancer tissue models play key roles in studying cancer biology and drug discovery. In efforts to recreate native breast cancer spatial organization, 3D in vitro models have received increased attention. These models can be categorized into two major classes: scaffold-based and scaffold-free systems. Scaffold based systems, such as pre-fabricated scaffolds and assembled hydrogels composed of natural and/or synthetic materials, promote cell-extracellular matrix (ECM) interactions. In the case of scaffolds, cells are seeded on the surface of a matrix, whereas in hydrogels, cells are surrounded by a matrix in all dimensions. In both cases, the cells can receive important physical and biochemical cues from the scaffolds that impact their function. In contrast, scaffold-free systems, such as cancer cell spheroids, promote extensive cell-cell interactions, as cells are densely packed in aggregate forms via cell-cell adhesion ligands. These cell-cell interactions via direct contact, in addition to secreted paracrine factors, are also important signals that regulate cell behavior. Despite substantial progress in developing 3D breast cancer models, significant challenges still remain. The breast cancer microenvironment typically possesses both strong cell-cell and cell-ECM interactions, and recapitulating them in in vitro 3D models is essential. However, in most in vitro systems, enhancing one of these interactions often results in decreasing the other.

Collagen fibers are one of the major ECM molecules in breast tumors, and analyses of patient biopsies indicate that breast cancer cells often reside in collagen fiber-rich ECMs. Collagen fibers are highly ordered and hierarchical. In nature, collagen molecules assemble into fibrils with diameters on the order of a hundred nanometers. These fibrils bundle to form fibers with diameters of ~1-20 microns. Collagen fibers provide structural, mechanical and biochemical signaling to resident cells, which influences their behavior. However, few biomaterial systems have been developed based on natural collagen fibers for 3D cell growth and tissue formation. Here, we developed a strategy for 3D breast tissue model construction in vitro using extracted collagen fibers from decellularized natural tissues. In this platform, breast cancer cells and supporting cells are cultured within the gaps between individual collagen fibers, which resembles natural conditions. This system maintains strong cell-ECM and cell-cell interactions for resident breast cancer cells and the surrounding stromal fibroblasts or mesenchymal cells. Using this platform, a number of in vitro breast cancer models have been established, including inflammatory breast carcinoma, ductal carcinoma, and pleomorphic breast carcinoma. Importantly, implanting the model tissue onto the chicken chorioallantoic membrane for 9 days resulted in tissue histologically resembling ECM-rich patient breast cancer biopsy tissues.

In summary, the extracted native collagen fibers enable the construction of breast cancer models in vitro through maintained cell-cell and cell-ECM interactions. These models histologically resemble in vivo tumor models and patient biopsies. With simple preparation, this platform can be easily scaled up for rapid deployment for downstream applications, such as drug discovery and mechanistic studies of tumor cell interactions as well as cancer progression. With the flexibility to change the cancer cell and surrounding cell types, this system is expected to have great utility for the study of other cancers as well.

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# Assessing racial differences in patients with metastatic triple-negative breast cancer: Real-world evidence from US community oncology practices

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**Background: Metastatic triple-negative breast cancer (mTNBC) is an aggressive tumor phenotype with a poor prognosis and few treatment options. The prevalence of mTNBC is disproportionately higher among African American (AA) women, compared with white women. Data identifying the drivers of racial differences in mTNBC or characterizations of treatment patterns and clinical outcomes in AA patients with mTNBC are limited. Methods: This retrospective study used the Flatiron Health electronic health record-derived de-identified database (January 2011-March 2020). Adult AA and white female patients with confirmed mTNBC treated in US community oncology practices were included. Differences in mTNBC prevalence among AA and white patients were assessed by age, health insurance coverage, geographic region and stage at initial diagnosis. Descriptive statistics were used to analyze clinical characteristics, treatment patterns and time to treatment initiation between AA and white patients. Racial differences in overall survival (OS) were examined using Kaplan-Meir analysis and a multivariate Cox regression model. Results: Of the 21,804 Flatiron patients diagnosed with metastatic breast cancer (mBC), 2116 eligible patients with mTNBC were identified; 383 (18%) were AA and 1155 (55%) were white. TNBC prevalence was twice as high among AA patients (23%) than white patients (12%). Racial differences in TNBC prevalence (AA vs white patients) were particularly higher among patients aged 45 to 65 y (26% vs 13%), patients in the Northeast (27% vs 11%) and those with initial diagnosis at Stage II (30% vs 13%) or Stage III (27% vs 15%). AA patients with TNBC were younger (mean age: 60 vs 63 y; *P* < 0.001) and more likely to have Medicaid at the time of diagnosis (10% vs 3%; *P* < 0.001) than white patients. Clinical characteristics were generally similar between AA and white patients, including the distribution of staging at initial diagnosis, disease recurrence, Eastern Cooperative Oncology Group performance status (ECOG PS), and sites and number of metastases. Regardless of race, 25% of all patients with mTNBC had no documentation of receiving anti-cancer treatment in the database. Untreated patients in both race groups were older, had poorer ECOG PS and were less likely to have visceral metastases than treated patients (all *P* < 0.001); they also had poorer survival than treated patients (median OS: 4.7 vs 13.1 months from diagnosis for all treated patients; unadjusted hazard ratio [HR], 0.51 [95% CI: 0.46, 0.57]). Among both AA and white treated patients, single-agent chemotherapy was the most prevalent first-line treatment (most common agent: capecitabine). More than half of treated patients initiated treatment in < 30 days, and median time-to-treatment initiation did not differ by race. Although OS was numerically lower in AA patients (median OS, 10.3 vs 11.9 months in white patients), the difference was not significant when adjusted for prognostic and treatment factors (adjusted HR, 1.09 [95% CI: 0.95, 1.25]). Conclusions: The prevalence of mTNBC was twice as high among AA compared with white patients in US community oncology practices. Unlike prior research, race did not show an association with OS in this population. Regardless of race, 1 in every 4 patients with mTNBC had not received documented anti-cancer treatment, potentially due to poor PS and concerns about treatment tolerance. OS was poor for both AA and white patients with mTNBC, particularly for untreated patients. Effective treatment remains a substantial unmet need for all patients with mTNBC. In light of the lack of racial differences in this patient cohort, prospective studies are needed to further elucidate underlying biological differences that may have predictive or prognostic significance for AA patients with TNBC.**

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# Healthcare costs for metastatic breast cancer patients treated with human epidermal growth factor receptor 2 targeted agents

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***Background*: Human Epidermal Growth Factor Receptor 2 positive (HER2+) breast cancer (BC) represents approximately 15% of early stage BC cases and is associated with a more aggressive clinical phenotype and poor prognosis with respect to most BC. Over the last decade new HER2-targeted therapies have become available that have prolonged survival for both early stage and metastatic breast cancer (mBC). However, the cost impact of these therapies has not been fully assessed in recent years. Given the evidence for major clinical benefit, it is imperative that health systems evaluate new treatments to maximize the value of health care expenditures. This study evaluated healthcare costs among mBC patients treated with HER2-targeted therapy.**

***Methods*: A retrospective cohort study using the IQVIA Real-World Data Adjudicated Claims Database (1/1/2015-7/31/2019) was conducted. Adult (≥18-years) female patients who initiated HER2-targeted therapy with evidence of mBC diagnosis in the prior year were identified. The study index date was the initiation date of the HER2-targeted agent after which, patients were required to have ≥12 months of follow-up. Annual all-cause and BC-related healthcare costs per patient (2019 USD) were computed using payer-paid amounts in the first and second year following the index date. BC-related costs were defined as costs for claims with a primary diagnosis for BC (ICD-9-CM: 174.% or ICD-10-CM: C50.%) or BC-related treatment (surgery – mastectomy or lumpectomy, HER2-targeted therapy, chemotherapy, hormone therapy, immunotherapy, and radiation).**

***Results*: 708 mBC patients treated with HER2-targeted therapy were included with a mean age (SD) of 53.2 (10.2) years and mean follow-up of about 2 years. During the follow-up period, trastuzumab (96.5%) and pertuzumab (81.2%) were the most common HER2-targeted therapies used followed by ado-trastuzumab (15.4%), neratinib (6.3%), and lapatinib (5.3%). Additionally, patients received other treatments including chemotherapy (88.0%), hormone therapy (56.6%), and radiation therapy (57.6%). Of note, 40.3% of patients underwent surgery (mastectomy or lumpectomy) following evidence of metastasis. Following initiation of HER2-targeted therapy, mean annual costs per patient in Year 1 and Year 2 were $330,784 and $196,139, respectively. Correspondingly, BC-related costs in Year 1 and Year 2 were $255,273 and $144,978, respectively. HER2-targeted therapies accounted for 72% of BC-related costs in both Year 1 and 2. Surgery patients incurred $37,822 higher BC-related costs in Year 1 compared to non-surgery patients. However, in Year 2, the opposite was noted with non-surgery patients having $70,885 higher BC-related costs, mainly due to a differences in BC treatment rates in Year 2 for HER2 targeted drugs, other BC drugs and radiation.**

***Conclusion*: Total BC-related costs of mBC patients treated with HER2-targeted therapy is highest in the first year following treatment initiation, with the main cost driver being the cost of HER2-targeted therapy. While total costs decreased in the subsequent year, the cost of HER2 targeted therapy remained the dominant component. Results of this study highlight the significant economic burden of treating HER2+ mBC and also the need for therapies that limit disease progression.**

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# Treatment (tx) patterns and clinical outcomes among patients (pts) with germline *BRCA1/2* mutated (g*BRCA1/2*mut) HER2+ advanced breast cancer (ABC): Results from a US real-world study

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**Background: g*BRCA1/2*mut ABC represents ~5% of all breast cancer (BC) including pts with HER2+ BC. While HER2-targeted therapy remains an effective tx for those pts, limited information is available on the use and effectiveness of PARP inhibitors (PARPi) for pts with HER2+ g*BRCA1/2*mut ABC. Recently, NCCN updated its guidelines (v1.2020) to support the use of PARPi in pts with g*BRCA1/2*mut metastatic BC regardless of subtype. In order to establish a baseline reference point, we assessed real-world tx patterns and clinical outcomes among pts with g*BRCA1/2*mut HER2+.**
**Methods: Oncologists retrospectively reviewed charts (July 2019-June 2020) of randomly selected pts ≥18 y, with g*BRCA1/2*mut HER2+ ABC who received ≥1 cytotoxic chemotherapy (CT) regimen(s) for ABC between Jan 2013-April 2018. Descriptive analysis was performed for 1st line ABC tx patterns. Clinical outcomes (1st line ABC PFS rates) were estimated using the Kaplan-Meier method. PARPi clinical outcomes data was immature given its recent launch. Additional analyses evaluating outcomes in pts receiving PARPi are planned.**
**Results: This is a placeholder abstract. Results will be provided during the final submission.**
**Funding: Pfizer**

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# Risk factors for lymph node metastasis and the role of SLNB in microinvasive breast cancer

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**Introduction Incidence of microinvasive Breast cancer (DCISM) along with ductal carcinoma in situ is increasing due to mammographic screening. However, DCISM is not a common pathologic entity and surgical management of the axilla, overall treatment, and prognosis of this entity still remains unclear. Our study aims to determine whether sentinel lymph node biopsy (SLNB) is necessary for all DCISM patients and analyze the characteristics of lymph node-positive patients among DCISM patients to identify risk factors associated with lymph node metastasis. Materials and MethodsA total of 184,007 Breast cancer patients treated were registered in the Korean Breast Cancer Society Registry between 1978 to 2020. A retrospective review of the database was performed and the analysis includes diagnostic and clinic-pathologic characteristics such as positive lymph node and immunohistochemistry. A univariate analysis was carried out to determine associations between lymph node positivity and the clinical variables via Fisher's exact test.ResultsOf the 184,007 patients, 2,556 (1.4%) breast cancer patients were classified as DCISM and 134 (5.2%) had at least one lymph node (node-positive), while 2,422 were node-negative patients. We found statistically significant results with hormone receptor status between node-positive and node-negative patients. Estrogen receptor (ER) and progesterone receptor (PR)-negative cases were associated with lower ORs (ER: OR=0.63, 95CI=0.43-0.92, P=0.016; PR: 0.67, 0.46-0.96, 0.026, respectively). A particularly interesting finding is that human epidermal growth factor receptor 2 (HER2)-negative cases were associated with higher OR (HER2: 2.03, 1.36-3.06, 0.001), suggesting hormone receptor status could be useful to identify potential lymph node metastases.ConclusionOur study suggests that we could omit axillary staging in DCISM patients, and consider optional SLNB in patients with ER, PR, and HER2 status with other overrepresented clinical entities such as palpable mass, BMI, and histologic grade.KeywordsMicroinvasive ductal carcinoma, Sentinel lymph node biopsy, lymph node metastasis**

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# Higher clinical lymph node stage predicts worse survival in patients with breast cancer who achieve a pathologic complete response after neoadjuvant chemotherapy

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**Background: Despite patients with breast cancer who achieve a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) generally demonstrate improved survival, some of these patients will develop breast cancer recurrence. Identification of factors associated with recurrence in patients with pCR after NAC would be helpful to optimize treatment strategies in breast cancer. In this study, we aim to particularly explore the factors associated with the prognosis of this patient population.Methods: Data of patients from three tertiary hospitals and treated with NAC between 2005 and 2019 were retrospectively collected. A pCR was defined as no invasive tumor in the breast and no tumor in the lymph node (ypT0/is, ypN0). Factors associated with pCR were analyzed using univariable and multivariable logistic regression analyses. Disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier method. The prognostic value of clinicopathological factors regarding DFS and OS were determined by univariable and multivariable Cox regression analyses.Results: A total of 897 patients were used for the analysis, including 287 patients with a pCR and 610 patients without pCR. Clinical TNM stage, histological grade, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Ki67, molecular subtype, NAC regimen and NAC cycles were associated with pCR status, with TNM stage and molecular subtype as independent predictors of pCR. Patients with a pCR had a superior DFS (pCR vs non-pCR, hazard ratio [HR] 0.26 (95% confidence interval [CI] 0.15-0.45, P<0.001) and OS (pCR vs non-pCR, hazard ratio [HR] 0.13 (95% confidence interval [CI] 0.05-0.35, P<0.001). In patients with pCR, clinical T stage, N stage and TNM stage were associated with DFS and OS, with higher N stage as an independent predictor of a worse DFS and OS.Conclusions:Clinical N stage of breast cancer is an independent predictor of worse DFS and OS in patients with a pCR after NAC. Possible this could support treatment escalation in this patient population in the future.**

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# Personalized breast cancer screening in a population-based study: Women informed to screen depending on measures of risk (WISDOM)

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**Background: WISDOM is a 100,000 healthy women preference-tolerant, pragmatic study comparing traditional annual screening to personalized risk-based breast screening. The novelty of WISDOM personalized screening is the integration of previously validated genetic and clinical risk factors (age, family history, breast biopsy results, ethnicity, mammographic density) into a single risk assessment model that directs the starting age, timing, and frequency of screening. The goal of WISDOM is to determine if personalized screening, compared to annual screening, is as safe, less morbid, enables prevention, and is more accepted by women. The study is registered on ClinicalTrials.gov, NCT02620852. Methods: Women aged 40-74 years with no history of breast cancer, DCIS or previous double mastectomy can join the study online at wisdomstudy.org. Participants can either elect randomization or self-select a study arm. Then, they provide electronic consent and sign the Release for Medical Information via DocuSign. For all participants, 5-year risk of developing breast cancer is calculated according to the Breast Cancer Surveillance Consortium (BCSC) model. Participants in the personalized arm undergo panel-based mutation testing (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2), and their 5-year risk is calculated using the BCSC score combined with a Polygenic Risk Score (BCSC-PRS) that includes 229 single nucleotide polymorphisms (SNPs) known to increase breast cancer risk. The SNPs and mutations are assessed by saliva-based testing through Color Genomics. Five-year risk level thresholds are used to stratify participants as low-, moderate- and high risk. Risk stratification determines age to start, stop, and frequency of screening in the personalized arm. Accrual: As of July 2020 the WISDOM Study is open to all eligible women in the United States. To date, 38,762 eligible women have registered, and 28,706 women have consented to participate in the trial. The median age is 56 years. Seventy-seven percent of participants are Caucasian, 2% African-American, 5% Asian, and 8% of self-reported Hispanic ethnicity. WISDOM is partnering with Blue Cross Blue Shield Association for regional plan opt-in coverage, self-insured companies (Salesforce, Genentech, Qualcomm, CalPERS) and Medi-Cal (Inland Empire Health Plan) using a coverage with evidence progression approach. Accrual expansion and diversity: To ensure that resulting data are meaningful and potentially practice-changing for all populations of women, the WISDOM Study is enhancing the diversity of our participant population by establishing WISDOM sites in diverse areas with large African-American (Alabama, Louisiana, Illinois) and Latina (Florida) populations. These new recruitment sites, intentionally selected for the diverse communities they serve, have established partnerships with community organizations and outreach navigators. Additionally, we have translated the WISDOM Study to Spanish to facilitate access by Latina communities. With the engagement of patient advocates and community partnerships, expanding diversity in the study population will strengthen our scientific knowledge of breast cancer risk and improve access to personalized breast cancer screening recommendations for all women. Enrollment will continue through 2022. Conclusions: Results of 5 years follow-up will enable us to demonstrate whether personalized screening improves outcomes for future patients and it improves healthcare value by reducing screen volumes and costs without jeopardizing outcomes.**

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# Subcutaneous fixed-dose combination of pertuzumab and trastuzumab for the treatment of metastatic breast cancer in Canada - a budget impact analysis

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Background: Recently, the FeDeriCa trial investigated a fixed-dose combination (FDC) of Perjeta and Herceptin (PH), administered by subcutaneous (SC) injection, and demonstrated non-inferior pharmacokinetics of serum Perjeta and Herceptin levels compared to PH IV, along with a similar efficacy and safety profile to the intravenous (IV) administration of PH. In Canada, the standard of care for first-line HER2-positive metastatic breast cancer (mBC) is PH plus taxane chemotherapy with PH until disease progression. Currently, PH are administered as sequential IV infusions. SC administration of PH FDC has the potential to relieve pressure on the healthcare system, decrease treatment burden, and improve the patient experience.
Objective: To estimate the incremental costs/savings, including time savings, associated with the use of PH FDC SC for the treatment of HER2+ mBC, if reimbursed with the same provincial funding criteria as PH IV in Ontario and Quebec, Canada.
Methods: An Excel-based budget impact model was developed to determine the economic impact of PH FDC SC in comparison to PH IV in Ontario and Quebec. Direct medical costs in the analysis included drug acquisition, drug preparation and administration, and systemic therapy infusion chair/suite costs. Nurse and pharmacist wages were obtained from the Government of Canada's Job Bank. Systemic therapy infusion chair/suite costs were derived from literature. Data related to time associated with preparation and administration of PH FDC SC and PH IV were collected through a survey completed by nurses and pharmacists involved in the FeDeriCa clinical trial in Canada.
Results: HER2+ mBC patients treated with PH FDC SC generate net cost savings to the health system compared to treatment with PH IV. These cost savings to the health system are generated due to fewer costs associated with drug acquisition, pharmacist and nurse wages directed towards drug preparation and administration respectively, as well as fewer overhead costs associated with the infusion chair/suite for PH FDC SC compared to PH IV. The use of PH FDC SC provides the healthcare payer with the opportunity to optimize drug and medical resources appropriately while offering a therapy that is aligned with patient and clinician preferences.

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# Prognostic significance of residual micrometastatic axillary involvement with complete pathologic breast response after neoadjuvant chemotherapy for early breast cancer

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Introduction and objectives Pathologic complete response (pCR, ypT0/Tis ypN0) after neoadjuvant chemotherapy (nCT) in early breast cancer (BC) is associated with higher survival rate. Controversy about the prognostic significance of low-volume or micrometastatic axillary residual disease (ypN1mi-RD) exists. Essentially, it is considered equivalent to high-volume nodal disease (ypN1/ypN2-RD) for the indication of lymphadenectomy after nCT. Clarifying ypN1mi-RD prognostic value would be useful for planning adjuvant therapy. Thus, our objective was to assess the prognostic significance of ypN1mi-RD in the context of primary breast tumor pCR. Material and methodsRetrospective, single-center analysis of a cohort of early BC patients treated with nCT between 2010 and 2018 who achieved breast pCR (ypT0/Tis) combined with axillary pCR (ypN0) or ypN1mi-RD or ypN1/ypN2-RD. Cases with pre-nCT sentinel lymph node biopsy were excluded. 5-year disease-free survival (DFS) and overall survival (OS) were analyzed using Cox regression models.ResultsAmong 470 early BC patients treated with nCT, 134 (28.5%) had in-breast pCR, of whom: 97 (20.6%) were ypN0; 7 (1.5%) were ypN1mic; 10 (2.1%) were ypN1 and 5 (1.1%) were ypN2. Clinicopathological characteristics of the groups are shown in the Table. Median follow-up: 33 months. Eight patients relapsed, 4 of 97 with nodal pCR and 4 of 22 with axillary residual disease: 2/7 ypN1mic; 1/10 ypN1 and 1/5 ypN2. Patients who relapsed predominantly presented pre-nCT clinical lymph node involvement, hormone receptor negativity, ki67<20% and absence of complete clinical response (100%). Globally, patients with axillary residual disease had lower DFS rates (95% vs. 69%, p = 0.03), with no apparent differences between ypN1-RD vs. ypN2-RD in the subgroup analysis (75% vs. 80%, respectively). ypN1mic-RD patients showed the poorest DFS (33%, p <0.01). In the multivariable analysis, ypN1mic-RD had worse DFS than nodal pCR (HR 13.98, 95%CI 1.95-100.24, p = 0.01), but no differences were observed between the low and high-volume residual axillary disease categories (HR 0.24, 95%CI 0.03-1.74, p = 0.16). Due to the low rate of events, no differences in terms of OS were observed (p = 0.77).Conclusion In the context of in-breast pCR after nCT for early BC, ypN1mic-RD not only presented a higher risk of relapse than nodal pCR, but also was not associated with a better prognosis than that observed for ypN1/ypN2-RD. Micrometastatic axillary residual disease behaves as an independent adverse prognostic factor, comparable to high-volume axillary residual disease, and might be considered as a factor for the indication of post-nCT adjuvant treatment.

Table. Clinicopathologic characteristics of the cohort of early BC patients treated with nCT between

| | | ypT0/TisypN1mic-RD(N=7) | ypT0/Tis ypN1/N2-RD(N=15) | pCR(N=97) |
|---|---|---|---|---|
| Age (median, range) | | 49 (25-83) | 47 (40-77) | 47 (25-80) |
| Menstrual status | Postmenopausal | 3 (42,8%) | 4 (26,7%) | 42 (43,3%) |
| | Premenopausal | 4 (57,1%) | 11 (73,3%) | 55 (56,7%) |
| ECOG | ECOG 0 | 5 (71,4%) | 13 (86,7%) | 78 (80,4%) |
| | ECOG 1 | 2 (28,5%) | 2 (13,3%) | 19 (19,6%) |
| Histologic subtype | Invasive ductal carcinoma | 7(100,0%) | 14 (93,3%) | 95 (97,9%) |
| | Other subtypes | 0 (0,0%) | 1 (6,7%) | 2 (2,0%) |
| Histologic grade | Grade 1 | 0 (0,0%) | 0 (0,0%) | 1 (1,0%) |
| | Grade 2 | 3 (42,9%) | 5 (33,3%) | 17 (17,5%) |
| | Grade 3 | 4 (57,1%) | 8 (53,3%) | 67 (69,1%) |
| | Unknown | 0 (0,0%) | 2 (13,3%) | 0 (0,0%) |
| cT | cT1 | 1 (14,2%) | 4 (26,7%) | 8 (8,2%) |
| | cT2 | 4 (57,1%) | 5 (33,3%) | 63 (64,9%) |
| | cT3 | 2 (28,6%) | 6 (40,0%) | 24 (24,7%) |
| | cT4a-d | 0 (0,0%) | 0 (0,0%) | 2 (2,1%) |
| cN | cN0 | 1 (14,3%) | 0 (0,0%) | 27 (27,8%) |
| | cN1 | 3 (42,9%) | 5 (33,3%) | 34 (35,1%) |
| | cN2 | 1 (14,3%) | 6 (40,0%) | 24 (24,7%) |
| | cN3 | 2 (28,6%) | 4 (26,7%) | 11 (11,3%) |
| Molecular subtype | HR+ HER2- | 1 (14,3%) | 8 (53,3%) | 11 (11,3%) |
| | HR+ HER2+ | 3 (42,9%) | 1 (6,7%) | 30 (30,9%) |
| | HR- HER2+ | 2 (28,6%) | 3 (20,0%) | 21 (21,6%) |
| | TNBC | 1 (14,3%) | 3 (20,0%) | 35 (36,1%) |
| Breast surgery | Conservative | 7 (100%) | 10 (66,7%) | 67 (69,1%) |
| | Mastectomy | 0 (0,0%) | 5 (33,3%) | 30 (30,9%) |
| Nodal surgery | SLN biopsy | 0 (0,0%) | 0 (0,0%) | 22 (22,7%) |
| | ALND | 7 (100,0%) | 15 (100,0%) | 75 (77,3%) |
| ypT | ypT0 | 5 (71,4%) | 7 (46,7%) | 80 (82,5%) |
| | ypTis | 2 (28,6%) | 8 (53,3%) | 17 (17,5%) |
| Relapse type | Metastatic | 2 (28,6%) | 2 (28,6%) | 2 (2,1%) |
| | Local/contralateral | 0 (0,0%) | 0 (0,0%) | 2 (2,1%) |

| | | | | |
|---|---|---|---|---|
| **Deaths** | | **0 (0,0%)** | **1 (6,7%)** | **1 (1,0%)** |
| ***BC: breast cancer. HR: hormone receptor. nCT: neoadjuvant chemotherapy. pCR: pathologic complete response. SLN: sentinel lymph node. TN: triple negative. ypN1mic-RD: micrometastatic axillary residual disease. ypN1/N2-RD: high-volume axillary residual disease.*** | | | | |

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# Racial differences in age-related DNA methylation changes in normal breast tissue

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**Age is a well-established risk factor for breast cancer development. While age-related epigenetic changes are believed to contribute to overall breast cancer risk, the underlying molecular mechanisms are poorly understood. In addition, racial disparity in breast cancer is well recognized. Compared to European American (EA) women, African American (AA) women are more often diagnosed with breast cancer at younger ages, have a more advanced or aggressive disease, and have poorer outcomes. We hypothesize that age-related DNA methylation (DNAm) may contribute to breast cancer risk differently for distinct racial groups. We investigated epigenome-wide age-related DNAm in normal breast tissue from 178 EA and 272 AA women separately using the Illumina TruSeq Methyl Capture EPIC library and NGS technology. We identified 3,944 and 506 CpG loci that were significantly associated with chronological age, of which 3,534 and 504 CpGs were increasingly hypermethylated with older ages and 410 and 2 loci were increasingly hypomethylated with older ages, in EA and AA women, respectively. Despite the different number, all 506 loci that were significantly associated with age in AA women were also significant for EA women. The low number age-related DNAm loci identified in AA women may reflect a more complex interplay of factors on epigenetic mechanisms in this racial group. Pathway analyses suggested these age-related loci are enriched in biological processes including cell communication, signaling, proliferation, and adhesion. We further examined 181 CpG loci that were previously reported to be associated with age in normal breast tissue but found that only six loci were replicated in our dataset. Our results suggested age-related biological pathways that potentially implicated in breast cancer development and a more complex epigenetic mechanisms in AA women.**

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# Clipping of involved axillary lymph nodes before Neo adjuvant chemotherapy may improve in identification rates & staging of axilla in breast cancer

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**Introduction: Neo adjuvant chemotherapy is increasingly being employed in breast cancer to reduce tumour size & down stage axilla. To reduce false negative rates in axillary lymph nodes after down staging with chemotherapy and to improve axillary conservation ultrasound guided clips were placed in involved axillary lymph nodes prior to commencement of NACT. The study aimed at whether preoperative lymph node clipping had any benefit in identification of lymph node after NACT.Methods: This is a single centre study of 55 patients (Mean age 53 years) with invasive breast cancer with biopsy proven involved lymph nodes (T1-3 N1) who underwent ultrasound guided axillary marker clip insertion before start of NACT. If Post chemotherapy imaging showed normal lymph nodes patients underwent SLNB with additional Lymph Nodes sampled to achieve a total of 4 lymph nodes. All sampled nodes were x rayed at the time of surgery to identify marker clip.Results: We had no procedure related complications with insertion of marker clip in any patients. The median number of nodes was 4.0. Average lymph nodes retrieved was 4.9. SLNB was identified in 47/55 patients (85.5%). Median number of sentinel nodes was 3.0 (Range 1-7) Marker was identified in 41/55 patients (74.5%) 30 (54.5%) patients had marker in sentinel node and 11 (20%) patients had marker in non-sentinel node. Histologically clip was reported in 21 (51.2%) patients. Overall pathological complete response (pCr) in axilla was seen 31/55 (56.45%). Tumours with Her2 over expression showed pCr in axilla 83% n=19/23 while triple negative tumours showed pCr in axilla 64% n=9/14. Er+ Her2- tumours showed low pCr rate 16.7% n=3/18. Completion axillary clearance was performed in 14/24 patients and 10/24 received radiotherapy to axilla.Conclusions: Clips in axillary lymph nodes are safe & relatively easy to deploy without any increased morbidity. Our clip identification rate (74.5%) co relates with other well-known publications (Caudel et al 80%, Z1071-76%). Our study findings validate that clip placement improves the identification of involved lymph nodes and hence improve the accuracy of limited axillary dissection in staging axilla.**

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# Hepatocyte growth factor regulates the expression of chemokine family in vascular endothelial cells; potential implications in clinical breast cancer

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**Background. Hepatocyte growth factor (HGF) is a powerful cellular migration stimulating cytokine (a motogen) of both epithelial and endothelial cells. The induced cell motility is mainly in the form of chemokinesis, namely undirectional movement of the cells in response to exogenous stimuli. HGF is a key angiogenic and lymphangiogenic factor, partially through its effects on endothelial cellular migration, adhesiveness and morphogenesis, which in turn contribute to the growth and spread of cancer cells including breast cancer cells. It has been suggested that HGF might directly or indirectly mediate chemotactic cell movement, namely chemotaxis. Here, we investigated the impact of HGF on the expression of the chemokine family, including the CCL (C-C Motif Chemokine Ligands) family and the CXCL (C-X-C Motif Chemokine Ligands) family and the subsequent consequence of these chemokines on endothelial and cancer cells.**
**Method. Human recombinant hepatocyte growth factor and human recombinant CCLs were used in the study. Human vascular endothelial cells were challenged with HGF and their gene expression was profiled using gene microarray technology. The effects of the responsive chemokines were further tested on endothelial cells and the expression of the respective CCLs was knocked down in endothelial cells by way of siRNA. The impact on the paracellular permeability was assessed by PCP (paracellular permeability) assay using a fluorescence tracer and by transendothelial electrical resistance (TER). TER and cellular migration were also evaluated using automated electric cell substrate impedance sensing (ECIS) methods.**
**Results. Within the concentrations known to induce biological functions in endothelial cells, HGF had a profound upregulatory effect on the expression of multiple chemokines, including CCL14, CCL20, CCL21, CCL28. CXCL family members also responded to HGF, including CXCL8 ($p<0.001$), CXCL3 ($p<0.01$), CXCL2 ($p=0.01$) and CXCL17 ($p<0.05$). We chose to further investigate the effects of a panel of CCLs which have significant clinical connections in breast cancer, notably CCL20 (otherwise known as LARC, Liver And Activation-Regulated Chemokine). High level CCL20 expression in breast cancer is correlated with a favourable relapse free survival ($p=0.0021$) of the patients (TCGA database, kmplot.com). CCL20 had a marginal inhibitory effect on the permeability of paracellular space, however, it had profound effects on the migration of cancer cells, seen by a marked increase in cellular migration. A similar stimulatory effect on cancer cells was seen in conditioned media from HGF activated endothelial cells, and partially abolished by siRNA to CCL20.**
**Discussion. HGF exerts an upregulatory effect on the expression of certain chemokines from endothelial cells, which in turn acted on cancer cells by inducing chemotaxic effects. HGF, via regulation of chemokines, may regulate both directional and unidirectional migration of cancer cells, and impact the disease progression in breast cancer.**

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# Single-centre retrospective study of treatment choices and outcomes of metastatic breast cancer post-progression on the CDK4/6 inhibitor palbobiclib

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**Background: For Hormonal Receptor positive/HER2 negative (HR+/HER2-) metastatic Breast Cancer (mBC) the optimal treatment post-progression on a CDK4/6 inhibitor is still not defined. We aim to identify real-world patterns of systemic treatment choice following palbociclib use at a large tertiary cancer centre and to determine the outcomes for this patient population.**
**Methods: We identified HR+/HER2- mBC patients treated with palbociclib between January 2016 and June 2020 using the institutional computerized prescriber order entry (CPOE) system. Patients with a 2nd primary other than breast, male, or with HER 2 overexpression were excluded. Electronic medical records were retrospectively reviewed to determine clinical, pathological characteristics, and treatment patterns. Our primary outcome was Time to Treatment Failure (TTF) for the subsequent treatment, using the Kaplan Meier survival method.**
**Results: A total of 136 patients were included. At first diagnosis the median age was 52 years; 52% were premenopausal, the most prevalent primary tumor features were ductal histology (79%), and lymph node positive disease (54%). Regarding initial treatment 77% underwent surgery, 52% had adjuvant radiation therapy, 61% had chemotherapy (CT) and 67% had endocrine therapy (ET). The most frequent metastatic sites were bone 70%, liver 36%, and lung 33%. 63 tumors were rebiopsied, in 21 (33.3%) biomarkers had changed. Palbociclib was indicated as 1 Line in 45% of patients, 2 Line 26%, and ≥ 3 Line 27%. The most tolerated dose was 75 mg (44% v 33% tolerating 125 mg). The most prescribed endocrine backbones were AI (66%) and fulvestrant (30%). mTTF was 29.9 mo. (95%CI 12.68-47.11) for 1L, 33.2 mo. (95%CI 22.45-44.08) for 2L, 7.03 mo. (95%CI 2.29-11.76) for ≥ 3L. After a median follow-up of 18.7 mo, 74 patients (54%) had discontinued palbociclib due to progression (46%), toxicity (5%), or death (4%). Sites of progression were liver 37%, bone 29%, pleura 11%, lung 10% and peritoneum 6.5%. 63 patients had subsequent systemic therapy, with mTTF of 5.6 mo. 46 patients (34%) received chemotherapy, 29 patients had capecitabine, mTTF was 4.8 mo. 13 patients (9%) received endocrine therapy, 9 patients had fulvestrant +/- others, mTTF was 8.9 mo. For 5 patients (4%) the subsequent treatment was CDKi-based, 4 patients continued with palbociclib plus another endocrine backbone, mTTF was 16.5 mo. Only 1 patient (.7%) received everolimus-based subsequent treatment, with a TTF 5.6 mo.**
**Conclusion: In this real-world analysis, we found that palbociclib was most tolerated at 75 mg and most prescribed with an AI. After progression on CDKi, the tendency was to prescribe a chemotherapy-based subsequent line, mainly capecitabine.**

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# Opportunities and lessons learned in using electronic health record patient portal (MyChart) for recruitment to the population-based WISDOM study

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Background: WISDOM is a preference-tolerant, pragmatic study comparing annual mammogram screening to personalized, risk-based breast screening in healthy women with a target accrual of 100,000. This sizable recruitment goal requires creative and broad-based strategies that are not typical for traditional clinical research. One of the recruitment methods is use of an electronic health record patient portal (Epic's MyChart) to invite patients to participate in research. We tested various MyChart implementation strategies across WISDOM recruitment sites and report response rates, barriers and lessons learned. The study is registered on ClinicalTrials.gov, NCT02620852. Methods: Women aged 40-74 years with no history of breast cancer, DCIS, or double mastectomy can join the WISDOM Study online at wisdomstudy.org. Participants either elect to be randomized or self-select one of the study arms, the control (annual mammogram screening) arm or the treatment (personalized, risk-based breast screening) arm. All study steps can be completed electronically, with no requirement to travel to a study site. University of California, Los Angeles (UCLA) was the first WISDOM site to gain approval to use MyChart as a recruitment tool as part of the Clinical Translational Science Institute pilot in Spring 2018. The pilot was designed to demonstrate feasibility, patient response, and recruitment metrics. Following UCLA's pilot, additional WISDOM sites received approval to use MyChart; however, implementation differed across sites based on local medical center leadership decisions. MyChart Implementation: As of July 2020, use of MyChart is ongoing at five of WISDOM's six initial recruitment sites (UCLA, Sanford Health, UCSF, UCSD, UCI). Three sites (UCLA, Stanford, and UCSF) implemented MyChart broadly, and two sites (UCI and UCSD) are phasing in MyChart recruitment. UCLA and Sanford Health implemented MyChart recruitment through a centralized approach targeting all eligible patients and sending a MyChart invitation with a link to the study's enrollment website. UCSF was approved to send WISDOM information on the MyChart portal, but the patients must opt in to learn more by outreach from a research coordinator. UCSD and UCI approaches are more limited requiring departmental or primary care provider approval for communications to be sent to patients. Results: MyChart enabled direct communication to a large number of potential study participants at UCLA and Sanford Health (UCLA 107,829, Sanford Health 86,684) during a 12-month period. The experiences of both sites were similar in that 50% of individuals read the MyChart message, 2.5-5% registered for additional information, and 1.5-2.5% consented to participate. UCSF's implementation approach was similar with 8005 individuals invited, 6.6% indicating interest to participate, and 2.4% consenting. Although the number of consented participants represented a small portion of the total women consented to join the study to date, the recruitment rates from using MyChart were 2.5-10X higher compared to sites that did not use it or were in pilot phase. Participating sites saw 30%-50% increased recruitment rates during periods when MyChart messages were in use. Implementations at the departmental (UCSD) and primary care provider level (UCI) demonstrated similar trends (3.8% and 3% consented respectively), albeit with smaller samples. Conclusions: Use of electronic health record patient portal (MyChart) recruitment for the WISDOM Study increased enrollment rate by site and is a cost-effective approach to recruiting for large scale trials with broad eligibility criteria like the WISDOM Study.

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# Palbociclib real-world data in metastatic breast cancer: A multi-site report of survival and adverse events in routine clinical practice in Scotland

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**Background: Palbociclib, with endocrine therapy, has demonstrated clinical benefit in patients with ER+ve HER2-ve metastatic breast cancer in randomised controlled clinical trials. Further observational data is beneficial to illustrate how these results translate into benefit in routine practice. Furthermore, detecting predictors of response aids clinical decision-making. Our primary aim was to report the survival data and adverse event (AE) rates in a real-life population treated with palbociclib. Secondarily, we aimed to identify predictors of response. Method: We retrospectively analysed 150 patients with metastatic breast cancer treated with palbociclib and endocrine therapy in routine clinical practice, over 3 years in three sites across South East Scotland. Baseline demographics (including disease site, prior treatment, bloods), progression data, AE rates, delays/dose reduction (DR) were recorded. For statistical analysis, we calculated actuarial rates of progression and breast cancer specific survival (BCSS) for the whole cohort. Survival analysis was performed using Kaplan-Meier and cox regression statistics. Statistical associations between variables were analysed by generalised linear models with chi-square statistics. Results: The average patient age was 61.4 years and most were post-menopausal (86.7%). Around two thirds (63.3%) were previously treated adjuvantly and most were performance status 0 (51.3%) or 1 (44.0%). Commonest disease sites were bone (76.0%), liver (46.0%), lung (42.7%) or nodes (36.7%). Patients were prescribed palbociclib with either; aromatase inhibitor (AI) (74.0%) as 1st line or fulvestrant (26.0%) as 2nd line. Standard starting dose was 125mg (87.3%). Rationale for a lower starting dose was mainly due to patient age (78.9%), by physician's choice.For the whole cohort, the actuarial progression rate at 24 months was 0.45 (95%CI±0.12) and BCSS rate was 0.69 at 24 months (95%CI±0.16). In the AI sub-group (n=111), at 12 months, the actuarial progression rate was 0.26 (95%CI±0.10) and BCSS rate was 0.86 at 12 months (95%CI±0.08). In the fulvestrant sub-group (n=39), the actuarial progression rate was 0.56 (95%CI±0.25) and BCSS was 0.82 (95%CI±0.14) at 12 months. Most common sites of progression were; visceral (84.1%), bone (40.1%), nodal (18.2%) or chest wall (6.8%). less had progressive disease (11.7% vs. 42.8%), compared to the fulvestrant group (n=28). The commonest AE was fatigue. During treatment, 67.1% had grade 3/4 neutropenia. Neutropenic sepsis rates were low (1.3%). Around half (47.9%) required DR, mainly for neutropenia (81.4%). A lower baseline ANC was associated with a lower ANC during cycle 1 (p<0.001) and increased likelihood of DR (p=0.001). Age, disease site and prior chemotherapy did not predict neutropenia. On multivariate analysis for predictors of response, patients were more likely to progress if they had liver involvement (OR 3.5, 95%CI 1.6-7.4, p=0.001) or had previous endocrine therapy in the adjuvant setting (OR 1.74, 95%CI 1.1-2.8, p=0.019). Those who had a DR were significantly less likely to progress (OR 0.23, 95%CI 0.9-0.6, p=0.001). Discussion: Our real-world clinical data of the use of palbociclib illustrates it is an effective therapy in a heterogeneous population, with a progression rate of 45% at 24 months. Neutropenia was common but neutropenic sepsis rates were very low, similarly to the pooled PALOMA safety data. The only predictor of neutropenia was baseline ANC. Those who had prior endocrine therapy or with liver involvement were more likely to progress. Interestingly, those with a DR were significantly less likely to progress. Other observational data has produced mixed results with regard to this relationship and therefore larger studies are needed to validate these findings.**

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# Examining and comparing the temporal changes and results of cosmetic, quality of life and patient satisfaction achieved with immediate and delayed-immediate implant-based breast reconstruction procedures and contralateral symmetrisation techniques after skin-sparing mastectomies with unilateral simple mastectomy and with bilateral skin-sparing mastectomies and immediate implant-based breast reconstructive surgeries. (ClinicalTrials.gov Identifier: NCT04356235)

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IntroductionThe immediate (I-BR) or delayed-immediate (DI-BR) implant-based breast reconstruction (BR) of the affected breast following nipple, areola, skin-sparing mastectomy (NSM, ASM, SSM) techniques requires almost in all cases symmetrization of the contralateral breast. The long term results of implant-based BR (subpectoral or prepectoral) and symmetrization following advanced postmastectomy BR techniques significantly decrease over time and later result in a limited patient satisfaction rate. Beyond the satisfactory early results BRs, there are only limited long term data on cosmetics and patient satisfaction. In fact with time patient dissatisfaction necessitates repeated surgeries, with an extra load for both to the patient and the health system. The aim of the study is to gain high quality data about the deteriorating cosmetic outcomes of bilateral BRs on the long term. Trial design In this response-adaptive prospective randomized study patients are sub-grouped into 6 study groups after BR surgery with silicone implant (following uni- or bilateral NSM, ASM, SSM) with symmetrization in case of unilateral mastectomy (mastopexy and/or silicone implant and/or mesh sling technique to suspend the breast with or without reduction) or simple mastectomy without symmetrization. The planned number of patients is a minimum of 528 cases. The measurements of the breast, the ptosis, photo documentation using valid BCCT.core software, BREAST-Q questionnaire and Likert scale are performed preoperatively, 4 weeks after delayed BR with symmetrization, 3 months after, every 6 months for 5 years.
Primary endpoint Using correlation analysis to measure objective changes over time in the quality of life (QoL) and patient satisfaction associated with the symmetry achieved by different surgical techniques up to five years of follow-up. To compare the QoL and the satisfaction rate in the control group with a simple mastectomy, bilateral SSM, ASM, NSM and BR.
Secondary endpoint To determine the prognostic factors, patient subgroups, and surgical techniques associated with patients, surgery, and oncological therapies in an optimal way. Furthermore, the study should give relevant data about the oncoplastic concept of prophylactic SSM, ASM, or NSM on the contralateral side and BR, without the presence of hereditary breast and ovarian cancer syndrome, using the same surgical technique than on the affected side. The long term PRO results of postmastectomy BR should be necessarily part of the initial patient information in the future.
Inclusion criteria- Under the age of 65 with uni- or bilateral primary breast cancer, needing advanced mastectomy independently of the axillary surgery, having I-BR os DI-BR on the ipsilateral side and symmetrization on the contralateral side - Control group: patients under 65 years with unilateral simplex mastectomy without BR. Exclusion criteria-Pregnancy-associated breast cancer-Prior breast surgery and/or radiotherapy -Severe non-surgical complication-Long-term steroid usage
Present accrual and target accrual The trial was activated on 22 April 2020 . As of 5 July, 23 patients have been randomized. Accrual is currently running according to protocol and is planned until 2025. Interim analysis performed after 2 years' median follow-up period. The final analysis is performed 5 years after closing the patient inclusion period.

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# The prognostic utility of AR/ER ratio in young women with breast cancer

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**Background: World over, less than a quarter of breast cancer diagnoses are in premenopausal women. However, in India premenopausal women constitute half of all women with breast cancer in most hospital case series. Most of these women present at advanced stages with aggressive subtypes of disease and hence the high mortality.The role and utility of detecting androgen receptor (AR) expression in the different sub-types of breast cancer, especially the ones without hormone receptor expression is yet to be firmly established. Evidence from previous studies is suggestive of its beneficial role in hormone receptor positive (HR+) breast cancer. The biological function of AR on the mammary epithelium is determined by the Estrogen receptor (ER) context, in that, it is found to be anti-proliferative in ER positive tumors while it is thought to promote growth in the absence of ER activity. An interesting approach to representing this interplay is as a ratio between AR/ER expressions. As expected, the ratio has been shown to be positively correlated with better outcomes in hormone receptor cancers, mostly in postmenopausal women. The effect of a high ratio in ER negative tumors seems more complicated. In this study, we have evaluated the AR/ER ratio specifically in patients younger than 50 years in whom the estrogenic influence is dominant due to their premenopausal status.Materials and Methods: Tumor samples from patients 50 years or younger were chosen from a larger cohort of 275 patients with median follow up of 72 months. Expression of ER and AR proteins were detected by immunohistochemistry (IHC), and the transcript levels of ESR1 and AR were determined by quantitative PCR. Relative normalized units of their gene expression were used to calculate the AR/ER ratio. A cut-off at the 3$^{rd}$ quartile was used to divide tumors into categories of high and low ratios. Clinical characteristics were compared between the low and high ratio groups along with IHC subtype distribution (HR+, HER2+ and Triple negative (TNBC)). Kaplan Meier curves was used for survival analysis and Cox proportional hazard analysis model was used to calculate the hazard ratio (HR). The results were validated in METABRIC dataset.Results: Eighty-eight (32%) patients were <50 years with a mean age of 43 years. AR/ER ratio ranged between 0.6 to 3.5 with a mean of 1.5. Sixty-six tumors were categorized as low and 22 were high based on the 3Q cut off (1.7). Clinical characters such as age, tumor size, grade, stage of disease was not different between the high and low ratio categories. Distribution of IHC subtypes among each group showed high ratio category had 64% TNBC tumors (p<0.0001). Tumors with high ratio had poor disease-free survival, (HR-2.6(95% CI-1-6.9) p-0.03). Trends in the METABRIC dataset was similar with 411(21%) patients <50 years. Ninety-seven patients with high ratio had significantly poor disease-free survival (HR-1.95 (95% CI-1.3-2.7) p-0.000).Conclusion: Interaction between AR and ER is known to influence the AR activity and our results reiterate prognostic ability of AR/ER ratio even in young patients of breast cancer. Our results suggest androgenic influences on clinical progression of breast cancer in this age group mediated through AR, has to be examined by its level in relation to the activity of ER, particularly in hormone receptor negative breast cancers. Even more importantly, examining these influences in the context of the menopausal status might help identify subgroups of patients most likely to benefit from interventions targeted at AR.**

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# Evolution of prescribing trends for HR+/HER2- metastatic breast cancer (mBC) in a post-CDK4/6i world

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**Background:**There is limited real-world (RW) evidence describing treatment patterns among oncologists since clinical guidelines have established a preference for CDK4/6 inhibitors (CDK4/6i) plus an aromatase inhibitor (AI) or fulvestrant for first-line (1L) HR+/HER2- mBC. The objective of this RW study was to assess the influence of common clinical attributes on prescriber trends in 1L HR+/HER2- mBC by conducting a Discrete Choice Experiment (DCE) and evaluating the clinical decision-making via retrospective medical chart review.
**Methods:**Via a web-based instrument, medical oncologists were presented four hypothetical clinical scenarios (CS) to assess the influence of three clinical attributes on CDK4/6i prescribing preference via DCE: pre-menopausal (pre-M) vs post-M, prior adjuvant (PA) vs no PA, and bulky liver metastases (BuLM) vs no or unknown BuLM. Respondents selected their preferred 1L treatment for each CS: single-agent chemotherapy, combination chemotherapy, hormonal therapy, or CDK4/6i. Proportion of providers selecting CDK4/6i were reported in each scenario (e.g., pre-M vs post-M). Next, a planned subset of providers completed a physician chart abstraction (PCA) summarizing demographics, clinical characteristics, 1L and subsequent regimens for HR+/HER2- mBC patients 18 years or older at diagnosis, and who initiated ≥1 line of mBC therapy. Descriptive statistics were used to examine differences between preferred (via DCE) 1L regimens (hormonal therapy, CDK4/6i, chemotherapy) and PCA 1L regimens (chart review).
**Results:**47 medical oncologists from all U.S. census regions participated in the DCE, of which 17 completed 52 unique PCAs. Provider characteristics: mean 22.7 (5, 50) years in practice; mean 23.3 (3, 80) unique HR+/HER2- mBC patients treated monthly. PCA patient characteristics: median age 61 (38, 87) years; post-M = 88.5% and PA = 40.4% (Table 1). Across DCE and PCA patients, overall 1L CDK4/6i preference was 67.6% (DCE) and 84.6% (PCA) (Table 1). By patient attribute, CDK4/6i DCE preference and PCA use were, respectively: pre-M= 55% vs 67%; post-M = 80% vs 87%; PA= 66% vs 87%, no PA = 70% vs 83%. CDK4/6i preference for patients with BuLM was 55% but could only be assessed in DCE (Table 2). Chemotherapy as an alternative to, or prior to, CDK4/6i was 23.3% in DCE (19.1% vs 4.2%) and 5.8% in PCA (5.8% vs 0%).
**Conclusion:**Our research demonstrates that RW use of a CDK4/6i regimen in 1L HR+/HER2- mBC is higher than reported preference for CDK4/6i as assessed through DCE overall and in all CS. CDK4/6i preference in DCE was lowest for pre-M (55%) and PA (66%), while RW use was above 80% in all cases except for pre-M (67%). The use of chemotherapy prior to, or as an alternative to, CDK4/6i was both a preference in DCE and an observation in RW patients, which may relate to continued guideline inclusion of 1L chemotherapy which may warrant additional research to address continued relevance in the CDK4/6i era.

**Table 1: Patient characteristics, HR+/HER2-**

| | DCE(N=188) | PCA(N=52) |
|---|---|---|
| Age, mean (median, range) | 54 (54; 38-71) | 61 (63; 38-87) |
| Menopausal status, n (%) | | |
| Pre-menopause | 94 (50) | 6 (11.6) |
| Post-menopause | 94 (50) | 46 (88.5) |
| Prior adjuvant therapy, n (%) | 94 (50) | 21 (40.4) |
| CDK4/6i | 0 (0) | 3 (5.8) |
| Site of Metastases, n (%) | | |
| Liver | 94 (50) | 0 (0) |
| Other/Unknown | 94 (50) | 52 (100) |
| 1L Therapy, n (%) | | |
| Hormone-based therapy | 14 (7.4) | 5 (9.6) |
| Chemotherapy | 27 (19.1) | 3 (5.8) |
| CDK4/6i-based therapy | 127 (67.6) | 44 (84.6) |
| Immediately following chemotherapy | 8 (4.2) | |

**Table 2: CDK4/6i use as a function of clinical characteristics**

| CDK4/6i Usen (%) | Pre-M(N=94) | Post-M(N=94) | PA(N=94) | No PA(N=94) | BuLM(N=94) | No/Unk BuLM(N=94) |
|---|---|---|---|---|---|---|
| DCE | 52 (55) | 75 (80) | 62 (66) | 65 (70) | 52 (55) | 75 (80) |
| CDK4/6i Usen (%) | Pre-M(N=6) | Post-M(N=46) | PA(N=23) | No PA(N=29) | BuLM(N=0) | No/Unk BuLM (N=52) |
| PCA | 4 (67) | 40 (87) | 20 (87) | 24 (83) | 0 (0) | 44 (85) |
| *p*-value | .59 | .30 | .05 | .15 | NA | .47 |

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# High compliance with choosing wisely breast procedures at a safety net hospital

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**The Choosing Wisely campaign has emerged recently in setting guidelines for surgical procedures of low utility and cost-ineffectiveness. Hospitals caring for underserved medical populations represent a unique opportunity to assess for quality of care and adherence to these guidelines. The Choosing Wisely campaign for breast surgery has highlighted: avoiding surgical re-excision for invasive cancer close to margins of excised breast tissue, avoiding double mastectomy in patients who have a single breast with cancer, avoidance of axillary lymph node dissection in women undergoing lumpectomy with limited nodal disease, and avoiding sentinel lymph node biopsy in patients ≥ 70 years of age with early stage breast cancer. Recent studies have shown variable adherence to these recommendations. In order to evaluate cost-effective surgery at our hospital serving a poorer patient population, we retrospectively analyzed patients who underwent surgery for breast cancer from 2015-2020. A total of 231 patients were identified. There were no patients who underwent re-excision for close margins of invasive cancer. Only 0.9% of patients (2/231) received contralateral mastectomy and only 1.6% of eligible patients (3/191) received axillary lymph node dissection instead of sentinel lymph node biopsy. Although 77.7% of patients ≥ 70 years of age with stage 1 hormone positive breast cancer (14/18) received sentinel lymph node biopsy, there was a downward trend during 2015 to 2020 from 100% to 50% of eligible patients receiving sentinel lymph node biopsy. De-implementation of traditional surgical practices, deemed as low-value care, towards newer cost-effective guidelines are achievable even at community hospitals serving a low socioeconomic community while preserving patient outcome and avoiding overtreatment. By avoiding overtreatment, cost savings can be achieved which allow for social distributive justice amongst breast cancer patients by ensuring careful utilization of scarce health economic resources.**

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# Mastectomy versus breast conserving surgery for the management of locally advanced breast cancer

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**Background: Breast conserving surgery (BCS) has become increasingly employed as a surgical option for patients with locally advanced breast cancer (LABC). However, guidelines on selecting appropriate LABC patients for BCS remain vague. Methods: Our Local Integrated Health Network (LHIN) conducted a multidisciplinary conference, known as the LHIN4 day, during which consensus criteria on which LABC patients may be safely offered BCS were established. These criteria included: clinical T3 or smaller, clinical and/or radiographic response to neoadjuvant therapy, patient seen by radiation oncology and deemed a candidate for post-operative radiation, and surgeon confident that negative margins could be achieved. A retrospective chart review was then performed of patients treated with neoadjuvant systemic therapy for LABC in the one year before, and three years after the LHIN4 day, which was between June 2015 and June 2019. Objectives: The primary objective of this study was to determine the rates of local and distant breast cancer recurrence in LABC patients treated with BCS using our consensus guidelines. The secondary objectives were: (1) to determine if there was an increase in BCS being performed following the LHIN4 educational day as compared to before this day, (2) to determine the rates of mastectomy followed by reconstruction among the patients treated within the past 3 years, and (3) to determine the rates of pathologic complete response (PCR). Results: A total of 391 patients were included in this study. Among the 26 patients who underwent BCS, the rate of local recurrence was 0% (0/26), and the rate of distant recurrence was 12% (3/26). Rates of BCS were 1.9% (2/108) before the LHIN4 day, and 8.5% (24/283) after the LHIN4 day. Rates of mastectomy followed by reconstruction were 12% (21/181) in the last 3 years. PCR was achieved in 15% (58/391) of all patients, of which 57% (33/58) were Her2 positive and 24% (14/58) were triple negative. Conclusion: We propose specific criteria for appropriately selecting LABC patients for BCS. Our results indicate that these criteria can be feasibly applied with low rates of local and distant breast cancer recurrence. A minority of patients with LABC who do not undergo BCS, either due to ineligibility or personal preference, are opting for mastectomy with reconstruction.**

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**Reactive oxygen species scavengers in triple negative breast cancer**

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**Reactive oxygen species (ROS) are well known to play important roles in cancer. In particular, ROS of mitochondrial origin (mtROS) promote DNA mutations and cell death when produced at high levels, but rather stimulate autophagy and metastatic spread when produced at subcytotoxic levels [1]. Multiple metabolic pathways and oncogenic regulators linked to ROS have been studied in cancer cells, including MAPK/ERK, PI3K/AKT, PTEN, PKD, BREF2, HIF-1, NF-κB and p53 [2]. Abnormalities in these pathways can contribute to tumor development.By producing mtROS, mitochondria control and could even trigger metastatic spread, meaning that the use of specific mitochondria-targeted superoxide inhibitors/scavengers, such as mitoquinol mesylate (MitoQ), could reduce and/or prevent metastatic dissemination. This has been studied and reported with the use of MitoTempo, which prevents metastasis of naturally metastatic MDA-MB-231 human breast cancer cells implanted in mice [1]. Here, we show that MitoQ impairs MDA-MB-231 and SkBr3 human breast cancer cell migration and invasion *in vitro*, and MDA-MB-231 metastasis to the lungs in mice *in vivo*. In metastatic take assays, tail vein-injected MDA-MB-231 cells pretreated with MitoQ formed significantly less metastases after 4 weeks compared to vehicle. In spontaneous metastatic assays, mice bearing orthotopic MDA-MB-231 tumors were treated with ± 20 mg/kg MitoQ (*per os*) for 6 weeks. Primary tumors were surgically removed to allow metastatic outgrowth. In this model, MitoQ decreased primary tumor recurrence as well as the number of lung micro-metastases. Additionally, RNAseq studies in two human breast cancer cell lines identified that MitoQ significantly modulated a common set of metabolic genes *in vitro* and *in vivo.* They can be used as biomarkers of response. These results, together with a successful Phase I clinical trial and the fact that MitoQ does not interfere with the cytotoxic effects of chemotherapy, confirm that MitoQ is a potential candidate to be clinically tested in triple negative breast cancer patients.**

**References:**

**1.Porporato PE et al. A mitochondrial switch promotes tumor metastasis. *Cell Rep*. 2014;8(3):754-66.2.Payen VL, et al. Pro- and antitumor effects of mitochondrial reactive oxygen species. *Cancer Metastasis Rev.* 2019;38(1-2):189-203.**

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# The affordable care act and breast cancer stage at presentation at an urban safety net hospital

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**Background: The Affordable Care Act (ACA) was signed into law March 31, 2010 and effective from January 1, 2014. Among several key provisions it allowed for expanded access to insurance coverage as well as emphasis upon prevention and wellness. We wanted to examine the impact of the ACA on stage at presentation as well as other demographics on breast cancer patients (pts) diagnosed and/or treated at a large urban public hospital. Methods: We assessed tumor registry data at a large, public safety-net hospital pre-ACA 2012-2014 and post-ACA 2015-2017 in pts with newly diagnosed breast cancer to compare demographics and stage at diagnosis. Medical record abstraction was used to complete demographic and/or stage at diagnosis data for those with incomplete data. Insurance status was obtained from institutional data. Results: A total of 1342 patients were identified that were newly diagnosed with breast cancer between 2012-2017 and had complete data. 899 (67%) of these pts were treated and diagnosed at our hospital, 418 (31%) were diagnosed elsewhere and treated at our hospital, and 25 (2%) were diagnosed at our hospital and treated elsewhere. 658 were diagnosed in the pre-ACA era compared with 684 in the post-ACA era. There were no significant differences in mean age at diagnosis (56 years) or racial distribution of cancers diagnosed between the two groups (44% African American, 28% Hispanic, 16% White, 12% Asian). In the pre-ACA era, distribution of stages at presentation was as follows: Stage 0 (13%), Stage I (24%), Stage II (30%), Stage III (17%), and Stage IV (15%). In the post-ACA era, the stage at diagnoses were Stage 0 (14%) Stage I (26%), Stage II (33%), Stage III (16%), and Stage IV (11%). Only the decrease in the diagnosis of Stage IV cancers in the post-ACA group was statistically significant ($p<0.001$). Hispanic pts (76%) were more likely to be younger than 60 at time of diagnosis compared with African American pts (56%), White pts (63%) or Asian pts (65%). Younger pts ($p<0.001$) and African American pts ($p<0.002$) were more likely to have triple negative disease. Changes in payor status between the 2 cohorts included a 20% increase in pts covered by Medicaid (11% to 31%) and a decrease in self pay (uninsured) status by 11% (56% to 45%). Conclusion: At a public safety net hospital, there was no significant change in the demographics or number of newly diagnosed breast cancers after implementation of the ACA. There was, however, a significant decrease in presentation of stage IV breast cancer at time of diagnosis during the post-ACA era as compared to the pre-ACA era which was offset by small but not statistically significant increases in early stage at diagnosis (Stages 0-2). Over 50% of pts were younger than age 60 at time of diagnosis, regardless of race or ethnicity. This is likely reflective of an overall younger pt population (e.g., age ineligible for Medicare) often cared for at a safety net hospital and may have contributed to a less robust increase in identifying earlier stage cancers in the post-ACA era. Additional factors to consider include expanded access to primary care and cancer screening among newly insured pts who in the pre-ACA era would have presented at a later stage to a public safety net hospital and were now able to seek care earlier at other institutions closer to their home. Further analysis should be done to try to elucidate reasons for this.**

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# Estimation of willingness-to-pay for breast cancer treatments through contingent valuation method in Japanese breast cancer patients (JCOG1709A); preliminary study findings

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BackgroundIn 2019, the Japanese government has decided to introduce the economic valuation to healthcare system. However, the threshold for determining cost-effectiveness-analysis has yet to be adequately studied. Therefore, we have designed a study to examine the financial value of “life” and “health” based on willingness-to-pay (WTP) considered by approximately 1,800 patients with primary and metastatic breast cancer (PBC and MBC) in Japan. Preliminary study has been conducted to set the amount of WTP prior to the main study. Methods This study is conducted by six leading hospitals under the Breast Cancer Study Group of Japan Clinical Oncology Group (JCOG). 168 patients (84 patients with PBC and 84 patients with MBC) from 20 to 79 years of age paying medical costs were examined their WTP for setting up the dichotomous-choice method survey form. Virtual scenario-specific treatments to avoid the recurrence and death of breast cancer for one year for PBC patients, and to prolong the survival period for one year for the patients with MBC were presented. The patients were evaluated how much money would pay to receive the treatment in a self-written answer. The amount of WTP that will be presented in the main study was determined by calculating the median price from these responses based on the protocol. In addition, we conducted surveys of quality-of-life by EQ-5D-5L, social background on patients, and of breast cancer medical condition on doctors. Results Completed surveys were collected from 166 doctors (98.8%) and 139 patients (82.7%). The range of the amount of WTP for scenario-specific treatments among the patients with the patients with PBC was from 0 to 5 million Japanese yen (JPY) (50,000 USD), and among the patients with MBC was from 0 to 10 million JPY (100,000 USD). In accordance with the criteria set forth in advance in the protocol, the amount of WTP that will be presented in the main study was set at 5 million JPY in both PBC and MBC patients. Conclusion We have fixed the cost that will be presented in the main study based on the findings of our preliminary study. The main study will commence around September 2020.

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# Clinical validity of compartmental analysis of tumor-infiltrating lymphocytes (TIL) in triple-negative breast cancer (TNBC) - The key is in spatial morphology?

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INTRODUCTIONAnalyzes reported to date on TIL in TNBC have evaluated mostly stromal (sTIL) and possibly intratumoral TIL (iTIL), but none evaluated TIL spatially, separately in compartments of central tumor (CT) and invasive margin (IM). Also, none evaluated connection between TIL and other clinicopathological factors.
METHODSWe retrospectively analyzed consecutive sample of 152 early TNBC patients treated at our institution 2009-2012. TIL were assessed morphologically, by hematoxylin - eosin (HE), using standard formalin - fixed - paraffin - embedded (FFPE) samples, according to recommendation of International Working Group for Evaluation of TIL, both sTIL and iTIL, spatially, in compartments of CT and IM. Available clinicopathological variables were analyzed, and correlations of all paramethers were calculated.
RESULTSMorphological analysis of TIL spatially by compartments showed as follows: median overall sTIL content was 19%, iTIL 5%, TIL in CT 5%, TIL at IM 18%, sTIL in CT 5%, iTIL in CT 1%, sTIL at IM 30%, and iTIL at IM 5%. Intermediate or high TIL content, defined as ≥10% was present in 48% cases of sTIL in CT, 23% of iTIL in CT, 86% of sTIL at IM, and in 47% of iTIL at IM cases. Quarter of patients had TIL>50% in any of four compartments. There was statistically significant positive correlation between sTIL in CT and age and menopausal status, and also tumor size (T), but w/out correlation to histologic subtype, nodal (N) status, grade, and Ki67; iTIL in CT were statistically significantly positively correlated to histologic subtype (precisely to NOS subtype), but negatively to age and menopausal status, exactly opposite to sTIL in this section, and w/out correlation to other tumor characteristics, such as T, N, grade or Ki67; sTIL on IM, as well as iTIL on IM, showed statistically significant correlation to grade and Ki67, and no correlation to age and menopausal status.
DISCUSSIONSection analysis reveals higher density of TIL content at IM, which directs attention towards this neglected tumoral compartment and it's possible role. It also shows, although in small numbers, that possibly iTIL, especially those at IM, could actually not only, as thought so far, serve as ,,satellites“ to sTIL, but an entirely autonomous, and even opposite biomarker. Moreover, all that could be concluded from just a simple and cheap HE morphological analysis of standard tumor specimen.

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# The role of resection of the primary tumour in patients with de novo oligometastatic breast cancer (OMBC)

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**Purpose: The role of resection of the primary tumour in management of patients with OMBC is controversial. Loco-regional treatment (LRT) with curative intent could be discussed considered for OMBC patients, who experience good response to systemic therapy. We retrospectively studied the impact of resection of the primary tumour on overall survival (OS) for de novo OMBC treated at Oscar Lambret Center in Lille.Patients and methods: Between 2005 and 2017, all consecutive patients were selected. De novo OMBC was defined by 1 to 5 metastases in 1 or 2 organs, diagnosed within three months after primary tumor. Clinical data, tumor characteristics, metastatic sites, locoregional treatment, systemic first line treatment were recorded retrospectively. We set up 2 groups according to therapeutic strategy. Group 1 patients were managed with a prior planned curative intent surgery and systemic treatments and group 2 included patients with systemic therapy alone, without plan of surgery.Results: 116 patients were included in our analysis; 78 patients in group 1 and 38 patients in group 2. Median age was 54,9 years (25,2-86,2) with no difference between both groups (p=0,08). TNM stage, cancer histologies were comparable in both groups, excluding that there were more HER2+ tumour in Group 2 (p=0.003). 81 patients underwent LRT, 69 patients in group 1 and 12 patients in group 2. 59% of them had radical mastectomy and 89% had axillary surgery. For 29% of them, surgery was performed before knowledge of metastatic disease. The other main indications of breast surgery included stable disease (50%), local progression (9%), palliation (5%), single metastasis (5%) and complete metastatic response after chemotherapy (2%). 59 of 81 patients had adjuvant radiotherapy. Regarding systemic first line treatment, patients in group 1 received more chemotherapy (63% vs 86%, p=0.01), anti-HER2 treatment was appropriate except for 6 patients because of heart disease and 69% of patients had hormone therapy with no difference in both groups. Regarding metastases at diagnosis, the mean number of metastases was 2,1 (SD=1,2), 103 patients (89%) had one metastatic site, and 13 patients (11%) had two metastatic sites, with no difference between both groups. Secondary bone involvement was most prevalent site (69%). There was no difference between both groups in metastasis distribution. Median OS was 70,2 months in our cohort. LRT did not improve OS (HR 1,23; 95% CI □0,75-2,00□ p=0,41), even after adjustment on age and HER2 status. Median progression free survival (PFS) was 30,2 months in our cohort. LRT did not improve PFS in comparison with systemic treatment alone (HR 1,38; 95% CI □0,91- 2,11□ p=0,13).Conclusion: We found that LRT did not improve outcome (PFS or OS) in OMBC patients. This is in line with recently issued large randomized phase III trial. LRT is not a standard of care in OMBC, nevertheless, further clinical studies are needed to better identify the subgroup of OMBC patients that could benefit from LRT, at least in term of quality of life.**

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# Volumetric analysis of the pectoralis major muscle as preoperative tool to select patients undergoing pre-pectoral versus sub-pectoral implant based breast reconstruction after risk reducing mastectomy

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***Background*: Proper patient selection is crucial to maximize aestethic outcome in breast reconstructive surgery. No specific patients selection criteria have been developed to choose between prepectoral versus subpectoral implant-based reconstruction. A quantitative tool able to determine the pectoralis muscle individual characteristics might be helpful to discriminate a priori the patients who will experience better aesthetic outcome and less complications following a pre-pectoral versus a sub-pectoral approach. Preoperative pectoralis muscle assessment may optimize patients' selection for the breast reconstructive technique. *Trial design*: This is a multicentric trial in which, patients candidated to risk reducing mastectomy fulfilling inclusion criteria, will undergo a preoperative MRI prior to randomization to pre-pectoral versus sub-pectoral implant placement in immediate breast reconstruction. Volumetric analysis of the pectoralis major muscle (cm2) and measurement of the subcutaneous adipose tissue in the breast region, will be performed to assess anatomic characteristics of the pectoralis muscle using a sagittal T1 fat suppressed sequence. The volume of the pectoralis muscle will be calculated by measuring differences in density with the MRI. In all patients, the pectoralis muscle area on the left and right side will be determined separately and the two values will be averaged. The volumetric assessment will be performed by two expert radiologists. BREAST-Q© questionnaire will be completed by each patient prior to surgery and at the follow up evaluations. Breast reconstruction will be performed immediately after nipple-sparing mastectomy (Arm 1: breast implant placed above the pectoralis major muscle (pre-pectoral); Arm 2: breast implant placed below the pectoralis major muscle (sub-pectoral)). Number of revisional surgeries, explantations, infections, seromas, flap necrosis, will be compared between two groups and correlated with MRI pectoralis muscle volume. Post-operative follow-up evaluations at 6 and 12-months to assess capsular contracture and BREAST-Q changes will be performed. *Eligibility criteria*:**

**Inclusion criteria:**

**•Female patient•Ages 18-60•Patients undergoing risk reducing mastectomy with immediate implant-based reconstruction •Signed informed consent**

**Exclusion Criteria:**

**•Prior chest wall irradiation •Patients with a contraindication to immediate breast reconstruction.•Patients with history of smoking, •BMI> 40, •D cup breast size•grade III ptosis**

***Aims:* To identify variables measured at preoperative MRI pectoralis muscle's volumetric analysis that correlate with aesthetic outcome and complication rate in pre-pectoral versus sub-pectoral implant based reconstruction.**

***Statistical methods:* The assumption of distributional normality will be tested using the Shapiro-Wilk test. Comparisons of two variables will be carried out using the Wilcoxon test for paired groups and the Mann-Whitney test for unpaired groups.**

***Present accrual and target accrual:* The trial has been submitted for IRB approval at the ethical commission of Italian Switzerland. Recruitment has not started yet. With an enrollment ratio of 1:1, fifty patients (25 per arm) need to be recruited to ensure a power of 80% with a two sides alpha error of 0.05.**

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# Factors associated with sexual problems during adjuvant endocrine therapy

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Background: Adjuvant endocrine therapy (AET) reduces recurrence and mortality in women with hormone receptor-positive (HR+) breast cancer (BC). Sexual problems are common during AET but are under-reported and under-treated in routine clinical care. Patient reported outcomes (PRO) improve clinician awareness of patient symptoms. We present an analysis of prospectively collected PRO from a clinic-based registry of women with HR+ BC receiving AET with the aim of identifying factors associated with developing or worsening sexual problems.

Methods: Women with stage 0-III BC initiating AET were enrolled in a prospective clinic-based registry Mar 2012-Dec 2016. Participants completed PRO surveys at baseline (BL) and 3, 6, 12, 24, 36, 48 and 60 months (mo). Sexual problems were evaluated by the MOS Sexual Problems (MOS-SP) measure (range 0-100; higher scores indicate more sexual problems). Respondents rate severity of problems in 4 domains of sexual function on a 4-point scale ("not a problem", "a little of a problem", "somewhat of a problem" and "very much a problem"). We considered participants who responded "somewhat of a problem" or "very much a problem" for ≥1 domain to have a sexual problem at that time point. Based on the empirical rule effect size method, we defined clinically significant developing or worsening sexual problems during AET as an increase in MOS-SP score by ≥8 from BL. Women with MOS-SP score >92 at BL were excluded. Other PRO surveys were the Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) scale and NIH PROMIS measures for pain interference, fatigue, depression, anxiety, physical function (PF) and sleep disturbance. We evaluated associations between worsening of PROMIS T-scores in 4-point increments and FACT-ES score in 5-point increments with change in the MOS-SP score by ≥8. Additional covariates were clinical and demographic factors including socioeconomic status (SES). We used neighborhood poverty (NP) rate >15% as a surrogate for low SES based on US census estimates of the % of persons in a zip code below the federal poverty line. We performed logistic regression with generalized estimating equations to account for repeated observations. The final multivariable model was determined with a forward stepwise selection algorithm.

Results: Among 300 participants, 195 (65%) were post-menopausal, 252 (84%) white and 30 (10%) black, 134 (45%) on tamoxifen and 166 (55%) on an aromatase inhibitor. Stage distribution was 0: 28 (9%); I: 180 (60%); II-III: 92 (31%). Prior to ET, 132 (44%) had mastectomy, 84 (28%) had chemotherapy and 199 (66%) had radiation (RT). 40 (13%) were of low SES. Median follow-up is 56 mo. 165 (55%) participants reported ≥1 sexual problem during participation. At BL, median MOS-SP score was 8.32 (range 0-92). There was no significant change in mean MOS-SP score from BL to 48 mo (p=0.74). In univariate analyses, worsening scores on all PRO measures were associated with increase in MOS-SP score by ≥8, however on multivariate analysis, only worsening endocrine symptoms (OR 1.34, 95% CI 1.21-1.48, p<0.001) and PF (OR 1.08, 95% CI 0.99-1.18, p=0.06) were retained in the final model. Clinical variables in the final model associated with increase in MOS-SP score by ≥8 were mastectomy (OR 2.00, 95% CI 1.19-3.36, p=0.01) and RT (OR 1.82, 95% CI 1.05-3.16, p=0.03). Women of low SES were less likely to have increase in MOS-SP score by ≥8 (OR 0.49, 95% CI 0.24-0.98, p=0.04). Age, race, stage and type of ET were not associated with developing or worsening sexual problems.

Conclusions: Women receiving AET at risk for developing or worsening sexual problems include those with worsening endocrine symptoms and worsening PF plus those who have undergone mastectomy or RT. Routine assessment for sexual problems in this population may reduce under-detection and identify women who can benefit from interventions to improve sexual function.

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# Skin and nipple sparing mastectomies - oncologic outcomes from an oncologic center

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**Introduction: Skin and Nipple Sparing mastectomies are an alternative for patients not eligible for conservative breast surgery, allowing for better aesthetic results than classical mastectomies. We aimed to evaluate oncological safety outcomes and identify risk factors for locoregional recurrence in patients submetided to sparing mastectomies. Methods: A retrospective analysis was conducted on all consecutive cases of skin sparing mastectomy (SSM) or nipple sparing mastectomy (NSM) for a primary diagnosis of invasive or *in situ* breast carcinoma, treated at an oncologic center, from january 2013 to may 2019. Primary outcome was locoregional recurrence. Secondary outcomes included overall survival and disease-free survival, median time to recurrence and median follow-up time. Risk factors for locoregional recurrence were analysed using chi-square test and t test where suitable, followed by a logistic regression model. Survival analysis was performed using Kaplan-Meier curve. Results: We included 461 cases; 59 cases (13%) presented with carcinoma *in situ* and 402 (87%) with invasive carcinoma. Median age was 46 (24-78) years. Seventy-one (15%) patients had locally advanced disease. SSM were performed in 226 (49%) cases and NSM in 235 (51%). Neoadjuvant chemotherapy was administered in 141 (31%) cases and adjuvant radiotherapy in 203 (44%). Locoregional recurrence rate was 3,4% with no nipple-areolar complex (NAC) recurrence. Median time to recurrence was 22 (1-54) months. Overall survival was 91,7% and disease-free survival was 80,4% at a median follow-up time of 39 (1-86) months.Factors associated with locoregional recurrence in univariate analysis were tumor size over 4cm, high histological grade, negative endocrine receptors, neoadjuvant chemotherapy and absence of endocrine therapy (p<0,05), however none of these factors were independently associated with recurrence as ascertained by logistic regression model. There was no association of recurrence with familial risk mutation. Conclusions: SSM and NSM present as a safe surgical approach to breast cancer requiring mastectomy, with a locoregional recurrence rate comparable to classical mastectomy. It was not identified a group of patients who are at risk of recurrence. Nonetheless, risk factors such as tumor size, histological grade, absence of endocrine receptors, neoadjuvant chemotherapy and absence of endocrine therapy may correlate with less favorable outcomes.**

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# Association of the prognostic nutritional index and survival of patients with breast cancer in a third-level care hospital in Mexico

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**Introduction. The prognostic nutritional index (PNI) is a convenient and accessible tool that reflects the nutritional and immunological conditions of patients with solid tumors. PNI is calculated based on the total lymphocyte count and serum albumin level. There is not an optimal well established cutoff value. Low PNI has been associated with lower overall and disease-free survival (OS and DFS) in breast cancer patients, however, there is no information regarding this prognostic value in patients from Mexico. The aim of this study was to analyze the association between PNI and survival of breast cancer patients from Mexico.**
**Methods. We retrospectively analyzed medical records of patients with histologically confirmed breast cancer treated at Medica Sur Oncology Center in Mexico City between January 2008 to December 2019. PNI was calculated using the following formula: 10 × serum albumin value (g/dL) + 0.005 × total lymphocyte count (mm3). Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal PNI cutoff value. The primary endpoint was OS. The secondary endpoint was DFS. Statistical analysis was performed with SPSS v25, the associations between PNI and clinicopathologic characteristics were analyzed using Pearson's χ2 test, survival curves were calculated with Kaplan-Meier method, and comparison among groups with log-rank. Proportional Cox model was used to perform multivariate analysis. A p value <0.05 was significant. Results. A total of 110 patients were included in the analysis, and classified into two groups: low and high PNI (ROC curve analysis showed an optimal cutoff value of 32.1). Median follow-up was 65 months. Mean PNI at diagnosis was 39.3 (SD 6.7). All patients had infiltrating ductal carcinoma, 15.5% had metastatic disease, 18.2% had triple negative breast cancer, 23.6% had HER 2 overexpression, and around 51% where positive for hormone receptors. Mean PNI in patients with locally advanced disease was significantly lower than in patients with localized disease, (p= 0.044), no other statistically significant associations were found between mean PNI and clinical characteristics. Median OS was not reached in the high PNI group vs 48.5 months (mo) in the low PNI group, while 5 -year OS rates were 89% and 41%, respectively (p= 0.03). The high PNI group had better DFS than the low PNI group (median DFS 65 mo vs 22.5 mo, 5-year DFS rates 65% vs 45% (p = 0.024). In univariate and multivariate analysis, triple negative histological subtype and low PNI were independent prognostic indicators for poor survival. Conclusion. High PNI in breast cancer patients is associated with superior DFS and OS. PNI is an independent prognostic factor for DFS and OS. PNI is an accessible prognosis factor that uses only regular laboratory assessment in patients with cancer.**

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# Breast cancer patients have reduced levels of short chain fatty acid producing beneficial gut bacteria

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**The role of the human gut microbiome has been increasingly appreciated in respect to its influence on human health and disease. It has been proposed that dysbiosis in the gut microbiome and subsequent induction of chronic inflammatory state might have an influence on breast cancer development and prognosis. Therefore this study was undertaken to determine the role of gut microbiome in breast cancer. The Breast Molecular Epidemiology Resource (BMER) resources of the Holden Comprehensive Cancer Center (HCCC) were used to recruit 23 women with breast cancer. Fecal samples were used to characterize the gut microbiome of our patient population using 16S rRNA amplification and Illumina sequencing. Reads were then mapped back to amplicon sequence variant using DADA2 pipeline and compared to a cohort of race, age, and gender matched cohort of regional healthy controls. In our preliminary analysis, we observed that breast cancer patients have distinct microbiota compared to age and gender matched healthy controls. We identified depletion of the anti-inflammatory short chain fatty acid producing bacteria specifically *Faecalibacterium, Anaerostipes, Parabacteroides* and *Phascolarctobacterium* in feces from BC patients*. Additionally,* breast cancer cohort *showed* enrichment of the pro-inflammatory bacteria such as *Eubacterium* (dolichum), *Bifidobacterium*, and *Blautia*. These bacteria have been previously been identified to change with clinical disease stage and/or BMI, as has genus *Bifidobacterium* (increased in BC cohort). Within BC group, patients with high grade showed lower levels of *Eggerthella lenta* and *Desulfovibrio* whereas patients receiving chemotherapy showed depletion of Sulphur reducing *Desulfovibrio* and methane producing archaea *Methanobrevibacter.* Further analysis may lead to insights into the interplay between gut microbiome and breast cancer, as well as the feasibility of therapeutic strategies in the form of novel and existing probiotics.**

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# Patient risk factors for loss to breast oncologic follow up

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For patients who complete treatment for breast cancer, national oncologic guidelines recommend yearly mammography surveillance and oncology follow-up especially during the first five years of survivorship. Some studies have shown that older age and insurance type may be risk factors for timely initial follow up after abnormal mammogram however the role in which racial and socioeconomic disparities may contribute to long term non-adherence or loss to follow-up (LTFU) is not known. Investigation into causes of LTFU or non-receipt of recommended surveillance are crucial in improving health care delivery and targeting interventions that prevent LTFU in high-risk patients. An ongoing study at Lifespan Breast Oncology aims to evaluate this issue further among patients treated for stage 1-3 breast cancer. We have completed data collection on 139 of 300 eligible patients diagnosed in 2014 and for whom 5 years of follow up have been completed. We measured adherence to yearly mammography, visit with breast oncologist, continuation of ET, and LTFU in each year of survivorship. LTFU was defined as patient without any further contact with the Lifespan Breast Oncology clinic. We then examined the association between these adherence measures and age, ECOG performance status at diagnosis, Medicaid insurance status, socio-economic factors, and specific adjuvant therapies, using univariate and multivariate generalized estimating equation models for longitudinal data. The models reported odds ratios (OR) for non-adherence or LTFU, with 95% confidence intervals (CI). Patients who experienced relapse or death were removed from the pool in the year of event. Adherence decreased for all measures between year 1 and year 5 of survivorship: from 99% to 82% for oncology visits, 92% to 80% for mammography, and 86% to 71% from ET. LTFU increased from 0% to 17%, respectively (OR per year, 1.96; 95%CI, 1.55-2.48). In univariate analysis, patients age >70 (compared with age ≤50) had a significantly higher risk of LTFU (Table), non-adherence to visits (OR=6.64 versus age ≤50, P=.002), mammography (OR=4.18, P=.020), or ET (OR=5.42, P=.002). Patients with performance status ECOG ≥2 had significantly lower adherence to all measures. Medicaid insurance was associated with significantly higher LTFU, non-adherence to mammography (OR=5.58, P=.008) or oncology visits (OR=6.53, P=.002). Marital, employment, or parenting status were not significantly associated with the risk of LTFU, but employed patients had a higher adherence to mammography and ET. Cancer stage, ER, or HER2 status were not associated with any adherence measure. LTFU was lower among recipients of ET, but not recipients of chemotherapy. In a multivariable model, Medicaid insurance (OR=3.99, P=.027) and receipt of ET (OR=0.32, P=.027) retained significant association with LTFU. Our findings show that Medicaid patients represent a high risk group with potential need for increased resources to ensure adequate follow-up. We plan to continue to expand this cohort and analyze more patients at our institution. Interventions to change barriers and circumvent financial limitations that these patients face in obtaining care could potentially decrease rates of recurrence and potentially impact overall survival. This data could be utilized in future studies to create a risk stratification tool to identify patients who would be at high risk for LTFU. Table. Factors associated with loss to follow-up.

| | N (%) | % LTFU at 5y | OR | 95%CI | P |
|---|---|---|---|---|---|
| All | 139 | 17 | | | |
| Age ≤50 | 32 (23) | 16 | 1 | | .003 |
| 51-70 | 70 (50.4) | 12 | 0.89 | 0.27-2.90 | |
| >70 | 37 (26.6) | 22 | 3.51 | 1.19-10.4 | |
| ECOG 0 | 15 (10.8) | 7 | 1 | | .007 |
| 1 | 108 (77.7) | 15 | 3.65 | 0.43-31.1 | |
| > 2 | 14 (10.1) | 29 | 20.28 | 1.90-216 | |
| Insurance: private | 78 (56.1) | 9 | 1 | | .001 |
| Medicaid | 15 (10.8) | 46 | 6.76 | 2.03-22.5 | |
| Medicare | 45 (32.4) | 19 | 5.13 | 1.98-13.3 | |
| Children: no | 70 (50.4) | 12 | 1 | | .34 |
| yes | 66 (47.5) | 19 | 1.71 | 0.56-5.22 | |
| Married: no | 56 (40.3) | 17 | 1 | | .68 |
| yes | 83 (59.7) | 16 | 0.84 | 0.38-1.88 | |
| Employed: no | 70 (50.4) | 20 | 1 | | .32 |
| yes | 66 (47.5) | 15 | 0.66 | 0.29-1.49 | |
| Stage:1 | 87 (62.6) | 18 | 1 | | .66 |
| 2 | 39 (28.1) | 12 | 0.64 | 0.24-1.69 | |
| 3 | 13 (9.4) | 22 | 0.8 | 0.19-3.46 | |
| ER- | 23 (16.5) | 26 | 1 | | .27 |
| ER+ | 115 (82.7) | 15 | 0.58 | 0.22-1.54 | |
| No ET | 38 (27.3) | 29 | 1 | | .033 |
| ET | 101 (72.7) | 12 | 0.41 | 0.18-0.93 | |
| No chemotherapy | 87 (62.6) | 17 | 1 | | .25 |
| Chemotherapy | 52 (37.4) | 16 | 0.6 | 0.25-1.43 | |

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# A randomized, multicenter, open-label phase II/III study of ARX788 vs Lapatinib and Capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer (ZMC-ARX788-211)

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**Background: ARX788 is a novel antibody drug conjugate (ADC) that consists of a human epidermal growth factor receptor 2 (HER2) targeting monoclonal antibody (mAb) site-specifically conjugated with payload AS269, a highly potent tubulin inhibitor. Results from a phase 1 study (CTR20171162) in cohorts dosing from 1.1 mg/kg to 1.5 mg/kg demonstrated promising antitumor activity with an objective response rate (ORR) of 52.0% (26 of 50) in heavily pretreated patients (median 5 prior regimens) with HER2-positive metastatic breast cancer. Among patients with tyrosine-kinase inhibitors (TKIs) prior treatment, the ORR was 48.5% (16 of 33). In 1.5mg/kg Q3W cohort, ORR was 68.4% (13 of 19) and median progression-free survival (PFS) was not reached due to majority subjects were still under ARX788 treatment. Here we describe a phase II/III study evaluating the efficacy and safety of ARX788 vs Lapatinib and Capecitabine in patients with HER2-positive advanced breast cancer.**

**Study Description: ZMC-ARX788-211 (CTR20200713) is a randomized, multicenter, open-label, phase II/III trial comparing ARX788 vs Lapatinib and Capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer. Approximately 440 patients (IHC3+ or ISH+) from 45 centers in China will be 1:1 randomized to receive ARX788 1.5 mg/kg every 3 weeks or Lapatinib plus Capecitabine until disease progression, intolerable toxicity, or death. Patients must have progression on ≥1 prior lines of HER2 therapy. Randomization will be stratified by therapy line (1 vs. >1) and visceral metastasis (yes vs. no). The primary outcome measure is PFS per Independent Review Committee (IRC). Secondary outcome measures are overall survival (OS), PFS per investigators, ORR, disease control rate (DCR), duration of response (DOR), safety, immunogenicity and population pharmacokinetic. Two interim analyses are planned for the study. The first interim analysis will be performed when 160 patients have completed Cycle 4 assessment to detect potential early futility trends. The second interim analysis will be performed when 2/3 of the IRC assessed PFS events have occurred, in which early superiority will be declared if the P-value crossed the O'Brien Fleming boundary, and sample size will be recalculated if the conditional power is promising but below 80%. Global phase II/III trial of ARX788 to include sites in US and other regions is under planning.**

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# Pre- versus sub-pectoral implant-based breast reconstruction after skin-sparing mastectomy or nipple-sparing mastectomy (OPBC-02 PREPEC): A pragmatic, multicenter, randomized, superiority trial

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***Background*** **The emphasis on aesthetic outcomes and quality of life (QoL) has motivated surgeons to develop skin- and nipple-sparing mastectomy (SSM/NSM) for breast cancer (BC) treatment or prevention. Immediate breast reconstruction is based on implants or autologous tissue. The optimal positioning of the implant is not clear: While pre-pectoral positioning respects the anatomic position of the mammary gland and avoids surgery-induced alterations of the pectoralis major muscle, the lack of muscle coverage may increase the risk of additional surgical interventions due to major complications. The Oncoplastic Breast Consortium (OPBC) identified this knowledge gap as research priority in 2019.**
***Trial design*** **International, multicenter study with a superiority trial design and two parallel groups with 1:1 random allocation to pre- or sub-pectoral implant-based breast reconstruction (IBBR). Following a pragmatic approach, randomly assigned IBBR will be performed according to the surgeons' usual care by use of a one- or two-stage approach with or without adjunctive mesh. Follow-up visits are performed within routine care (visits at 10 days and at 1, 6, 12, 18 and 24 months after surgery). Oncological follow-up will be conducted annually for 10 years. ClinicalTrials.gov identifier: NCT04293146.**
***Eligibility*** **We include women ≥ 18 years, with an indication for NSM or SSM and IBBR in the therapeutic or risk-reducing setting, the ability to complete QoL questionnaires and the adequateness of skin flap(s) for pre-pectoral IBBR (intraoperative decision of the surgeon).**
***Specific aims*** **The primary objective is to test whether pre-pectoral IBBR provides better QoL with respect to long-term (24 months) physical well-being of the chest (BREAST-Q) compared to sub-pectoral IBBR for patients undergoing SSM or NSM for prevention or treatment of BC. Secondary endpoints include loss of expander or implant, complications, other BREAST-Q QoL and patient satisfaction domains, aesthetic outcomes and recurrence free survival. Interference of different dose distributions of radiation therapy and its consequences on the distribution of local tumor recurrences will be assessed.**
***Statistical methods*** **The primary analysis will be performed on the full analysis set following the intention-to-treat principle. To test the primary hypothesis, a linear mixed model will be fitted with the BREAST-Q score as response variable and treatment assignment as independent variable. The analysis will be adjusted for baseline BREAST-Q score, stratification factors (i.e. uni- vs bilateral surgery and NSM vs SSM) and other potential confounders. A random intercept to account for the center effect will be included. As a sensitivity analysis, an unadjusted t-test will be performed on the BREAST-Q score change from baseline to compare the two treatment arms. The sample size was determined for the primary endpoint, with an expected mean score of 76 points for sub-pectoral and 80 points for pre-pectoral implants. The clinically relevant difference to be detected in this superiority design is 4 points, with an expected common standard deviation of 13 points. A sample size of 334 patients provides an 80% power for a two-sided t-test at level α = 0.05. Compensating for a 10% dropout rate, the total sample size was calculated to include 372 patients.**
***Present accrual and target accrual*** **By June 2020, one study site (Basel) has been initiated. During a 21-month recruitment period, we plan to include 372 patients at 21 sites in Switzerland, USA, China, Austria, Germany, Hungary and Sweden.**
***Contact information*** **Prof. Dr. Walter Paul Weber, Chefarzt Brustchirurgie, Breast Surgeon SSO, Universitätsspital Basel, Spitalstrasse 21, CH-4031 Basel, Tel: +41 61 328 61 49, Walter.Weber@usb.ch**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS6-58**

# The impact of baseline modified glasgow prognostic score (mGPS) on survival outcomes in in indigenous and non-indigenous patients with advanced breast cancer patients of Western Australia

**Azim Khan[1], Hilary Martin[1], Lisa Spalding[2] and Andrew Redfern[1]. [1]Fiona Stanley Hospital, Perth, Australia[2]University of Western Australia, Perth, Australia**

**Introduction: The modified Glasgow prognostic score (mGPS) is known to be useful in prognostication of multiple cancers. The mGPS, which integrates albumin and C-reactive protein, could assist as a possible prognostic marker in breast cancer. Indigenous women have inferior breast cancer survival to non-Indigenous women and may also have a differing inflammatory environment. Here, we examine the utility and impact of baseline mGPS on survival outcomes in women with metastatic breast cancer by Indigenous status.**
**Methods: We retrospectively collected data from the Western Australian Cancer Registry and electronic records for patients diagnosed with breast cancer between 2001 and 2016 with confirmed metastatic disease. Overall survival (OS) were measured from the date of diagnosis until death. mGPS comprised scores of one point given for CRP > 10 mg/L and/or albumin < 3.5 g/dL, therefore having a value of 0 to 2.**
**Results: Of 152 patients with metastatic breast cancer, 89 patients had all relevant data available and were included with a median follow up of 120 months. The median age was 55.3 years. Baseline mGPS was 0 in 46.6 %, 1 in 34.8 % and 2 in 18.6 %.**
**Median OS across Indigenous and non-Indigenous patients combined was significantly worse moving from the mGPS-0 group through mGPS-1 to mGPS 2, 50.0 v 30.0 v 8.0 months respectively (p<0.0001). Looking at the groups separately, both cohorts separately demonstrated inferior median OS in mGPS-2 compared to mGPS-1 patients, 9 v 32 months (p=0.02) for Indigenous patients, and 2.0 vs 25.0 months for non_Indigenous patients (p=0.001).**
**The correlation between mGPS and the neutrophil-to-lymphocyte ratio (NLR) was weak with a Pearson correlation R-value of 0.184 (p=0.085)**
**Conclusion: The study shows that the mGPS is an independent prognostic factor in advanced-stage disease. A higher baseline mGPS score was associated with worse survival in Indigenous and non-Indigenous patients. A larger prospective study is needed to validate the results, inclusive of assessing links between mGPS and OS in different breast cancer sub-types.**

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# *Pparg1* induces an EGF-EphA2 receptor tyrosine kinase module to promote ErbB2- mammary adenocarcinoma in mice

**Richard G Pestell[1], Xuanmao Jiao[1], Andrew V Kossenkov[2], Adam Ertel[3], Wei Tong[4], Zhao Zhang[1] and Peter A McCue[5]. [1]Baruch S Blumberg Institute, Doylestown, PA;[2]The Wistar Institute, Philadelphia,, PA;[3]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA;[4]Children's Hospital of Philadelphia, Philadelphia, PA;[5]Thomas Jefferson University, Philadelphia, PA**

**ErbB2 is overexpressed in approximately 25% of human breast cancers, associated with clinically aggressive disease. No soluble ligand has been identified and the receptor is regulated by heterodimerization with other ErbB family receptors, including EGFR, and other receptor tyrosine kinases including EphA2. EGFR is activated by seven different growth factors including EGF and Amphiregulin. Downstream signaling modules required for ErbB2 induced tumorigenesis in genetically engineered mouse models (GEMM) include the phosphatidylinositol 3-kinase/Akt (PKB) pathway, the Ras/Raf/MEK/ERK1/2 pathway and the phospholipase C (PLCγ) pathways. ErbB2-mediated tumorigenesis involves activation of receptor tyrosine kinases, induction of cyclin D1/CDK activity, and functional restraint by tumor suppressors. The receptor tyrosine kinase EPH receptor A2 (EphA2), a member of the Eph RTK family, is overexpressed in aggressive breast cancer and EphA2 forms a complex with ErbB2 thereby enhancing ErbB2-induced tumor onset and progression.**

**The host immune system participates in the therapeutic response of HER2$^+$ breast cancer. The tumor microenvironment (TME) is regulated by chemokines and their G protein coupled receptors binds several ligands, including Cxcl5 which binds Cxcr2, to augment the pro-tumor immune response, tumor growth and metastasis.**

**Identifying genetic programs that participate in ErbB2-induced tumors may provide the rational basis for co-extinction therapeutic approaches. Peroxisome proliferator-activated receptor γ (PPARγ), which is expressed in a variety of malignancies, governs biological functions through transcriptional programs.**

**Herein, genetic deletion of endogenous *Ppary1* restrained mammary tumor progression, lipogenesis, and induced local mammary tumor F4/80$^+$ tumor-associated macrophage infiltration, without affecting other tissue hematopoietic stem cell pools. *Ppary1* induced peroxisomal target genes in the mammary tumors as evidenced by increased expression of *PEX-11, together with PPARGC1* and *ESRR induced regulator, muscle 1*, *Perm1 (PGC-1 and ERR-induced Regulator in Muscle 1).* Peroxisomes induced by *Ppary1*, activated Type1 interferons (IFNs) and IFN-stimulated gene expression, including Cxcl5. Endogenous *Ppary1* induced expression of both an EphA2-Amphiregulin and an inflammatory INFγ -Cxcl5 signaling module. *Ppary1* bound directly to growth promoting and proinflammatory target genes in the context of chromatin. We conclude *Ppary1* promotes ErbB2-induced tumor growth and inflammation and represents a relevant target for therapeutic coextinction.**

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# Is immediate breast reconstruction safe in post neoadjuvant chemotherapy patients? A single centre audit

**Fatima Mansour, Joseph Meilak, Kirti Kabeer, Manoj Gowda, Sadaf Jafferbhoy, Sekhar Marla, Vallipuram Gopalan, Sankaran Narayanan and Soni Soumian. Royal Stoke University Hospital, Stoke on Trent, United Kingdom**

**Introduction: Neoadjuvant chemotherapy (NACT) is increasingly utilised in the treatment of aggressive breast cancers. There are concerns that this could impact patient recovery following extensive oncoplastic procedures. The literature regarding this is limited and conflicting. We aimed to assess the impact of neoadjuvant chemotherapy on patients undergoing immediate breast reconstructions.**
**Method: A 5-year retrospective single centre audit of prospectively collected data on patients undergoing immediate breast reconstruction following NACT, was completed. The oncoplastic procedures performed included myocutaneous and perforator flaps, therapeutic mammoplasty and implant based reconstruction. Demographic data, length of stay, biochemical measurements, rates of wound infection, haematoma, explantation rates and return to theatre, were collected. For comparison a matched cohort of patients who underwent primary reconstruction without NACT, during the same period, was selected.**
**Results: One hundred and fourteen patients were included in the study (52 post NACT vs 62 controls). There were 52% that underwent implant based reconstruction, 33% flaps and 15% mammoplasties. Overall, the NACT group appeared to have slightly improved outcomes including lower complication rates (19% vs 23%, p= 0.042) and length of stay (1.45 vs 1.59 days, p>0.05). Hypoalbuminemia (25.0%) and low WCC (65.2%) were significantly higher in the NACT group but this was not associated with increased complication rates. Conclusion: Our audit suggests that NACT does not cause a significant increase in post-operative morbidity. Further studies with larger numbers will be required to validate these results.**

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# Pooled efficacy analysis from two phase 3 studies in patients receiving eflapegrastim, a novel, long-acting granulocyte-colony stimulating factor, following TC for early-stage breast cancer

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**Background: Eflapegrastim (Rolontis®, Efla) represents the first novel, long-acting granulocyte-colony stimulating factor (G-CSF) to be introduced in more than 15 years. Efla consists of a recombinant human G-CSF analog conjugated to a human IgG4 Fc fragment via a polyethylene glycol linker. Preclinical, clinical, and pharmacodynamic/pharmacokinetic data have shown increased potency for Efla versus pegfilgrastim (Peg). Both independent, randomized Phase 3 studies comparing Efla and Peg for prophylaxis of chemotherapy-induced neutropenia in patients with early-stage breast cancer (ESBC) met the primary endpoint of non-inferiority in duration of severe neutropenia (SN; ANC<0.5×10$^9$/L) (p<0.001) for Efla vs Peg in all 4 treatment cycles. Additionally, one of the studies exhibited a statistically significant reduction in the relative risk of SN in Cycle 1 with Efla. Here we provide a pooled analysis across the two pivotal studies comparing Efla vs Peg for SN in various subgroups. Methods: Patients with ESBC, who were candidates for adjuvant or neoadjuvant chemotherapy, were randomized 1:1 in two open-label Phase 3 studies to fixed-dose Efla (3.6 mg G-CSF) or standard Peg (6 mg G-CSF) administered on Day 2 following TC (docetaxel/cyclophosphamide) for a total of 4 cycles. ANCs were collected daily in Cycle 1 and 5 times in Cycles 2-4. SN was evaluated between treatment groups in Cycle 1 using Fisher's exact test at 5% level of significance and was analyzed using multivariate logistic and Cox proportional hazards regression models. Results: A total of 643 patients who received either Efla (n=314) or Peg (n=329) were included in the analysis. The two treatment groups were well balanced for demographics and baseline characteristics. The mean age was 59 years, 38% were ≥65 years old, and 54% weighed >75kg. The safety profiles, including AEs and discontinuations, for Efla and Peg were comparable, and >99% of all patients received full dose of TC on schedule. The majority (67%) of patients with SN experienced a 1 day duration, occurring between Days 7 and 8 after TC. Mean duration of SN for Efla was statistically lower than for Peg (0.24 vs. 0.36 days; p=0.029). The above statistical significance was maintained for Efla after adjusting for demographic and baseline characteristics, namely age, weight, enrolling geographical region, and treatment setting in a multivariate model. Similarly, the incidence of SN for Efla was statistically lower than Peg in Cycle 1 (17.5% vs 24%; relative risk reduction [RRR]=27%; p=0.043). Univariate analysis of the incidence of SN showed a significant risk reduction in favor of Efla (8.6% vs 14.1%; p=0.034) for patients weighing >75kg (p=0.034). Multivariate analysis of SN showed significant odds ratio of SN for age ≥65 years and baseline ANC >6×10$^9$/L in favor of Efla (OR=0.42 and 0.39, respectively). The incidence of SN in Cycles 2-4 was comparable between treatment groups. Also, the incidence of febrile neutropenia and neutropenic complications was similar with <5% in each treatment group. No leukocytosis, splenic rupture, or anaphylaxis was reported in any patient receiving Efla or Peg. Conclusion: A pooled analysis of two, randomized Phase 3 studies evaluating Efla vs Peg, administered once-per-cycle for prophylaxis of SN, showed Efla and Peg had similar safety profiles with Efla demonstrating a statistically significant risk reduction in SN overall and in patients weighing >75kg. Eflapegrastim is a novel, long-acting and potent recombinant human G-CSF which may provide an attractive option in supporting patients at risk for SN-related complications.**

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# Phase I study combining ipatasertib with chemotherapy and atezolizumab in patients with metastatic triple negative breast cancer

**Yuan Yuan, Susan E. Yost, Jin Sun Lee, Paul H. Frankel, Christopher Ruel, Mireya Murga, Aileen Tang, Norma Martinez, James Waisman, Niki Patel, Mina Sedrak, Daphne Stewart, Sayeh Lavasani and Joanne Mortimer. City of Hope, Duarte, CA**

**Background: The PI3K-ATK pathway is one of the most common cancer drivers in breast cancer, and the AKT inhibitor ipatasertib (ipat) has shown great efficacy in patients (pts) with metastatic triple negative breast cancer (mTNBC). The current phase I trial is designed to test the safety and efficacy of the following ipat combinations: ipat + carboplatin (C) + paclitaxel (T); ipat + C; ipat + capecitabine (cape) + atezolizumab (atezo). Trial Design: This is a Phase I open-label study for pts with mTNBC. Eligible pts receive one of three regimens: A) weekly carbo AUC 2 plus taxol 80 mg/m$^2$ days 1, 8, 15 and daily ipat 300 mg every 28 days; B) weekly carbo AUC 2, days 1, 8, 15 and daily ipat 400 mg every 28 days; C) cape 750 mg bid 1 week on 1 week off, ipat 300 mg daily and atezo 840 mg iv days 1, 15 every 28 days. Eligibility Criteria: Eligible patients must have histologically confirmed mTNBC (ER/PR ≤ 10%, HER2- per ASCO/CAP); RECIST 1.1 measurable disease; 0-2 lines of chemotherapy prior for mTNBC; AEs recovered to ≤ Gr 2 per CTCAE 5.0; adequate bone marrow, hepatic and renal function. Prior exposure to AKT targeted therapy is excluded.Specific Aims: Primary objectives are to evaluate the safety and tolerability of the combinations and determine the recommended Phase II dose (RP2D) of the combinations. Secondary objectives are to evaluate response rate, clinical benefit rate, progression free survival, and overall survival. Statistical Design: For the safety-lead in, a "3 at risk design" will be utilized to assess toxicity for the combination therapy. The DLT period is 1-cycle (28 days). Each participant will remain on the dosing level according to the escalation dose level they were enrolled in, and intra-dose level escalations will not be allowed, even if the MTD is defined at a higher dose level. Rules for escalation are as follows: if escalating from Level 1, two dose levels will be open, Level 2A, and Level 2B. Only if both 2A and 2B result in a decision to escalate will dose level 3 for this triplet be open. When both 2A and 2B are both open, slots will be given to the arm with the most open slots (starting with 2A if there are ties). When a maximum tolerable dose level has been defined by the dose escalation portion of the study, and the recommended phase 2 dose (RP2D not to exceed the MTD) has been selected, additional patients will be accrued to confirm the tolerability of the regimen. For Arm C, at least 12 patients will be treated at the RP2D to confirm tolerability. Additional patients can be accrued if the total number of patients accrued does not exceed 21 patients (e.g. if the RP2D is dose level 1, with 2A and 2B not well-tolerated based on 3 patients on each 2A and 2B, the total at RP2D could be 15). If one agent is discontinued due to toxicity, then the participant may continue to receive the remaining single agent or doublet agent therapy on protocol. With 12 patients, any specific severe toxicity with 20% incidence will be observed with 93% probability.**

2020 San Antonio Breast Cancer Symposium®

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# The impact of nurse navigation on adherence to care for patients treated for breast cancer in a safety net hospital

Christine Rehr[1], Susan Coples[2], Zhensheng Wang[3], Roland Matthews[4], Pooja Mishra[2], Jamil Facdol[2], Rosalyn Garrett[2], Kimberly Fritz[2] and Sheryl Gabram[1]. [1]Emory University School of Medicine, Atlanta, GA;[2]Grady Health System, Atlanta, GA;[3]Rollins School of Public Health, Emory University, Atlanta, GA;[4]Morehouse School of Medicine, Atlanta, GA

Background/Objective Adherence to recommended care remains challenging for patients with breast cancer (BC), particularly those from disadvantaged groups. Although our Center has historically used lay BC navigators to meet with newly diagnosed patients, our team identified the need to improve care for vulnerable cancer patients (pts) through nurse (RN) navigators. This project aimed to investigate adherence to care over two-time intervals, pre and post RN navigators, and investigate the level of out migration (patients who leave our system) of BC patients during the same time.

Methods An RN breast oncology navigator started navigating patients and collecting data on Jan 1st, 2018. The RN navigator meets with all newly diagnosed BC pts during clinic and tracks their progression of care, often expediting work up and treatment. A tumor registry audit of refusal of care as coded by “pt or pt guardian refused care” was conducted for two-time intervals: 2016-2017 (pre-RN navigation) and 2018-2019 (post-RN navigation). Out-migration of analytic BC patients was also measured during these time intervals.

Results The tables below show total analytic cases and refusal of care rates. Refusal of care rates decreased from 17.8% pre- to 13.2% post-RN navigation.

Table 1: Total BC pts and refusal of care

| BC Patients | 2016-2017(Pre RN navigation) | 2018-2019(Post RN navigation) | *P*-value |
|---|---|---|---|
| Total analytic | 325 | 376 | |
| Total Refusal of care | 58 (17.8%) | 50 (13.2%) | 0.128 |

Table 2: Refusal by type of recommended care

| Time Interval | Chemo | Hormonal | Immunotherapy | Radiation | Surgery |
|---|---|---|---|---|---|
| 2016-2017 | 29(62%) | 18(60%) | 0(0%) | 22 (48%) | 10(45%) |
| 2018-2019 | 18(38%) | 12 (40%) | 2 (100%) | 24(52%) | 12(55%) |

Out-migration was 3.6% for 2016-2017 and 3.6% for 2018-2019.

Conclusions Implementation of an RN breast navigator in 2018 trended towards less refusal of care by our patients diagnosed or receiving at least one treatment in our safety net hospital. Refusing chemotherapy and hormonal therapy were treatments that were most impacted by RN breast navigation. RN navigation may enhance compliance through: offering personalized education, dispelling myths of therapy, proactively working with patients when side effects/complications occur, and supporting patients when questions or concerns arise. While there was no difference in “out-migration” to other cancer centers identified during this time interval, the number of patients leaving the system remains low. We plan to continue to track our BC navigated patients and collect patient satisfaction with navigation as a future initiative. This effort was supported by a grant from the Merck Foundation Alliance to Advance Patient-Centered Cancer Care.

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# Cost effectiveness of routine cardiac imaging during adjuvant trastuzumab in HER2-positive breast cancer

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**Background:** Guidelines recommend patients treated with trastuzumab (TRA) undergo a multiple gated-acquisition (MUGA) scan or echocardiogram (ECHO) at baseline and every 3 months thereafter. In this retrospective study, we evaluated the incidence of clinically significant cardiotoxicity and analyzed cost effectiveness of routine cardiac imaging during adjuvant TRA.
**Methods:** HER2-positive breast cancer patients treated with adjuvant TRA between 2015 and 2019 were investigated. Information regarding comorbidities, clinical diagnosis of cardiotoxicity, and alterations in therapy were collected. ECHO and MUGA scans were reviewed to monitor trends in ejection fractions (EF). Data was analyzed via the FREQ procedure. We defined clinically significant cardiotoxicity as holding or discontinuing TRA regimen.
**Results:** We found 108 patients. Median age was 57 years (interquartile range (IQR) of 47-68 years); 86% Caucasian and 12% African American. 3% had preexisting heart failure, 43% hypertension, 14% diabetes, 4% coronary artery diseases, 32% hyperlipidemia, 2% chronic kidney disease, 6% stroke, and 38% were smokers. No patients received anthracycline containing regimens. 30 patients (27.7%) had EF drop >10% from baseline. Six patients (5.5%) were identified with clinically significant cardiotoxicity; 4 (3.7%) had EF < 50% and 3 of those 4 were symptomatic (2.7% of total). Median time from initiation to decline in EF > 10% was 6 months (IQR of 4.5-7.5 months).
**Conclusions:** Current practice for TRA cardiotoxicity monitoring consists of cardiac imaging every 3 months. The average cost for a MUGA scan and ECHO is approximately $3700 and $2500, respectively. We determined that clinically significant cardiotoxicity, occurred in 5.5% of the patients approximately 6 months into treatment. With TRA causing reversible cardiotoxicity and 2.7% of the patients being symptomatic, cardiac imaging every 3 months appears excessive, especially in patients without comorbidities. Baseline cardiac imaging with repeat assessment in 6 months appears sufficient in non-anthracycline containing regimen. This strategy allows cost savings of approximately $6000 per patient.

**Characteristics of patients with clinical cardiotoxicity**

| Clinically Significant Cardiotoxicity (N=6) | Stage | Chemotherapy Regimen | Heart Failure Symptoms | EF drop below 50% | Initiation to Drop in EF >10% (months) | Discontinuation to Recovery in EF (months) |
|---|---|---|---|---|---|---|
| 1 | IIB | TCHP | No | No | 3.2 | 1.1 |
| 2 | IA | TCHP | Yes | Yes | 6.1 | 2.8 |
| 3 | IIA | TCH | No | No | 9.3 | 1.3 |
| 4 | IB | TCH | Yes | Yes | 6.5 | 4.8 |
| 5 | IIA | TH | Yes | Yes | 6.1 | 2.6 |
| 6 | IIA | TCHP | No | Yes | 6.3 | 1.2 |

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**Publication Number: PS1-61**

# Clinical and patient reported outcomes in oncoplastic breast conservation surgery from a single surgeon's practice in a busy community hospital in Canada

**Ashley DiPasquale, Zofia Prus-Czarnecka, Lindsay Delmar and Lashan Peiris. University of Alberta, Edmonton, AB, Canada**

**Introduction: Oncoplastic breast surgery combines oncologic partial mastectomy with ipsilateral defect repair using volume displacement and volume replacement techniques with contralateral symmetrising surgery as appropriate. Oncoplastic surgery aims to maintain quality of life by pre-empting and mitigating against breast asymmetry whilst not compromising oncological effectiveness. Although growing in popularity in North America, many patients still do not have access to these techniques which usually involve longer operation times and require a surgeon with specialized oncoplastic training. This study demonstrates the implementation of an effective oncoplastic surgical practice in a community hospital within Canada and shows low rates of peri-operative complications as well as high levels of patient-reported outcome measures. Methods:A retrospective chart review of consecutive patients diagnosed with Stage 0-3 breast cancer treated with level I and level II oncoplastic techniques by a single breast surgeon was undertaken. Patient demographics, tumor characteristics, procedure types, and clinical outcomes were collected. Patient satisfaction was assessed with the Breast-Q questionnaire administered pre-operatively as well as 3 months and 9 months post-operatively. Results:Oncoplastic breast conservation surgery was performed in 340 patients over a 31 month period from 2017-2019. The average size of breast lesion was 1.8 cm with 96 patients having lesions 2-5 cm in size, and 10 patients having tumours >5cm. Thirty (8.8%) patients experienced a complication requiring intervention. Margin revisions were required in 21.8% of patients which reduced to 18% after the implementation of the new margin consensus guidelines. The completion mastectomy rate was 4.7%. Contralateral symmetrizing procedures were performed in 31 (9.1%) of patients by the surgeon performing the patient's breast conservation surgery. Breast Q scores increased across breast satisfaction, process of care, psychosocial, physical, and sexual satisfaction domains post-operatively. Conclusion:This study demonstrates the feasibility of an oncoplastic breast surgery practice in a busy community hospital in Canada. This adds to the growing body of North American data on the clinical and oncological safety of these techniques and introduces the idea of collecting patient-reported outcome measures within a Canadian population. We hope that this will serve to aid in the recruitment of oncoplastic-trained surgeons to both teaching and community hospitals and enable these techniques to become the standard of care in North America.**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS9-60**

# Insomnia is the most disturbing symptom during breast cancer treatment: Results from a Brazilian cohort using a patient-reported outcomes: PRO tool - Tummi App

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**Background: PRO have been shown to enhance our ability to communicate with patients and to control their symptoms. There are data that suggest a positive impact on survival when there is active participation of the patient in the reporting of symptoms. However, PRO data are not commonly collected in routine cancer care due to challenges like cost and due to the obsolete technology of many existing electronic health records. Methods: in an effort to bridge the unmet needs of PRO collection and integration into routine cancer care, we developed a symptom monitoring and management system that was launched as a free mobile app in August, 2018. Tummi app is designed for reporting 28 symptoms based on the National Cancer Institute's Common Terminology Criteria for Adverse Events. Symptoms are reported in a 3-point scale (mild, moderate, severe) and patient reported an overall well-being scale represented by emojis. Tummi has the ability to record symptoms, summarize the reporting in physical printout, and automatically store and analyze the input symptoms into graphical interpretations. Results: since august 2018, 281 patients with the diagnosis of invasive breast cancer, during their treatment, downloaded and enjoyed the app. The most common side effect registered was back pain. When assessing the most intense symptoms reported by patients (grade 3), insomnia appears as the most remembered, followed by headache. Regarding general well-being reports, patients totaled 4501 records. Of these, at 62.40% of the time the patients were well, while at 33.16% they were average and at 4.44% they felt bad. Conclusions: in this group of patients evaluated by the Tummi App, insomnia is the most disturbing symptom. Although it appears in the literature as quite prevalent in this scenario, we see that its approach to day-by-day oncology clinics is far from ideal. We believe that the monitoring by a PRO tool can lead to a greater effort to improve this symptom that has such an impact on the quality of life of our patients.**

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# Presence of comorbidities and use of concomitant medications associated with QTC prolongation/torsades de pointes in patients with HR+/HER2- advanced breast cancer

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BACKGROUND: Corrected QT (QTc) prolongation is a cardiac condition that may increase the risk of ventricular arrhythmias, including Torsades de Pointes (TdP), and cardiac-related death. QTc prolongation is a notable concern in oncology as drug-induced QTc prolongation is a documented side effect of several anticancer therapies. Moreover, patient-specific risk factors for QTc prolongation such as increased age and a history of cardiovascular disease/events can be common among patients with metastatic breast cancer, which puts this population at an increased baseline risk for QTc prolongation. Female sex is a risk factor itself. The objective of this study was to characterize the presence of comorbidities and use of concomitant medications associated with QTc prolongation/TdP among patients receiving first-line (1L) treatment for HR+/HER2- locally advanced or metastatic breast cancer (aBC).METHODS: Oncologists in France, Germany, Israel, Italy, Spain and the United States abstracted clinical characteristics and medication data from the medical records of patients, aged ≥18, who received 1L treatment for HR+/HER2- aBC between 10/2019 and 02/2020. The presence of comorbidities (e.g., congestive heart failure, myocardial infarction, history of atrial arrythmias) and utilization of concomitant medications (excluding anti-cancer therapies) with known, possible, or conditional risk for QTc prolongation/TdP were summarized. The list of comorbidity risk factors was compiled from a targeted literature search and clinician review. The list of concomitant medications was obtained from crediblemeds.org.RESULTS: A total of 1164 patients with aBC were sampled across the six countries. Among them, 99% were female and the mean age was 62 years. The majority of patients had metastatic disease (85%); 15% had locally advanced disease. Among those with metastatic disease, 47% had visceral metastasis and 34% had bone-only metastasis. At 1L initiation, 84% of patients had an ECOG score of 0/1. Comorbidities associated with risk of QTc prolongation/TdP were observed in 8% of patients; the most frequently observed were congestive heart failure (3%) and history of myocardial infarction (2%) (Table 1). The proportion of patients who received at least one medication associated with risk of QTc prolongation/TdP was 39%. Overall, 42% of patients had at least one comorbidity or medication associated with risk of QTc prolongation/TdP.

Table 1. Presence of Comorbidities and Use of Concomitant Medications with known, possible, or conditional risk for QTc prolongation/TdP in Patients Who Received First-Line Therapy for HR+/HER2- Advanced Breast Cancer

| | N | % |
|---|---|---|
| Total Patients | 1164 | 100 |
| Comorbidities | | |
| Myocardial infarction | 20 | 2 |
| Congestive heart failure | 32 | 3 |
| Moderate or severe liver disease | 3 | <1 |
| History of QT prolongation | 3 | <1 |
| Bradyarrhythmia | 3 | <1 |
| History of atrial arrhythmias | 28 | 2 |
| History of ventricular arrhythmias | 1 | <1 |
| Hypo/hyperkalemia | 8 | 1 |
| Hypo/Hypercalcemia | 8 | 1 |
| Disorders of magnesium metabolism | 8 | 1 |
| Disorders of phosphorus metabolism | 2 | <1 |
| Unstable angina | 4 | <1 |
| Presence of comorbidity QTc risk factor | 94 | 8 |
| Mean (SD) number of conditions per patient | 1.3 (.4) | |
| Received medication considered a risk factor for QTc prolongation | 450 | 39 |
| Presence of QTc risk factor condition or medication | 490 | 42 |

CONCLUSIONS: Approximately 2 out of 5 patients receiving 1L treatment for HR+/HER2- aBC had a comorbidity or utilized a concomitant medication that could increase risk of QTc prolongation/TdP. As cardiovascular toxicity is a known side effect associated with several anticancer therapies, the high prevalence of coexisting risk factors among patients receiving 1L treatment underscores the importance of assessing patients' existing risk when selecting treatments for advanced breast cancer.

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# Impact of Cholecystectomy in Breast Cancer Recurrence

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**Background: Several published studies demonstrate that bile acid metabolites may influence the growth of breast cancer cells in vitro. Our group has shown reduced plasma concentrations of cholic acid and chenodeoxycholic acid (primary bile acids) and deoxycholic acid and lithocholic acid (secondary bile acids) in breast cancer patients that later on develop tumor recurrence. Cholecystectomy reduces the circulating bile acid pool. In patients with prior cholecystectomy, changes in bile acid metabolites may contribute to breast cancer tumorigenesis and recurrence. This study investigates our institutional rate of cholecystectomy in women diagnosed with breast cancer and its impact on breast cancer recurrence.**

**Methods: A retrospective review of patients with an invasive breast cancer diagnosis between 2014-2015 was conducted. Demographics, preoperative variables, surgical history and clinical outcome data was collected. 5-year disease-free survival (DFS) was compared using a Log-rank (Mantel-Cox) test.**

**Results: The study included 264 patients with mean age of 60.9. Most were Caucasian (83.5%). The majority were diagnosed at Stage II or lower (80.3%) and had hormone receptor positive, HER2 negative breast cancer (72.9%). Approximately 22.7% of patients had prior cholecystectomy surgery. The only statistically significant heterogeneity in demographic data between patients with and without cholecystectomy was body mass index (BMI). Patients with cholecystectomy had a mean BMI of 33.3, versus 29.1 in patients with intact gallbladders. The 5-year DFS in breast cancer patients with cholecystectomy was 91.6%, versus 97.1% in patients with intact gallbladders (p=0.06).**

**Conclusion: Women with breast cancer who had a history of cholecystectomy had increased rates of breast cancer recurrence over a 5-year period compared to women with breast cancer with intact gallbladders. Although this result was not statistically significant, a trend was seen. Future study of a larger patient sample size sample may lead to a statistical significant difference. The statistically significant difference in BMI between the two patient groups is likely a confounding factor, given increased BMI is a known risk factor for developing cholecystitis and breast cancer. This data supports existing in vitro studies that bile acids may influence the growth of breast cancer cells. There may be utility in closer follow-up of women with breast cancer and a history of cholecystectomy given the increased rate of breast cancer recurrence in this population.**

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# ABEMACARE: Abemaciclib in combination with endocrine therapy as first line therapy in metastatic breast cancer patients with symptomatic visceral metastases or high tumor burden

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**Background:**
Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors in combination with endocrine therapy are well established in the therapy of estrogen receptor (ER) positive, HER2 negative metastatic breast cancer. They have shown excellent results regarding disease control and survival in numerous trials while maintaining good quality of life for patients. In the subgroup analysis of the MONARCH 2 and MONARCH 3 trials, patients with liver metastases derived a particularly large benefit from the combined endocrine treatment with Abemaciclib. Despite this evidence, in real world many patients with endocrine sensitive metastatic breast cancer are still being treated with first line chemotherapy. Especially in patients with symptomatic visceral disease and/or high tumor burden, use of upfront chemotherapy remains common even in the absence of visceral crisis. With this study we aim to determine the efficacy of Abemaciclib in combination with endocrine therapy as first line treatment in this specific patient population.
**Study design:**
In this prospective multicenter observational study, we intend to enroll 120 patients in 10 German cancer treatment centers who will receive first line therapy with Abemaciclib in combination with endocrine therapy within clinical routine. Recruitment is planned to start in August 2020. Patients with documented ER positive, HER2 negative metastatic breast cancer with measurable visceral disease are eligible if they fulfill one of the following inclusion criteria: Presence of clinical signs or symptoms of visceral disease (e.g. pleural effusion, ascites, abdominal pain from liver or peritoneal metastases, dyspnea from pleural effusion or lymphangiosis of the lung, elevated liver enzymes or bilirubin level (> 2x ULN)) or signs of high tumor burden (e.g. LDH > 399 U/l with K in normal range, abnormal CEA or CA 15-3 level (> 2x ULN), radiographic signs of lymphangiosis of the lung, cytologically proven bone marrow infiltration). Patients may have received chemotherapy or endocrine therapy in the adjuvant setting, but no prior therapy with CDK 4/6 inhibitors and no first line therapy for metastatic disease. Primary endpoint is best objective response rate (ORR) defined by the proportion of patients who are evaluated as having partial (PR) or complete response (CR) while being on study treatment using RECIST V1.1. ORR will be analyzed using the one group $\chi^2$ test at the 5% significance level. The test hypotheses are as follows: $H_0$: ORR = 0.43, $H_A$: ORR ≠ 0.43. In addition, ORR will be reported with a 95% CI.Several additional endpoints regarding disease control and patient reported outcomes will also be evaluated. At the same time translational research to identify possible early predictive biomarkers for tumor response (e.g. circulating tumor DNA) will be conducted.
**Contact information:**
For further information please contact the leading physician Dr. Johannes Ettl via johannes.ettl@tum.de
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# Comparative study of breast tumors with differential expression of intracellular energy sensor adenosine monophosphate kinase

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**Adenosine monophosphate kinase (AMPK), encoded by mammalian gene *PRKAA1* is a central energy sensor which acts as a metabolic switch and directs cellular response based on AMP/ATP ratio in cells. AMPK has been shown to be involved in tumorigenesis as part of metabolic reprogramming. Further, chronic metabolic disorders like obesity and insulin dependent diabetes are linked to increased cancer recurrence and poor prognosis. Interestingly, AMPK expression and activity are affected in both obesity and insulin dependent diabetes. Structurally, AMPK is a heterotrimeric protein with alpha (α), beta (β) and gamma (γ) subunits. AMPKα subunit is the catalytic subunit, AMPKβ is the scaffold subunit and AMPKγ subunit provides the competitive binding site for AMP or ATP. In case of nutrient/ energy deprivation, AMP/ATP cellular ratio increases, and AMPK is activated to suppress anabolic pathways and promote catabolic pathways. On the other hand, under excess nutrient, AMP/ATP cellular ratio is decreased, and AMPK function is impeded leading to promotion of anabolic pathways over catabolic pathways. In metabolic disorders like obesity and insulin dependent diabetes, AMPK expression and function are suppressed. Current literature and our research indicate that AMPK can be the bridge between understanding the links between metabolic disorders and cancer. In the current study, we explored the clinical and molecular differences between breast tumors expressing relatively low and high AMPK, indicated as $AMPK^{low}$ and $AMPK^{hi}$ breast tumors.**

**The cBioPortal (http://cbioportal.org) for Cancer Genomics platform was used for this study. The data mining was focused on METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) Breast cancer study, which reports clinical and molecular data for over 2500 breast cancer patients. Among the 2500 breast cancer tumors, $AMPK^{hi}$ and $AMPK^{low}$ expressing breast tumors were 310 and 311 in numbers, respectively. The $AMPK^{hi}$ and $AMPK^{low}$ expressing breast tumors in RNA-seq dataset were queried using cBioPortal embedded SQL feature as PRKAA1: EXP>1 and PRKAA1: EXP<-1, respectively. Comparative analysis of $AMPK^{low}$ and $AMPK^{hi}$ expressing breast tumors was performed for clinical impact and mRNA expression profiles. The mRNA data was further analyzed for integrated networks using Reactome.**

**The query for $AMPK^{hi}$ and $AMPK^{low}$ resulted in non-overlapping cohorts of breast tumors. Analysis revealed that significantly higher percentage (65.45%) of $AMPK^{low}$ breast tumors were positive for Estrogen receptor with high proliferative index. Overall patient survival (months) is significantly more in patients with $AMPK^{hi}$ breast tumors compared to patients with $AMPK^{low}$ breast tumors. Microarray mRNA expression data revealed unique profile of mRNA expression in both the cohorts. The top 10 most significant differentially expressed genes are KLHL2, COX6C, SLC29A3, SPRY2, RAMP1, ANXA3, HAGH, TLCD3B, KLHL24 and ACVR2A. Pathway enrichment analysis with the top 100 differentially expressed mRNA using Reactome suggested significant enrichment of Wnt, Notch, MAPK and ESR signaling pathways. The molecular profile of $AMPK^{hi}$ and $AMPK^{low}$ expressing breast tumors are unique and have different mRNA expression signatures. In addition, cancer stem cell homeostasis signaling pathways seem to be critical in the molecular functioning of the two groups. Clinical and molecular data suggests that further investigations into the two molecular subtypes of breast cancer can provide useful insight towards the links between metabolic disorders and cancer.**

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# Phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with hormone receptor-positive / HER2-negative resected isolated locoregional recurrence of breast cancer - The POLAR Trial

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Background: Isolated local or regional recurrence (ILRR) of breast cancer (BC) after mastectomy or lumpectomy indicates a poor prognosis and patients with ILRR hold a substantial risk of developing subsequent distant metastasis. Limited randomized evidence supports the recommendation of systemic treatment for hormone receptor-positive (HR+) ILRR. Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, such as palbociclib, have shown activity and safety in the first-line treatment of metastatic HR+/HER2-negative BC.
The POLAR hypothesis is based on the results of the CALOR trial (IBCSG Trial 27-02), which showed effectiveness of adjuvant chemotherapy among patients with resected HR-negative ILRR, but not for HR+ ILRR. Considering these findings and compelling evidence supporting the activity of the combination of CDK4/6 inhibitors and endocrine therapy (ET), we hypothesize that palbociclib in combination with ET may be effective as adjuvant therapy in patients with HR+/HER2-negative resected ILRR of BC.
Trial design: POLAR is a phase III open-label, multicenter, randomized trial of adjuvant palbociclib in combination with standard ET versus standard ET alone for women and men with histologically confirmed HR+/HER2-negative resected ILRR of BC. Protocol treatment consists of palbociclib (125 mg/d orally for 21 days, followed by 7 days rest) for 3 years plus standard ET for at least 3 years (Arm A) or standard ET for at least 3 years (Arm B). Patients must be enrolled within 6 months of complete gross excision of the ILRR. Patients may have started standard ET prior to entry.
Randomization (1:1) is stratified according to (1) gender and menopausal status; (2) planned ET (oral aromatase inhibitor or tamoxifen vs. fulvestrant).
The primary endpoint, invasive disease-free survival (iDFS), will be compared between treatment groups using a stratified log-rank test. The sample size provides 80% power to detect a 50% reduction in hazard (HR=0.50) for palbociclib plus ET versus ET-alone, using a log-rank test with two-sided $\alpha=0.05$ test with 66 iDFS events. The 3-year iDFS is assumed to be 76% on the basis of patients in the CALOR trial who had ER+ ILRRs.
Accrual: The trial will recruit 400 patients from approximately 50 Centers in Austria, France, Hungary, Italy, Spain and Switzerland. The first patient was randomized in August 2019. Accrual as of mid-June 2020 was 25 patients.
The POLAR trial (IBCSG 59-19 / BIG 18-02) is sponsored and coordinated by IBCSG with financial support from Pfizer. The trial is conducted under the BIG umbrella in collaboration with ABCSG, GEICAM, SOLTI, SAKK and Unicancer.
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# Adenosquamous carcinoma of the breast: A population-based study using the SEER database

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**Objective:** The present study is aimed at summarizing the clinicopathological characteristics, prognosis, and management of breast adenosquamous carcinoma (ASC).

**Introduction:** ASC is a rare and unique form of invasive mammary carcinoma with poorly understood clinicopathological characteristics and disease progression, so identification of the features associated with ASC patient survival is warranted.

**Methods:** A population-based study was performed using retrospectively extracted data from the Surveillance, Epidemiology and End Results (SEER) database for breast cancer patients with histological diagnoses of ASC, infiltrating duct carcinoma (IDC) and squamous cell carcinoma (SCC) from 2004 to 2016. End-points were overall survival (OS) and breast cancer-specific mortality (BCSM). Propensity Score Matching (PSM) was employed to minimize selection bias of baseline characteristics. Univariable and multivariable analyses were used for identifying valuable prognostic factors.

**Results:** The average age at onset of ASC was close to that of IDC. ASC presented similar tumor size but low histological grade and less lymph node metastasis compared to IDC. ASC expressed less positive rate of hormone receptors and barely HER2 receptor, which was similar with SCC (estrogen receptor (ER): ASC 27.74% and SCC 21.53%, progesterone receptor (PR): ASC 18.06% and SCC 12.85%, HER2: ASC 4.44% and SCC 7.53%). ASC patients underwent the same treatment as IDC (chemotherapy 36.99% vs. 41.86%, BCS 50.58% vs 52.83%, $P > 0.05$), only with less radiotherapy (39.88% vs. 48.34%, $P < 0.05$). Median follow-up data of 78 months showed that the prognosis of IDC patients was better than that of ASC patients (all $P < 0.05$ for BCSM and OS). After adjustment for clinicopathological and therapeutic factors in Cox proportional hazards models, ASC was no longer an independent poor prognosis factor. In matched groups, no significant difference in BCSM nor OS was observed between ASC and IDC groups. In HR-negative patients, the prognosis of ASC was similar with that of IDC, and both were superior to SCC. In HR-positive patients, the five-year survival rate of ASC was only about 60%, which was far less than that in ASC of HR-negative, the poor prognosis of ASC was closer to that of SCC. Multivariate analysis showed that older age (age≥60) and advanced AJCC stage (III and IV) were independent factors of poor prognosis in ASC, breast-conserving surgery was also ideally suited for ASC.

**Conclusion:** ASC have unique clinicopathological characteristics and prognosis. To improve the clinical and biological understanding of ASC can make breast cancer patients get more individualized treatment.

**Keywords:** adenosquamous carcinoma, infiltrating duct carcinoma, squamous cell carcinoma, prognosis, SEER database

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# A clustering and mutual information based analysis of the ELIMA study results: The additive value of multi-parametric liquid biopsies, including CTCs, EVs and cfDNA, in metastatic breast cancer

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**Background: To gain comprehensive insights into the aspects of genomic and transcriptomic complexity which could be beneficial for therapy management in metastatic breast cancer (MBC), we established the isolation and analysis of mRNA and gDNA from circulating tumor cells (CTCs), mRNA from extracellular vesicles (EVs), and cell-free DNA (cfDNA) from a minimized blood volume. Here, we aimed to assemble the results of all four analytes and elucidated the relevance of the diverse parameters within a multimodal data set. Methods: EDTA blood (2x 9 ml) was drawn from 26 MBC patients with hormone receptor-positive and HER2 negative primary tumors at the time of disease progression. CTCs and their mRNA were isolated using the AdnaTest EMT2/StemCell Select/Detect. Plasma of CTC-depleted blood was used for cfDNA isolation, while mRNA from EVs was isolated by exoRNeasy using the remaining blood. The mRNA purified from CTCs and EVs was analyzed by a multimarker qPCR panel. gDNA from CTCs was isolated from the mRNA-depleted CTC lysates using the AllPrep DNA/RNA Nano Kit prototype. CTC gDNA and cfDNA were analyzed with a customized QIAseq Targeted DNA Panel for Illumina with unique molecular indices. Consumables: QIAGEN, Germany. The statistical tools for evaluating the results included: Hierarchical clustering according to Ward's method with Euclidean distance, singular value decomposition, mutual information calculation, and k-means clustering. Results: Isolation of mRNA and gDNA from CTCs, mRNA from EVs, and cfDNA was successfully established in a condensed workflow. 88% of the patients showed at least one variant in CTC gDNA or one overexpression signal in the CTC mRNA fraction. The mean number of variants/signals was also higher in CTC gDNA/mRNA when compared to cfDNA/EV mRNA. The analysis of individual analytes identified a similar number of patients (50%-73%) with actionable markers, but a multi-parametric evaluation of all four analytes identified actionable markers in 96% of the patients. After hierarchical clustering of the results of each individual analyte into four clusters, combining the two patient clusters with the worst overall survival resulted in prognostic value for CTC gDNA, cfDNA, and EV mRNA. Combination of the information above analyte borders showed additive value and resulted in a prognostic factor defined here as the 'ELIMA score'. A calculation of the mutual information showed that CTC gDNA has the highest potential to describe the other three analytes. However, an Eigenvector analysis based on singular value decomposition revealed that the 10 most influential vectors contain parameters from all four analytes. This indicates that each of the analytes add valuable information not conveyed by the other analytes. K-means clustering was used to generate clusters based solely on CTC gDNA and based on all four analytes. A comparison of the clusters based on these two criteria showed that clustering based on all four analytes resulted in a division of patients according to their tumor histology type and *ERBB2* variants in CTCs; thereby, underscoring the importance of taking all four analytes into consideration. Conclusion: We established a workflow for parallel isolation of multiple liquid biopsy analytes from a minimized blood volume. Though the mutual information calculation showed that CTC gDNA has a relatively greater ability to describe the other three analytes, further statistical analysis showed that each analyte carried information of additive value. Thus, a comprehensive picture of the genomic and transcriptomic complexity obtained by a multi-parametric liquid biopsy might enable easier identification of the most suitable therapy regimen for each individual patient in the future.**

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# Incidence of intravenous (IV) hydration post anthracycline-cyclophosphamide (AC) chemotherapy in breast cancer patients

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Background: Managing delayed chemotherapy-induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) is an unmet need. AC-based HEC is often administered to breast cancer patients. The National Comprehensive Cancer Network and American Society of Clinical Oncology antiemetic guidelines recommend that if breakthrough CINV occurs, treatment should include an antiemetic agent from a different class not used in prophylaxis, as well as intravenous hydration and/or dexamethasone. The primary objective of this study is to retrospectively determine the incidence of IV hydration in post AC chemotherapy in breast cancer patients.
Methods: The charts of 270 breast cancer patients receiving AC chemotherapy at University of Alabama at Birmingham (UAB) and on initial 3-drug prophylactic antiemetic regimens were retrospectively reviewed to determine the frequency, incidence, and timing of IV hydration. The hydration incidence was determined for 4 consecutive cycles of AC chemotherapy. The need for hydration was recorded post chemotherapy (e.g., nausea, vomiting, anorexia, loss of appetite, decreased oral intake). Physician and nurse chart notes were reviewed, including documented hydration visits post AC chemotherapy to outpatient infusion areas, local hospital emergency departments, or local hospital inpatient admissions. This report focuses on the patients who were on a guideline-recommended 3-drug regimen (palonosetron [Palo] + Neurokinin-1 [NK1] + dexamethasone [Dex], or ondansetron [Ond] + NK1 + Dex). These patients were followed and monitored for 4 consecutive cycles of AC chemotherapy, and the incidence of hydrations in different cycles was evaluated.
Results: 270 patients were included in this analysis; 179 patients received Palo + NK1 + Dex (Group 1) and 91 patients received Ond + NK1 + Dex (Group 2) antiemetic regimens. Of the 179 patients in Group 1, 28 (16%) received hydration post chemotherapy, and 20 (22%) of the 91 patients in Group 2 received hydration (*P*=0.198, Chi-square test). Demographics and clinical characteristics of the 48 patients receiving hydration are presented in the Table. 28 patients in Group 1 had a total of 36 hydrations, the majority (20 [56%]) of which were in Cycle 1. 26/28 patients received rescue antiemetic treatment at the time of hydration, and 11 had a change in their prophylactic antiemetic regimen after hydration in subsequent chemotherapy cycles. Similarly, in Group 2, 20 patients had a total of 25 hydrations, with the majority (13 [52%]) in Cycle 1. 19 patients received rescue antiemetic treatment at the time of hydration, and 10 had a change in their prophylactic antiemetic regimen in subsequent chemotherapy cycles.
Conclusions: The incidence of IV hydration post chemotherapy in breast cancer patients following AC-based HEC regimens occurred predominantly in the first cycle. Unscheduled hydrations, which occur when patients require evaluation in the clinic, and/or emergency department, may be complementary events for breakthrough measurement in CINV and could serve as a surrogate of associated healthcare utilization costs. Further clinical trials may consider evaluating unscheduled hydrations rates as part of a composite complete response endpoint (no breakthrough, no rescue medication, no unscheduled hydration).

| Table: Demographic and Antiemetic Regimens for Patients Requiring Post-chemo Hydration | | |
|---|---|---|
| | Group 1<br>Palo + NK1 + Dex<br>(n=179) | Group 2<br>Ond + NK1 + Dex<br>(n=91) |
| Post-chemo hydration, n (%) | 28 (16) | 20 (22) |
| Demographics and Clinical Characteristics of Patients with Post-chemo Hydration (n=48) | | |
| Median age, years (range)s | 56 (35-73) | 58 (33-70) |
| Sex, n (%) | | |
| Female | 27 (96) | 20 (100) |
| Male | 1 (4) | 0 |
| ECOG Performance Status, n (%) | | |
| 0 | 15 (53) | 12 (60) |
| 1 | 12 (43) | 7 (35) |
| 2 | 0 | 1 (5) |
| Unknown | 1 (4) | 0 |
| IV access, n (%) | | |
| Central | 26 (93) | 20 (100) |
| Peripheral | 2 (7) | 0 |
| Antiemetic Regimens Prior to Chemotherapy and Hydration Requirements | | |
| Total number of patients requiring hydration, n (%) | 28 (16) | 20 (22) |
| Total number of hydrations, n | 36 | 25 |
| Number of hydrations in Cycle 1, n (%) | 20 (56) | 13 (52) |
| Visits, n (%) | | |
| Office | 16 (57) | 12 (60) |
| Emergency department | 12 (43) | 8 (40) |
| Rescue antiemetic(s) at time of hydration, n (%) | 26 (93) | 19 (95) |
| Prophylactic antiemetic regimen switched, n (%) | 11 (39) | 10 (50) |
| Dex = dexamethasone; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; NK1 = Neurokinin-1; Ond = ondansetron; Palo = palonosetron. | | |

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# Two decades of experience with sentinel node staging of axilla - is false negative no longer a worry?

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**Aim: To review current literature and standard practices in various techniques of sentinel node biopsy for staging the axilla for treating early breast cancer. The purpose is to provide evidence based recommendation as guidance platform for optimal true sentinel node retrieval irrespective of surgeon expertise. Background: Axillary conservation is the way forward after game changing trials like ACOSOG Z0011, surrogate trials like IBCSG,AMAROS, ALMANAC, ongoing POSNOC, and newbie ATNEC have progressively or plan to decrease the need to unnecessarily fiddle with the axilla thereby increasing the chances of arm related and other morbidities. Axillary sentinel node biopsy entails retrieval of first draining lymph node in the breast-axilla pathway to plan treatment in breast cancer by appropriate staging of axilla. Current standard is the utilisation of double agent technique with radioactive isotope and blue dye injection to decrease false negative rates for true sentinel node retrieval. Novel techniques like magnetic and infrared tracing are still being investigated for validation. Method: PMC, Medline, EMBASE, PubMed and Cochrane library searched for clinical trials, randomised trials, systematic reviews and meta-analysis on techniques of axillary sentinel node biopsy in early breast cancer. This covered the last 25 years literature on the topic. Results: The search yielded 197 publications which were subjected to a meticulous review and narrowed to a select pertinent body of evidence to extrapolate suggested guidance rationally, the bibliography of which is provided at the end. Conclusion: Single agent preferably radioisotope for lymphatic mapping is recommended in palpable and good biology tumours. Use of single agent blue dye can be standardised in axillary tail tumours. It is also recommended as being effective when isotope mapping is logistically not feasible or during pandemics like COVID 19 where looming infrastructure challenges are prevalent. Dual agent technique should be considered in previously treated breast and axilla, neoadjuvant chemotherapy cohort, bad tumour biology, high BMI and macromastia groups for true nodal retrieval. Optimal number of nodes taken out should not be more than three (n=3). Lower axillary sampling of not more than 3 nodes is recommended for troubleshooting with any localising agent technique. Triple site injection at peri-tumoural, subcutaneous and sub areolar regions and larger volume of blue dye agent injection of up to 8mls increases the localisation success in the dual technique group for lymphatic mapping. Magnetic tracing can be used as an adjunct to either single agent radioactive isotope or blue dye (RI/BD) technique when there is failure to localise the sentinel node.**

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# Survivin immunoexpression: An independent prognostic marker of recurrence in early-stage breast cancer

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Survivin is a small protein member of the inhibitor of apoptosis protein family. Its expression occurs in G2/M phase of cell cycle, acting inhibiting apoptosis blocking caspases cascade directly or indirectly, and also controlling cell division. Survivin was found to be overexpressed in breast cancer, and its expression have been associated mostly with poor outcome. The aim of this case-control study was to evaluate the prognostic value of Survivin immunoexpression in early stage (pT1pN0 or pT2pN0) breast cancer. The study was conducted collecting data from 170 women with invasive breast carcinoma. The case group (n=57) and control group (n=113) consisted of patients with and without tumor recurrence, respectively. Immunohistochemical Tissue Microarray analyses were conducted to detect Survivin expression. In addition, molecular classification was done based on immunohistochemistry, and classic clinical and histological breast cancer variables were collected. The findings were submitted to the chi-square test and Fisher's exact test, followed by multivariate analysis with multinomial logistic regression. The level of statistical significance was set at 5% ($p<0.05$). Median follow-up time was 6 years, ranging from 4 to 13 years. In the univariate analysis, patients with recurrence presented a higher histologic grade (p=0.005), percentage of tumor cells expressing survivin ($p=0.006$) and stronger immunostaining for this protein ($p=0.021$). In the multivariate analysis, stronger immunostaining for survivin (OR 1.850; $p=0.023$) and greater percentage of survivin expression (OR 2.290; $p=0.016$) persisted independently associated which higher rates of recurrence. Higher immunoexpression of survivin was independently associated with recurrence in early stage invasive breast tumors.

Table 1 - Clinical-pathological characterization of the 170 cases of early stage breast cancer patients with and without recurrence.

| | | Recurrence | | |
|---|---|---|---|---|
| | Total | No | Yes | *p* |
| Age | | | | |
| ≤ 55 years | 86 | 58 | 28 | 0,786 |
| | 50,6% | 51,3% | 49,1% | |
| > 55 years | 84 | 55 | 29 | |
| | 49,4% | 48,7% | 50,9% | |
| Histological subtype | | | | |
| Ductal | 158 | 104 | 54 | 0,244 |
| | 92,9% | 92,0% | 94,7% | |
| Lobular | 5 | 5 | 0 | |
| | 2,9% | 4,4% | ,0% | |
| Others | 7 | 4 | 3 | |
| | 4,1% | 3,5% | 5,3% | |
| Stages | | | | |
| pT1a | 7 | 5 | 2 | 0,902 |
| | 4,1% | 4,4% | 3,5% | |
| pT1b | 21 | 13 | 8 | |
| | 12,4% | 11,5% | 14,0% | |
| pT1c | 65 | 45 | 20 | |
| | 38,2% | 39,8% | 35,1% | |
| pT2 | 77 | 50 | 27 | |
| | 45,3% | 44,2% | 47,4% | |
| Histological grade | | | | |
| I | 33 | 28 | 5 | 0,005 |
| | 19,4% | 24,8% | 8,8% | |
| II | 75 | 49 | 26 | |
| | 44,1% | 43,4% | 45,6% | |
| III | 41 | 19 | 22 | |
| | 24,1% | 16,8% | 38,6% | |
| Ignored | 21 | 17 | 4 | |
| | 12,4% | 15,1% | 7,0% | |
| Breast surgery | | | | |
| Mastectomy | 85 | 57 | 28 | 1,000 |
| | 50,0% | 50,4% | 49,1% | |
| Conservative | 85 | 56 | 29 | |
| | 50,0% | 49,6% | 50,9% | |
| Sentinel lymph node biopsy | | | | |
| No | 32 | 20 | 12 | 0,353 |
| | 18,82% | 17,7% | 18,2% | |
| Yes | 137 | 93 | 44 | |
| | 81,5% | 82,3% | 80,0% | |
| Ignored | 1 | 0 | 1 | |
| | 0,6% | 0,0% | 1,8% | |
| Chemotherapy | | | | |

| | | | | |
|---|---|---|---|---|
| No | 51 | 35 | 16 | 0,697 |
| | 30,0% | 31,0% | 28,1% | |
| Yes | 119 | 78 | 41 | |
| | 70,0% | 69,0% | 71,9% | |
| Trastuzumab | | | | |
| No | 156 | 105 | 51 | 0,761 |
| | 92,3% | 92,9% | 91,1% | |
| Yes | 13 | 8 | 5 | |
| | 7,7% | 7,1% | 8,9% | |
| Hormone therapy | | | | |
| No | 29 | 18 | 11 | 0,581 |
| | 17,1% | 15,9% | 19,3% | |
| Yes | 141 | 95 | 46 | |
| | 82,9% | 84,1% | 80,7% | |

**Table 2 - Patterns of Survivin expression in tumors of patients with breast cancer with and without recurrence.**

| | | Recurrence | | |
|---|---|---|---|---|
| | Total** | No | Yes | *p* |
| Subcellular localization | | | | |
| Absent | 4 | 2 | 2 | 0,942 |
| | 2,7% | 2,1% | 3,8% | |
| Cytoplasmic | 89 | 57 | 32 | |
| | 60,1% | 60,0% | 60,4% | |
| Nuclear | 23 | 15 | 8 | |
| | 15,5% | 15,8% | 15,1% | |
| Cytoplasmic and Nuclear | 32 | 21 | 11 | |
| | 21,6% | 22,1% | 20,8% | |
| Intensity | | | | |
| Absent | 4 | 2 | 2 | *0,021* |
| | 2,7% | 2,1% | 3,8% | |
| Weak | 73 | 53* | 20 | |
| | 49,3% | 55,8% | 37,7% | |
| Moderate | 62 | 38 | 24 | |
| | 41,9% | 40,0% | 45,3% | |
| Strong | 9 | 2 | 7* | |
| | 6,1% | 2,1% | 13,2% | |
| Percentage of expression | | | | |
| ≤ 50% | 109 | 77 | 32 | *0,006* |
| | 73,6% | 81,1% | 60,4% | |
| > 50% | 39 | 18 | 21 | |
| | 26,4% | 18,9% | 39,6% | |

***p<0,05** 22 patients (12,9%) of sample loss in tissue microarray.**

**Table 3 - Cox survival regression model of patients diagnosed and treated for invasive breast carcinoma.**

| | p-Valor | Adjusted OR |
|---|---|---|
| Model 1 | | |
| Histological grade | **0,007* | 2,108 |
| Survivin - intensity | **0,023* | 1,850 |
| Survivin - percentage of expression | 0,100 | 1,876 |
| Breast cancer subtype classified by immunohistochemistry | 0,263 | 1,126 |
| Model 2 | | |
| Survivin - percentage of expression | **0,016* | 2,290 |
| Breast cancer subtype classified by immunohistochemistry | 0,093 | 1,170 |
| Model 3 | | |
| Breast cancer subtype classified by immunohistochemistry | 0,241 | 1,107 |

**Multinomial logistic regression model. In the first model, variables with p <0.200 were used in order to highlight the first order factors independently associated with disease-free survival. In the second model, variables with a significant association in model 1 were excluded in order to highlight second order factors independently associated with disease-free survival. In the third model, there were no factors independently associated with disease-free survival.**

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# Biopsychosocial approach in the rehabilitation of patients with early breast cancer

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Relevance: early breast cancer is detected in more than 60% of cases. Maintaining the quality of life of patients with early breast cancer at the highest possible level is a priority, along with the treatment of patients. Under a complex antitumor treatment as well as after its completion, more than 60% of patients with early breast cancer report the occurrence of functional disorders.An important aspect is to improve the effectiveness of the rehabilitation process of patients with early breast cancer taking into account scientifically-based and proven recommendations.Objective: to evaluate the event-free survival rate (EFS) of patients with EBC undergoing rehabilitation within a biopsychosocial approach.Materials and methods: 228 patients with breast cancer who received complex treatment from 2015 to 2019 were included in the study. The prospective part of the study included 114 patients with early breast cancer undergoing rehabilitation measures within the biopsychosocial approach. The control group which was selected retrospectively, using the method of "pairwise selection", included 114 patients with early breast cancer comparable in age, stage of the disease, volume of surgical treatment and menopausal status, undergoing physical and psychological rehabilitation prescribed by a doctor. Patients in both groups were stratified depending on preoperative chemotherapy. EFS was calculated over a 2-year follow-up period. Events that were censored were a disease progression, the appearance of metastases, the occurrence of another cancer, a new concomitant disease, an exacerbation of the concomitant pathology and death.Results: Rehabilitation measures within the biopsychosocial model improve the indicators of EFS in the group of patients with EBC: EFS was 18.3 months against 14.5 months in the control group (HR=0.91, 95% CI [0.83; 0.99]; p=0.0034). In a multi-factor analysis the key factors affecting EFS were neoadjuvant chemotherapy (HR=0.79, 95% CI [0.69; 0.94]; p=0.0025), age (HR=0.87, 95% CI [0.71;1.09]; p=0.0027) and menopausal status (HR=0.85, 95% CI [0.84; 0.95]; p=0.0022) (table 1).

| Characteristic | | Number of patients | HR (95% CI) |
|---|---|---|---|
| Preoperative chemotherapy | yes | 152 | 0,84 (0,77; 1,1) |
| | no | 76 | 0,79 (0,69; 0,94) |
| Menopause | yes | 130 | 0,84 (0,77; 1,04) |
| | no | 98 | 0,85 (0,84; 0,95) |
| Age group | 25-44 | 61 | 0,87 (0,71; 1,09) |
| | 45-60 | 103 | 0,89 (0,74; 1,1) |
| | 61-75 | 64 | 1,01 (0,82; 1,24) |
| Event | Disease progression | 28 | 1,11 (0,86; 1,26) |
| | Exacerbation of the concomitant pathology | 16 | 0,83 (0,74; 0,96) |

Table 1- Multi-factor analysis of event-free survival of patients with early breast cancer in the group of biopsychosocial model of rehabilitation versus control group.

Conclusions: Rehabilitation measures within the biopsychosocial model improve the indicators of EFS in the group of patients with early breast cancer, the key factors affecting EFS were neoadjuvant chemotherapy, age and menopausal status.

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# Racial disparities in *CYP3A* variants in the metabolism of ribociclib in breast cancer patients

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**Background:Ribociclib is an inhibitor of the cyclin dependent kinases 4 and 6 (CDK 4/6) and is approved in combination with endocrine therapy for patients with advanced hormone receptor (HR) positive metastatic breast cancer (mBC). CYP3A inhibitors increase ribociclib area under the curve (AUC) by 3.2-fold; this is of clinical concern given possible associations between exposure and toxicity (e.g., QTc prolongation and neutropenia). Although there is an FDA recommendation to modify therapy for patients prescribed CYP3A inhibitors, it is unknown if modifications are needed in patients who intrinsically lack enzyme activity (e.g., genetic CYP3A5 poor metabolizers). CYP3A function is largely derived from CYP3A4 and CYP3A5 isozymes in adults. It is difficult to differentiate relative contributions of CYP3A4 and CYP3A5 on CYP3A function due to sequence homology (~ 84%) and overlapping substrate specificity. Genetic variations in *CYP3A5* can translate into poor, intermediate, or normal CYP3A5 metabolism of different substrates and some pharmaceutics metabolized by CYP3A have dosing recommendations based on genotype. We hypothesize that patients harboring genetic variants causing CYP3A5 poor metabolism experience increased exposure to ribociclib and likely more toxicities. Race is likely to be significant factor when exploring ribociclib pharmacokinetics (PK) and the role of CYP3A. There are known race-based differences in CYP3A4 and CYP3A5, with alleles associated with CYP3A5 loss prevalent in European Americans (EA) and not in African Americans (AA). Ribociclib PK have not been adequately studied in AA with 3% of participants in the pivotal trials AA. We aim to determine the pharmacokinetic and pharmacogenomic association between ribociclib exposure and *CYP3A* variants in AA and EA patients. Our findings should allow clinicians to tailor treatments to maintain therapeutic doses while limiting toxicities. Methods:This prospective, multicenter, open-label pilot study will assess ribociclib (600 mg PO daily) PK and pharmacogenomics in female patients with HR+/HER2- mBC. This design will be two independent, race-based cohorts: 18 AA patients and 18 EA patients. Eligibility include: female, >18, HR+/HER2- mBC and candidates for treatment with a CDK 4/6 inhibitor and endocrine therapy. Patients are ineligible if currently prescribed a medication that inhibits or induces the CYP3A isozymes, have baseline EKG abnormalities, or are otherwise considered to be ineligible for ribociclib. Participants will provide serial blood samples during the first cycle. Plasma samples will be analyzed via mass spectrometry to characterize the PK (e.g., $AUC_{0-24}$, $C_{max}$).**

**Pharmacogenetic testing will be performed using the PharmacoScan™ microarray, which tests 4627 markers in 1191 genes, including 73 variants in *CYP3A4* and *CYP3A5*. The primary endpoint will compare ribociclib AUC between CYP3A5 poor metabolizers vs. intermediate or normal CYP3A5 metabolizers within separate, race-based cohorts. Secondary endpoints include characterization of PK properties of ribociclib in the AA and EA populations. We also will seek to identify if *CYP3A5, CYP3A4,* or other variants are associated to different toxicity profiles. In addition, we will perform a hypothesis-generating PGx correlative analysis for potential biomarkers of ribociclib PK or toxicity. The primary outcome is powered to detect a minimum clinically meaningful change, a 2-fold change in AUC, which is less than the 3.2-fold change seen in the mentioned CYP3A drug interaction pharmacokinetic study. Based on *CYP3A5* allelic frequencies, a sample size of 36 will provide 80% power to independently test the primary outcome in the two race-based cohorts.**

**Funding: Breast Cancer Research Foundation.** **Contact: Sandra Swain MD, sandra.swain@georgetown.edu**

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# The Neat-HER Virtual Registry: Results on HER2+ breast cancer patients receiving neratinib as extended adjuvant therapy

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Background: While data from traditional registries are typically limited to patients treated at study sites, virtual registries can enroll a broader real-world population. Neat-HER is a U.S.-based virtual registry pilot through PicnicHealth that is enrolling patients with HER2+ breast cancer receiving neratinib as extended adjuvant therapy.
Methods: Neat-HER evaluates the feasibility of enrolling patients and answering research questions using a novel electronic platform. Eligibility includes receipt of neratinib in the extended adjuvant setting, signed informed consent for medical record retrieval/data abstraction and age >18 years. Patients who do not complete enrollment procedures, are participating in a clinical trial or have metastatic disease are excluded. Patients are recruited through multiple mechanisms including private social media groups, treating clinicians and patients enrolled in the Puma Texting Program. Patient health records for breast cancer-related treatment are collected from time of diagnosis to 1-year post-enrollment in the registry. Research questions focus on patient and tumor characteristics, receipt of therapy (e.g. radiotherapy, adjuvant therapy), neratinib duration, and diarrhea prophylaxis.
Results: 22 patients with HER2+ early-stage breast cancer who received neratinib as extended adjuvant therapy have been enrolled in this registry study since December 2018. Median age was 51 years, with 77% of patients self-identifying as white. 73% of patients had hormone receptor-positive (ER/PR) disease and 73% of patients had node-positive disease. Prior HER2-targeted adjuvant therapy regimens were as follows: trastuzumab with paclitaxel (9%); trastuzumab/pertuzumab in combination (91%; all but 1 of whom also received docetaxel). 16 patients (73%) completed 12 months of neratinib treatment; 3 patients (14%) discontinued treatment early; 3 patients (14%) were still ongoing at the time of data cutoff. 6 patients (27%) had dose holds and 3 patients (14%) had a dose reduction during the course of neratinib treatment. 21 patients (95%) had diarrhea prophylaxis discussed prior to the start of neratinib treatment.
Conclusions: Neat-HER provides useful information on patient/tumor characteristics and treatment patterns in a real-world cohort receiving extended adjuvant neratinib. Preliminary results show that this pilot virtual registry is a feasible and efficient modality to collect important data on descriptive characteristics and treatment patterns for a patient population derived from real-world practice settings. Validation of this method is needed and could be used to evaluate important trends such as the frequency of neoadjuvant therapy and associated outcomes in a larger population.

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# A survey of radiation oncologists on contemporary axillary management in post-mastectomy breast cancer patients

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**Background: Local-regional treatment (LRT) of the axilla in breast cancer has evolved over the past several decades. The AMAROS trial demonstrated that dedicated axillary radiation therapy (aRT) can provide local control and allow for less invasive axillary surgery in select patients. Since the AMAROS data was published in 2014, there are no large-scale studies specifically analyzing how this data has impacted clinical practice. Methods: An anonymous case-based survey was sent to 4,254 Radiation Oncologists (RO) who identified as practicing physicians in the US as of May 2020. Those who identified that they do not treat breast cancer patients were excluded. The survey was conducted through the Qualtrics™ platform. Descriptive analyses were performed by the survey software and analytical statistics were performed using R (v4.0.2) utilizing ANOVA, t-tests, and chi-squared analysis. Results: A total of 293 RO completed the survey. Mean years in practice was 18.4 and most were in private practice (41.4%), followed by academic practice (28.2%) and hospital-employed (25.7%). Most (65%) reported that the type of post-mastectomy breast reconstruction does not influence their axillary treatment algorithm. Cases and responses are as follows: Case 1: A 57-year-old female with a cT1N0, ER-positive, Her2-negative breast cancer undergoes mastectomy and sentinel node biopsy (SLNB). Pathology reveals a T1 tumor with 2 of 3 sentinel lymph nodes with 2mm tumor deposits. The majority (75.4%) of RO reported they would proceed with aRT, while 8.7% preferred ALND alone, 7.1% elected for both aRT and ALND, 3.3% chose no further axillary therapy, and 4.5% needed more case information to make a decision. Treatment decision was dictated by clinical trial evidence (62.2%) and national guidelines (26.4%), but 11.2% reported their decision was largely impacted by clinical experience. The ACOSOG Z11 and AMAROS trials had the largest impact on clinical decision-making. For RO who chose to treat with aRT, AMAROS and MA-20 had the highest impact in determining radiation fields, and 88.7% would give RT to both the chest wall and axilla. Choice of axillary treatment did not differ by years in practice (p=0.54), percentage of breast patients treated (p=0.22), or by clinical practice setting (p=0.44). Case 2: A 69-year-old female with a cT1N0 ER/PR-negative, Her2-positive breast cancer undergoes mastectomy and SLNB. Pathology demonstrates a T1 tumor and 4 of 4 sentinel nodes with disease but without extra-nodal extension. Treatment results were mixed: 45.5% recommended both ALND and aRT, 38.5% chose aRT alone, and 14.3% recommend ALND alone. Most (85%) cited that their decision was based upon clinical trial evidence and/or national guidelines. MA-20 and AMAROS were cited as having the highest impact on the decision to perform aRT and determining RT fields. 96.2% of those recommending RT would treat both the chest wall and axilla. On average, RO who were in practice for a shorter period of time preferred both ALND and aRT, while those in practice for more years preferred that patients undergo either ALND or aRT alone (mean 12.9 vs 20.3 years, p<0.001). Treatment decision to undergo dual or single LRT was not associated with percentage of breast patients treated (p=0.41), or by practice setting (p=0.92). Conclusion: There remains significant heterogeneity in axillary treatment patterns for N+ breast cancer patients amongst RO in the US. Those patients with significant nodal burden (≥4+ nodes) were more likely to receive additional axillary therapy, and with combination LRT when treated by RO in practice for a shorter number of years. Physician education on clinical trial inclusion criteria and development of clearer axillary treatment guidelines can aid in appropriate identification of axillary de-escalation opportunities.**

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# Solti-1801. Analysis of the efficacy of CDK4/6 inhibitors in combination with hormonal treatment in luminal breast cancer in relation to the intrinsic subtype and markers of immunity (CDK-PREDICT)

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**Introduction. The incorporation of cyclin-dependent kinase inhibitors 4 and 6 (CDK4/6 inhibitors) with endocrine therapy in patients with advanced hormone receptor-positive (HR+) breast cancer and without overexpression of the HER2 (HER2-) oncogene has demonstrated its efficacy improving progression-free survival (PFS), overall response rate (ORR) and, more recently, overall survival (OS). However, patients eventually progress due to resistance to treatment. To date, no clinical or molecular markers defining the HR +/HER2- patient population that obtains the greatest benefit from these drugs have been found, apart from estrogen receptor positivity. However, there are data from multiple retrospective analysis suggesting that within HR+/ HER2- disease, the non-luminal intrinsic subtypes (20-30% of these patients) have a worse prognosis and may not benefit from CDK4/6 inhibitors. Furthermore, the prognostic impact of tumor infiltrating lymphocytes (TILs) and gene expression related to the immune response in the context of HR + / HER2- advanced breast cancer have not been deeply investigated.**

**Design. CDK-PREDICT is an observational, non-interventional, multicenter study that will include 114 patients with advanced breast cancer who have received, are receiving or are going to receive endocrine therapy plus a CDK4/6 inhibitor for, at least, 8 weeks as first-line treatment. The primary objective is to correlate the intrinsic subtypes (defined by PAM50) with the efficacy (measured as PFS) of CDK4/6 inhibitors + hormone therapy. As secondary objectives, the correlation of the intrinsic subtypes with ORR and with the histopathological characteristics of the tumor will be analyzed. In addition, the expression of immune response and cell cycle genes, as well as the presence of TILs, will be correlated with the intrinsic subtypes and with PFS and ORR. Overall, we aim to develop a predictive score combining clinical, genomic and immune expression data integrating tumor biology and microenvironment. For inclusion in the study, a metastatic sample taken within 90 days prior to CDK4/6 inhibitors treatment will be required. Once this sample has been collected, registered and assessed for quality, patients will be followed up every 6 months until disease progression, death or withdrawal from the study.**

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# Real world data on the adoption of trastuzumab biosimilars in the treatment of HER2-positive breast cancer

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**Background: Biosimilars for trastuzumab were introduced into the US market for the treatment of HER2-positive breast cancer in 2019, with the goal of providing the clinical benefit of the brand product at a lower price (increased value). Adoption of trastuzumab biosimilars may be affected by multiple factors, including physician confidence in biosimilar efficacy and efficacy across stages, practice reimbursement, payer medical policy/redirection. To look at the adoption of trastuzumab biosimilars in the US medical oncology community, we queried a database of submitted treatment plans for patients with breast cancer. Methods: Data from a pre-authorization platform used by multiple commercial insurance companies in the US (NantHealth Eviti) was analyzed. Cases were identified from approved treatment plans for patients with breast cancer by inclusion of brand trastuzumab or trastuzumab + hyaluronidase-oysk, or trastuzumab biosimilars. Results: As of July 1, 2020, 10,557 treatment plans trastuzumab-based therapy were submitted, 1740 (16.5%) of which used a trastuzumab biosimilar. Adoption of trastuzumab biosimilars increased over time, from 1.6% (27/1676) treatment plans in Q3-2109 to 43.3% (753/1736) in Q2-2020. No clear differences were observed between use in stage 0-IIIc disease (17.4%) vs stage IV/recurrent disease (14.5%). Using the July 1, 2020 CMS pricing for these drugs at normalized dose of 440 mg for trastuzumab/trastuzumab biosimilars or 600 mg of trastuzumab + hyaluronidase, the average cost/cycle/patient for brand therapy and biosimilar therapy is $4502 and $3618, respectfully, representing a savings of $1,374,620/cycle across the biosimilar-treated population. Additional analyses to be presented will include Q3 2020 utilization and patterns of utilization across payers with/without medical policy favoring biosimilars. Conclusions: Adoption of trastuzumab biosimilars in this commercial population has been rapid since their introduction. Use of these drugs provides a substantial opportunity for societal savings in the treatment of HER2-positive breast cancer.**

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# Tumor characteristics of young age breast cancer patients using a nationally representative sample of the Korea central cancer registry (KCCR)

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**BACKGROUND The incidence of breast cancer is increasing in Korea. Breast cancer in young Korean women (< 40 years) is rare, but the rate of young age breast cancer incidence in Korea is higher than that in western countries. This study was aimed to evaluate the tumor characteristics of young age breast cancer patients (< 40 years) among Korean women. METHODS Among the Korean women, who were diagnosed with breast cancer from 2010 to 2015, we identified 10,897 cases of nationally representative sample data. The data was made through 10% systematic sampling of the Korea Central Cancer Registry (KCCR). We conducted a chart review survey to collect the data about tumor size, regional lymph node status, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status according to the Collaborative Stage version 2 (CSv2) Data Collection System. We described the number and percentage of the breast cancer stage distribution, tumor grade and intrinsic subtypes by the patient age groups (< 40 years, 40-49 years, 50-59 years, and ≥ 60 years), and evaluated the tumor characteristics in young age breast cancer patients (< 40 years). RESULTS The number of young age breast cancer patients was 1,245 (11.4% of < 40 years vs 35.4% of 40~49 years vs 30.8% of 50~59 years vs 22.4% of ≥ 60 years; P<.001). Young age breast cancer patients were more likely to be diagnosed with larger tumors (T2: 41.6% vs 36.4% vs 36.5% vs 38.4%; T3: 10.1% vs 7.3% vs 6.5% vs 6.2 %; P<.0001), more positive lymph node status (41.2% vs 32.7% vs 35.7% vs 32.5%; P<.0001), and higher tumor grade (grade 3, 26.8% vs 19.4% vs 23.5% vs 22.1%; P<.0001). According to intrinsic subtypes using ER, PR, and HER2, triple negative subtype was found more in young age breast cancer (18.2% vs 11.0% vs 12.2% vs 13.5%; P<.0001). CONCLUSION This study shows that young age breast cancer patients (< 40 years) in Korea have more aggressive tumor including advanced cancer stage at diagnosis, higher tumor grade, and triple negative intrinsic subtype. Therefore, we need to identify high risk group for young age breast cancer (< 40 years) and support their active surveillance. These findings using national cohort provide important information for establishing a national strategy of cancer care to manage young age breast cancer patients.**

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# Prepectoral implant-based breast reconstruction with TiLOOP-bra pocket - a single-center retrospective study

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Aim: To evaluate the perioperative outcome and cosmetic outcome of prepectoral implant-based breast reconstruction using the TiLOOP® Bra Pocket.Background: Besides acellular dermal matrix (ADM), synthetic meshes have revealed good surgical and aesthetic outcomes. We present our data using TiLOOP® Bra Pocket, a ready-to-use mesh pocket which is made out of nonresorbable, titanized, lightweight polypropylene with a monofilament structure and designed to ensure optimal fixation of the breast implant following mastectomy. The idea behind the mesh pocket is to fix the implant to the muscle and provide coverage and stabilization for the implant by serving as an ´internal bra´, which will
create an inferior and lateral sling to support the position and stability of the implant and prevent it from dislocating or twisting.
Materials and Methods: A single-center retrospective study was performed to assess short-term complication rates and cosmetic outcomes in patients with immediate or delayed implant-based breast reconstruction using the TiLOOP® Bra Pocket after nipple- or skin-sparing mastectomy. The primary endpoint was complication rates, which were divided into major and minor complications during the first 6 months. Minor complications were defined as those treated conservatively, major complications were those requiring surgical therapy. The secondary endpoint was short-term cosmetic outcome after 6 to 12 months, which was judged by two professionals using the Harvard score (1 = poor, 2 = fair, 3 = good, 4 = excellent).
Results: A total of 63 breasts (43 patients) were reconstructed by implant using the TiLOOP® Bra Pocket between 2018 and 2020, of which 57 were immediate reconstructions. Mean follow-up was 12 months. The overall complication rate was 30,2 % (n = 19/63). Major complications occured in 7 breasts (n = 7/63; 11,1 %) and minor complications occured in 12 breasts (12/63; 19,0 %). The cosmetic outcome was good (Harvard score: mean 3, range 1-4; SD 0,75). Seventeen cosmetic complications were observed (17/63; 27,0 %) and 6 cosmetic revision surgeries were performed (6/63; 9,5 %).
Conclusion: Immediate prepectoral implant-based breast reconstruction with the TiLOOP® Bra Pocket seems to be a feasible method with moderate complication rates and good cosmetic outcomes. Careful patient selection and preparation techniques considering flap viability are vital in order to achieve acceptable complication rates and satisfying cosmetic results. Long-term follow-up is needed. The next follow-up will be performed after 24 months.

**Perioperative Outcome**

| | |
|---|---|
| Complications | 22 |
| Seroma with punction | 7/63 (11,1%) |
| Seroma without punction | 1/63 (1,6 %) |
| Hemorrhage | 2/63 (3,2 %) |
| Nipple necrosis | 2/63 (3,2 %) |
| Implant Infection | 3/63 (4,8 %) |
| Skin Infection | 3/63 (4,8 %) |
| Wound healing deficiency | 2/63 (3,2 %) |
| Implant loss | 2/63 (3,2 %) |
| Unplanned resurgery < 3 mo | 8 (12,7 %) |

**Cosmetic Complication (N=17)**

| | |
|---|---|
| Rippling | 2 (3,2 %) |
| Asymmetry | 4 (6,3 %) |
| Capsule contracture | 3 (4,8 %) |
| Fat defects | 3 (4,8 %) |
| Rotation | 2 (3,2 %) |
| Cranialisation | 3 (4,8 %) |

**Cosmetic Outcome (Harvard score; 1 = poor, 2 = fair, 3 = good, 4 = excellent)**

| | |
|---|---|
| Observer 1 | 3,0 (1 - 4), SD 0,8 |
| Observer 2 | 3,4 (1-4), SD 0,7 |

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# Clinical implications of epithelial protein lost in neoplasm (EPLIN) associated proteins in breast cancer

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**Background. EPLIN, Epithelial Protein Lost In Neoplasm, also known as LIMA1 (LIM Domain And Actin Binding 1) is a cytoskeletal protein involved in the regulation of cellular actin dynamics (1). The protein has been shown to be lost or reduced in a wide range of cancer cells and reduced expression has been noted in a number of human solid cancers, including breast cancer. The reduction of EPLIN has been shown to be linked to poor prognosis of patients with breast cancer (2). Although EPLIN is known to regulate the cytoskeleton and subsequently certain cellular functions, the intercellular coordination during regulation is not fully understood with a number of potential partners implicated, including the CTNN family, CDH family and paxillin. In the present study, we have evaluated the connections between EPLIN and a number of protein partners together with their larger families in the context of clinical breast cancer.**

**Methods. The gene transcripts of EPLIN and its potential partners were quantitatively determined in a Cardiff cohort of human breast cancer, which forms part of a database and is supported by clinical, pathological information. The molecules were cross correlated and explored for the individual and most importantly collective power in their link with patient's clinical outcomes.**

**Results. EPLIN, previously shown to be expressed at a reduced level in tumour compared to normal mammary tissues, exhibited an intimate correlation with the larger CTNN family and the cadherin family, namely with cadherin-1 ($p<0.0001$) and alpha- and beta-catenins ($p<0.0001$); there was no correlation with gamma-catenin ($p>0.05$). Of the protein phosphatase protein family, EPLIN was significantly correlated with two of the PTPs that have cell-cell adhesive functions, namely PTPRM and PTPRK. One of the most interesting findings was the relationship between EPLIN and tight junction (TJ) protein family members in that 27 of 35 TJ molecules, including the claudin/TAMP/JAM family members were found to be highly correlated with EPLIN. It is noteworthy that EPLIN was inversely correlated with SIPA1 (Signal-induced proliferation-associated protein 1) ($r= -0.23$, $p=0.03$), one of the few known intracellular TJ regulators. Despite the importance of caveolin in EPLIN's function, no significant connection was found between the two. From the comprehensive network of EPLIN partner families, we have identified a total of 12 key partner proteins, of which the expression pattern of the protein network was significantly correlated with overall survival (141 (136-146) months for favourable expression pattern vs 111 (92-130) months with unfavourable pattern, $p<0.001$, Log ranked). Similarly, the network expression pattern also appeared as a significant predictor of disease-free survival ($p<0.0001$). Multivariate analyses have indicated that the EPLIN network protein pattern is an independent prognostic factor for overall survival and disease-free survival.**

**Discussion. EPLIN is a cytoskeletal associated protein that is reduced in solid tumours. EPLIN is well connected to the cell-cell adhesion protein complex and tight junction protein complex as well as their regulators, which can be seen from the clinical cohort. Key members of the EPLIN interaction network have a strong power to predict the clinical outcome of patients with breast cancer. Collectively, this study indicates that EPLIN partner proteins are important factors in the development of breast cancer as well as prognostic indicators.**

**Reference1. Maul RS and Chang DD. EPLIN, epithelial protein lost in neoplasm. Oncogene. 1999, 18:7838.**

**Reference2. Jiang WG, Martin TA, Lewis-Russell JM et al, Eplin-alpha expression in human breast cancer, the impact on cellular migration and clinical outcome. Mol Cancer, 2008, 7, 71**

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# Cause of death discordance between death certificates and medical files: Impact on cancer survival assessment in a Belgian case study

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Introduction Accurate information on cause of death is essential for correct breast cancer-specific mortality assessment. However, registration and coding of cause of death is prone to error since determining the exact underlying condition related to the death is challenging. In this study, an expert review of medical files was done to determine the principal cause of death for breast cancer patients of a Belgian tertiary hospital. The retrieved cause of death was compared to death certificate information to assess concordance between both sources. Secondly, the impact of discordant reporting on cause-specific survival (CSS) and other net survival approaches were examined. Methods Breast cancer patients diagnosed and treated at University Hospitals Leuven (UHL) between 2009 and 2014 with follow-up until December 31st, 2016, were included in the study. Information on cause of death was obtained from death certificates (following ICD-10 rules) and medical files. The latter were reviewed by a board of experts at UHL. Agreement was calculated using Cohen's kappa coefficient, and reasons for discordant reporting were assessed. CSS was calculated based on cause of death information from both sources using the Kaplan-Meier method. These survival estimates were compared to the relative survival probability (RS) using the Ederer II and Pohar Perme method. Results A total of 2,862 patients were included, of whom 354 died after a median follow-up of 54.6 months. We found overall substantial agreement (kappa-value of 0.69 (95% C.I.: 0.62-0.77)) between cause of death reported by death certificates and medical files (Table 1). In 84.8% of cases, there was concordance between both methods. When comparing to medical files, misattribution of breast cancer-specific death in death certificates (4.5% of cases) was linked to the presence of comorbidities (43.7%), metastases (37.5%), or unspecified causes (18.8%). Five-year CSS based on medical files (93.1% (95% C.I.: 91.9-94.1)) was only slightly higher compared to CSS based on death certificates (92.3% (95% C.I.: 91.2-93.4)). RS measures using Ederer II and Pohar Perme were comparable to CSS measures. Conclusions Overall, substantial agreement of cause of death was seen between death certificates and medical files. Attribution of cause death to comorbidities was the most common reason for discordant reporting of breast cancer-specific death. Five-year breast cancer-specific survival was slightly higher based on cause of death information from medical files, compared to death certificates. Periodic reviews and implementation of ICD-10 guidelines for classification of cause of death could improve accuracy in cause of death annotation.

Table 1: Discordance for the principal cause of death between medical files and death certificates

| | | medical files | | |
|---|---|---|---|---|
| | | other causes | breast cancer | |
| death certificates | other causes | 136 (38.4%) | 16 (4.5%) | 152 (42.9%) |
| | breast cancer | 38 (10.7%) | 164 (46.3%) | 202 (57.1%) |
| | | 174 (49.2%) | 180 (50.9%) | 354 (100%) |

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# PALVEN: A phase 1b study of palbociclib, letrozole and venetoclax in estrogen receptor, BCL2-positive metastatic breast cancer

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**Background: CDK4/6 inhibitors are integral to the treatment of Estrogen Receptor (ER) positive metastatic breast cancer (MBC). Although they are potent inhibitors of proliferation, tumor cell death (by apoptosis) may be curtailed. Venetoclax, an inhibitor of the pro-survival protein BCL2, has shown promise in an early phase clinical trial in ER+ MBC[1]. Moreover, preclinical studies suggest that venetoclax could improve tumor response to endocrine therapy and a CDK4/6 inhibitor by triggering apoptosis, including in growth arrested/senescent cells[2]. PALVEN is a phase 1b study (NCT NCT03900884), aiming to combine venetoclax with letrozole and the CDK4/6 inhibitor palbociclib. Trial Design: Eligible patients will be treated with letrozole (2.5 mg), palbociclib (75-125 mg) and venetoclax (100-800 mg) using a 3+3 dose escalation study design, with a maximum of 6 patients per dose cohort. Both palbociclib and venetoclax will be administered on day 1-21 of a 28 day cycle. Dose limiting toxicity (DLT) will be evaluated in the first 4 weeks of treatment. Tumor assessment will be performed every 8 weeks for 24 weeks and then every 12 weeks until progression. The primary endpoint is to describe DLTs reported within the first 4 weeks of treatment and determine the maximum tolerated dose (MTD), in order to define a recommended phase 2 dose (RP2D). Secondary endpoints include type and worst grade adverse events per patient (CTCAE v5.0), tumor response (RECIST v1.1), clinical benefit rate (CBR), progression free and overall survival (PFS, OS) as well as patient reported outcomes. Exploratory endpoints include metabolic response (using FDG-PET), changes in circulating tumor DNA (ctDNA), peripheral blood leukocyte subsets, and tumor phenotype in paired and progression biopsies. Eligibility Women with ER+ (≥10% positively stained carcinoma cells) and BCL2+ (≥50% cells with at least moderate cytoplasmic staining; intensity 2-3 on a 0-3 scale), unresectable locally advanced or MBC are eligible. Patients must have measurable or evaluable disease as per RECIST v1.1 and ECOG performance score of 0-1. Participants must not have had >2 prior lines of treatment in the metastatic setting and no previous treatment with CDK4/6 inhibitor or venetoclax in the adjuvant or metastatic setting. Statistical methods This is a proof-of-concept, dose escalation study and any statistical analysis of responses will be exploratory. Analysis will be focused primarily on adverse events, particularly DLTs reported in the DLT observation period. All secondary endpoints will be analysed separately combining all dosing cohorts. The response rate and CBR will be estimated with 95% confidence intervals calculated using exact methods based on the binomial distribution. Time-to-event endpoints (PFS and OS) will be described using Kaplan-Meier methods to calculate the median survival. Response rate, CBR and time-to-event endpoints (PFS and OS) will also be described for patients treated in the 1st versus 2nd and 3rd line setting. Accrual Target accrual is 6-36, depending on the number of dose cohorts required to reach DLT. Recruitment is active at 2 sites in Australia.** **References [1] Lok, S.W., *et al.* (2019). *Cancer Discov 9*, 354-369. [2] Whittle, J.R., *et al.* (2020). *Clin Cancer Res* Advance online.**

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# Impact of online education regarding novel HER2 therapies on translating evidence to practice

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**Background:The treatment armamentarium for patients with refractory metastatic HER2+ breast cancer was limited due to a lack of effective agents after the use of ado-trastuzumab emtansine, trastuzumab, and pertuzumab. Novel therapies such as trastuzumab deruxtecan and tucatinib provided high response rates to a patient subgroup with unmet clinical needs for having effective therapy. As data from clinical trials become available, landmark trials are published, and FDA approvals and guidelines incorporate novel therapies, continuing medical education (CME) for oncologists is necessary to facilitate the translation of evidence to their clinical practice. Methods: A series of 4 CME-certified activities were launched to educate physicians on new therapies in metastatic HER2+ breast cancer following data releases from the 2019 San Antonio Breast Cancer Symposium. Education followed adult learning principles starting with a goal of increasing awareness on novel agents and outcomes presented at national conferences and then integrating these agents into clinical practice, including adverse event management. Panel discussions were utilized to provide multiple faculty perspectives and clinical examples. Effectiveness was analyzed using 3 multiple-choice and 1 self-efficacy question measuring knowledge, competence, and confidence, presented as pre-/post-CME repeated pairs for each of the activities. Oncologists who completed both the pre- and post-CME questions were included in analysis and McNemar's tests were conducted to assess statistical significance of the results with *p* < .05 being considered significant. The CME activities launched from December 2019 through March 2020 and data collected June 2020. Results:As of 6/9/2020, 6,473 global physicians had participated in the activities including 3,036 oncologists. 62% of the Oncologists identified themselves as practicing in a community setting, with 87% reporting a plan to make changes to their practice. Analyses from the activities found significant improvements in knowledge, competence, and confidence, measured as relative changes in % of correct responses or % of confident physicians from pre- to post-CME, across the various themes of learning objectives in metastatic HER2+ breast cancer:•**
**62% increase in knowledge of clinical trial outcomes (n = 339; pre: 53% vs. post: 86%, *p* < .001)•35% increase in understanding the mechanism or rationale for novel agents (n = 368; pre: 52% vs. post: 70%, *p* < .001) •15% increase in the ability to identify patients eligible for novel therapies (n = 210; pre: 61% vs. post: 70%, *p* < .05) •38% increase in managing adverse events of novel therapies (n = 158; pre: 37% vs. post: 51%, *p* < .001) •83% increase in the percent of oncologists who were mostly or very confident in treating metastatic HER2+ breast cancer patients (n = 368; pre: 18% vs. post: 33%, *p* < .001) Conclusions: This series of online, expert-led, CME-certified educational activities resulted in significant improvement in knowledge, competence, and confidence among learners regarding the use of novel anti-HER2 therapies in the management of metastatic breast cancer. These results demonstrate the effectiveness of on-demand education to translate information from data to clinical practice and directly benefit patients.** **Grantors:This educational initiative was supported through educational grants from Astra Zeneca Pharmaceuticals LP and Daiichi Sankyo.**

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# Validation of CTS5 as a predictor of distant late recurrence risk in HER2 negative luminal breast cancer: Latin American experience

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Background: Breast cancer (BC) is the most commonly diagnosed cancer worldwide, 91% diagnosed in early stages and 80% of them expressing estrogen receptor (ER +). It is known that distant late recurrence (DLR) represents about 50% of all relapses. Thus, identifying patients with a higher risk of DLR is a essential need in ER + BC, leading to a potential personalized management. Within this scope, CTS 5 (Clinical Treatment Score after 5 years) was developed as a simple clinical-pathological tool that aims to estimate the residual risk of distance recurrence after 5 years of endocrine therapy (ET).
Methodology: The validity of CTS5 was tested in a retrospective cohort. Patients diagnosed between 2005 and 2011 with early BC, ER+/HER2- tumors, alive and without recurrence within the first 5 years were selected. The primary endpoint was the time for distant late recurrence (DLR). Cox regression models were used to determine the prognostic value of CTS5 and to produce Kaplan-Meier curves with associated risks of DLR.
Results: A total of 797 women were included with a median follow-up of 105 months. According to the CTS5, 424 (53.2%), 239 (30.0%), and 134 (16.8%) patients were classified into the low-, intermediate-, and high-risk of DLR, respectively (table 1). CTS5 results were prognostic for DLR: patients with CTS5-high showed a fivefold relative risk of developing an DLR compared to patients with CTS5-low (HR, 5.1 IC95% [2.24-11.47], p <0.0001) (table 2). When assessing continuously, an one-point increase in CTS5 increased the relative risk of DLR by 87% (HR, 1,87 95% CI [1,324 - 2,632] p <0.0001). These results were confirmed when we stratified by age (age≤50 years vs. age>50 years).
Conclusion: Our results support its use in clinical practice as a predictor for patients with early-stage BC, ER +, and HER2- in real life. Besides, our study serves as a hypothesis generator for future confirmations through prospective studies. Thus, we will be able to assess, through prospective studies, whether the CTS5 can be used to personalize the patient's follow-up or even evaluate its usefulness in the decision to prolong or not ET. Such results would be extremely important, given the known difficulty in accessing genomic assays, especially in developing countries.

Table 1 Risk groups classifed according to the CTS5 and the clinicopathological characteristics

| Factors | No. (%)<br>Low<br>424 (53.2) | Intermediate<br>239 (30.0) | High<br>134 (16.8) | *P value* | Total |
|---|---|---|---|---|---|
| Age, years<br><50<br>>50 | 175 (41.3)<br>249 (58.7) | 100 (41.8)<br>139 (58.2) | 47 (35.1)<br>87 (64.9) | .383 | 322 (40.4)<br>475 (59.6) |
| Number of the positive nodes<br>0<br>1<br>2-3<br>4-9<br>9+ | 389 (91.7)<br>31 (7.3)<br>2 (0.5)<br>2 (0.5)<br>0 (0.0) | 133 (55.6)<br>81 (33.5)<br>21 (8.8)<br>3 (1.7)<br>1 (0.4) | 12 (9.0)<br>28 (20.9)<br>41 (30.6)<br>32 (23.9)<br>21 (15.7) | < .0001 | 534 (67.0)<br>139 (17.4)<br>64 (8.0)<br>38 (4.8)<br>22 (2.8) |
| Histological grade<br>1<br>2<br>3 | 88 (20.7)<br>196 (46.2)<br>140 (33.1) | 25 (10.4)<br>129 (48.5)<br>85 (35.6) | 7 (5.2)<br>38 (28.4)<br>89 (66.4) | < .0001 | 120 (15.0)<br>363 (45.6)<br>314 (39.4) |
| Tumor size, mm<br>< 10<br>10-20<br>20-30<br>> 30 | 193 (45.5)<br>199 (47.0)<br>22 (5.2)<br>10 (2.3) | 9 (3.8)<br>94 (39.3)<br>82 (34.3)<br>54 (22.6) | 3 (2.2)<br>29 (21.6)<br>41 (30.6)<br>61 (45.5) | < .0001 | 205 (25.7)<br>322 (40.4)<br>145 (18.2)<br>125 (15.7) |
| Histological Type<br>Ductal<br>Tubular<br>Others | 342 (80.7)<br>57 (13.4)<br>25 (5.9) | 207 (86.6)<br>21 (8.8)<br>11 (4.6) | 112 (83.6)<br>17 (12.7)<br>5 (3.7) | < .0001 | 661 (82.9)<br>95 (11.9)<br>41 (5.1) |
| Chemotherapy<br>Neoadjuvant<br>Adjuvant | 10 (2.4)<br>153 (36.1) | 22 (9.2)<br>146 (61.1) | 25 (18.7)<br>92 (68.7) | < .0001 | 57 (7.2)<br>391 (49.1) |
| Radiotherapy<br>Yes<br>No | 271 (63.9)<br>153 (36.1) | 184 (77.0)<br>55 (23) | 119 (88.8)<br>15(11.2) | < .0001 | 574 (72.0)<br>223 (28) |
| Administered endocrine therapy<br>5 years tamoxifen<br>5 years used aromatase inhibitor<br>> 5 years tamoxifen<br>> 5 years used aromatase inhibitor | 183 (43.2)<br>210 (49.5)<br>20 (4.7)<br>11 (2.6) | 66 (27.6)<br>146 (61.1)<br>18 (7.5)<br>9 (3.8) | 29 (21.6)<br>78 (58.2)<br>19 (14.2)<br>8 (6.0) | < .0001 | 278 (34.9)<br>434 (54.4)<br>57 (7.2)<br>28 (3.5) |
| ET time, years<br>5<br>7 - 10 | 393 (92.7)<br>31 (7.3) | 212 (88.7)<br>27 (11.3) | 107 (79.9)<br>27 (20.1) | < .0001 | 712 (89.3)<br>85 (10.7) |
| Vital status<br>Alive<br>Dead | 420 (99.1)<br>4 (0.9) | 236 (98.7)<br>3 (1.3) | 128 (95.5)<br>6 (4.5) | .016 | 784 (98.3)<br>13 (1.7) |
| Distant recurrence<br>No<br>Yes | 415 (97.9)<br>9 (2.1) | 222 (92.9)<br>17 (7.1) | 118 (88.1)<br>16 (11.9) | < .0001 | 755 (94.7)<br>42 (5.3) |

**Table 2. Survival analyses for DLR and Overall Survival in diferent subgroups (CTS5 as categorical)**

| Distance Late Recurrence | | | | | |
|---|---|---|---|---|---|
| | Low risk | Intermediate risk HR (95% CI) | *p* | High risk HR (95% CI) | *p* |
| All patients | Reference | 3.155 (1.406 - 7.080) | .005 | 5.067 (2.239 - 11.467) | < .0001 |
| >50 years old | Reference | 2.889 (1.049 - 7.952) | .040 | 4.701 (1.737 - 12.723) | .002 |
| <50 years old | Reference | 3.730 (.964 - 14.435) | .057 | 5.494 (1.311 - 23.029) | .02 |
| Overall Survival | | | | | |
| | Low risk | Intermediate risk HR (95% CI) | *p* | High risk HR (95% CI) | *p* |
| All patients | Reference | 1.152 (.258 - 5.150) | .853 | 3.948 (1.113 - 14.00) | .034 |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS1-65**

# What lessons can be learned from the poly implant prothese scandal ? A french retrospective study

**Lea Pauly, Benoit Couturaud and Fabien Reyal. Institut Curie, Paris, France**

**Background : Silicone breast implants from the French manufacturer Poly Implant Prothese (PIP) were recalled from the French market after the use of a non-medical silicone filler has been established. The systematic explantation of the implants had been proposed to women with PIP implants in France, a preventive measure concerning approximately 30,000 patients.Objectives : This study aimed to evaluate the consequences of having at least one PIP breast implant on overall and disease-free survival after breast reconstruction for cancer or prophylactic surgery.Materials and Methods : We performed a multicentric retrospective cohort study on women who underwent immediate or delayed implant-based reconstruction after curative or prophylactic mastectomy between January 01,2002 and March 30,2010 in three French private health institutions of public interest. These dates correspond respectively to the arrival of PIP breast implants on the French market and the decision to withdraw them by the French government. The primary endpoints were disease-free and overall survival, depending on whether or not having a PIP breast implant used during breast reconstruction of prophylactic surgery.Results : We identified 2499 patients with the use of 4106 breast implants between 2002 and 2010.The median age of cancer diagnosis was 47 years (19-77). This patient population selected for breast reconstruction had good prognosis criteria (77% T1 and 68% N0). PIP was the most common brand used between 2002 and 2010 and represented 45% of all breast implants (1764 implants). PIP has been preferentially used in courses with immediate breast reconstruction. On the 1764 PIP, 1408 (80%) were removed, mainly after the preventive measure recommending systematic explantation. Censored data on March 30, 2010, showed that the incidence of PIP implants removal is lower than other brands (Log-rank test : $p<0.001$). Overall survival of patients who had at least on PIP was no different from that of patients who never had a PIP (Log-rank test : $p=0.2$). Disease-free survival was also similar between these two populations (Log-rank test : $p=0.12$).Conclusion : We did not identify any increase in local-regional recurrence or overall mortality associated with the use of PIP.**

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# Breast cancer in young women in a tertiary-level hospital in Guatemala

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Background: Breast cancer is the frequent neoplasia in young women, which in developing countries is associated with more adverse outcomes. In Latin America, reports have shown an increased incidence of breast cancer in young women. No information exist regarding breast cancer characteristics in young Guatemalan women. We aimed to describe the clinical-pathological features among women aged 45 years or less treated in a tertiary-level hospital in Guatemala. Methods: We examined data from 119 women aged 45 years or less diagnosed with primary invasive breast cancer at the Oncology Unit Roosevelt Hospital in Guatemala between 2016 and 2020. Data were drawn from medical files on sociodemographic characteristics, histology, clinical stage, and breast cancer subtypes.Results: Of the total sample, breast cancer in women aged 45 years or less represented 31.2% of the cases. Of these, 24.36% is before 35 years, 28.57% between 35 to 39 years, and 47.05% between 39 to 45 years. Advanced clinical stages affected 66.6% of young women (48.33% for stages III and 18.33% stage IV). Data from specific breast cancer molecular subtype showed that 72.35% of cases in young women expressed an aggressive molecular subtype (Her-2 positive 27.06%, triple-negative 21.76%, and luminal/Her-2 positive 23.53%). Regarding treatment, most young patients received surgical treatment, as well as neoadjuvant or adjuvant chemotherapy. Only 24.37% received hormonal and 26.89% radiation therapy. Conclusions: Our finding suggested that young women treated for breast cancer at a tertiary-level hospital in Guatemala had a high proportion of aggressive molecular subtypes and a high rate of locally advanced disease. This aggressive cancer behavior among young women is consistent with findings in other Latin American countries. Evidence examining risk factors for aggressive cancer in young women, such as delay in diagnosis and treatment timing, is warranted.

Table 1. Distributions of socio-demographic and cancer-related characteristics variables

| | % (SE)n = 119 |
|---|---|
| ETHNIC GROUP | |
| Mayan Indigenous | 12.61 (3.05) |
| No-Mayan Indigenous | 87.39 (3.05) |
| HISTOLOGY | |
| Ductal | 96.64 (1.66) |
| Lobular | 1.68 (1.18) |
| Other | 1.68 (1.18) |
| CLINICAL STAGE* | |
| I | 1.67 (1.17) |
| II | 31.67 (4.26) |
| III | 48.33 (4.58) |
| IV | 18.33 (3.54) |
| BREAST CANCER SUBTYPE | |
| Luminal | 27.65 (4.76) |
| Her2 positive | 27.06 (5.11) |
| Triple-negative | 21.76 (5.05) |
| Luminal/Her2 | 23.53 (6.61) |
| TREATMENT | |
| Surgery | 55.46 (4.58) |
| Neoadjuvant Chemotherapy | 82.35 (3.51) |
| Adjuvant Chemotherapy | 47.06 (4.59) |
| Radiotherapy | 26.89 (4.08) |
| Hormonotherapy | 24.37 (3.95) |

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS1-66**

**Current practice in implant-based breast reconstruction: A french long-term follow-up study**

**Lea Pauly, Benoit Couturaud and Fabien Reyal. Institut Curie, Paris, France**

**Background: There is a lack of data on the use of breast implants and the path of patients reconstructed after breast cancer in France. This study aims to identify the paths of patients reconstructed by breast implant in France and assess their impact on survival, but also estimate the quality of the reconstruction, determined by early removal or replacement of implants.Methods : We performed a multicentric retrospective cohort study on women who underwent immediate or delayed implant-based reconstruction after curative or prophylactic mastectomy between 2002 and 2010 in three French private health institutions of public interest.Results : We identified 9 care pathways according to the type of disease, the type of surgery, the addition or not of adjuvant radiotherapy, and the timing of reconstruction. Theses courses concern 2,499 patients, and 3,191 breasts on which at least one implant has been placed. Five implant brands were mainly used during this period: PIP, Mentor, Allergan, Sebbin, and Perthese - with a total of 4,106 implants. The median of follow-up is 6 years [0 ;12 ;1]. The number of implants per breast is significantly different according to the reconstruction pathways (p<0.001). The overall survival and removal incidence of implants are significantly different according to the differents profiles of reconstruction (Log-Rank test: p <0.001).Conclusion : The profiles of patients reconstructed by implants are very heterogeneous, according to their disease, their surgery, the adjunction of adjuvant radiotherapy, and the reconstruction time. This leads to very differents overall survival and breast implants removal rates. By identifying specific pathways despite the heterogeneity of the population, this study makes it possible to identify patients at risk more precisely and to have a more global vision on implant reconstruction in France in the 2000s, over a decade of PIP breast implant use.**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS9-65**

# Effect of virtual education on the knowledge, competence, and performance of oncology pharmacists attending a national symposium

**Vanessa Carranza, Joan B Fowler, Susan H Gitzinger and Bryan C Taylor. Creative Educational Concepts, Lexington, KY**

**Background:We evaluated the effect of this virtual education on knowledge, competence, and performance in oncology pharmacists who participated in a virtual symposium held during the Hematology/Oncology Pharmacy Association Annual Conference. The educational initiative reviewed the role of ADCs in HER2-positive breast cancer, current and emerging agents, and how to incorporate these agents into practice.**
**Methods:•Learning and knowledge was objectively assessed by analyzing pre- and post-test results during the educational activity. Competence was assessed via post-activity evaluation where participants were asked to identify changes they intended to make in practice and any anticipated barriers that would hinder them from making changes.•Follow-up assessments were sent to participants 4-6 weeks after the live activity to determine retention of knowledge. Case study assessment questions were utilized to see if participants translated knowledge into practice. The follow-up assessments also inquired about changes made and actual barriers experienced in practice.•Statistical testing between pre- and post-tests and from pre-test to follow-up were conducted via chi square analysis with *a priori* significance set at 0.05.**
**Results:•Improved knowledge was observed in several specific topic areas from pre- to post-test ($P<0.05$) and from pre-test to follow-up ($P$=NS).•Learning, Knowledge, and Performanceo Therapy Selection based on National Guidelines 1st line (50% pre-activity vs. 93% post-activity vs. 75% follow-up)o Therapy Selection based on National Guidelines 2nd line (58% pre-activity vs. 86% post-activity vs. 75% follow-up)oToxicity Prevention and Management (53% pre-activity vs. 100% post-activity vs. 75% follow-up)• Competence and PerformanceoThe top intended practice changes were the same at follow-up as they were immediately following the activity. The percentage of those who intended to make changes compared to those actually made changes were also fairly similar.· Collaborate with others in the oncology care team to ensure appropriate and successful use of ADCs 60% à 50%· Share knowledge obtained with colleagues 53% à 50%· Incorporate the latest clinical guidelines for HER2+ breast cancer into practice 53% à 50%oMost barriers participants listed were experienced less often than anticipated. Notably, 40% of participants listed “formulary/insurance” as an anticipated barrier, but 0% reported facing this at follow-up. “Staying current with evolving clinical guidelines” was a barrier that nearly doubled at follow-up (53% to 100%). Specific changes from activity to follow-up are below.· Staying current with evolving clinical guidelines 53% à 100%· Lack of colleague knowledge about the latest safety/efficacy data 40% à 25%· Lack of time/staff to monitor/follow-up with patients about ADC toxicity 12% à25%· Lack of patient/caregiver recognizing and communicating toxicities 26% à 25%· Formulary/insurance 40% à 0%Conclusions:**
**A virtual method of education was found to have a positive impact on knowledge and performance in oncology pharmacists, as evidenced by the improved scores in pre- and post-test polling, that was sustained at follow-up. The top changes actually made by participants of this activity involved collaborating with members of the oncology care team and to share knowledge obtained with their colleagues. However, the most frequently cited anticipated barrier in practice was “staying current with rapidly evolving guidelines”, which was actually experienced in practice by 100% of participants at follow-up. This demonstrates the ongoing need for additional education on this topic.**

2020 San Antonio Breast Cancer Symposium®

Publication Number: OT-28-01

# HER2CLIMB-02: A randomized, double-blind, phase 3 study of tucatinib or placebo with T-DM1 for unresectable locally-advanced or metastatic HER2+ breast cancer

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Background - Tucatinib (TUC), an oral tyrosine kinase inhibitor (TKI) highly selective for HER2 with minimal inhibition of EGFR, is approved in the US for use in combination with trastuzumab (Tras) and capecitabine for treatment (tx) of adult patients (pts) with metastatic HER2+ breast cancer (MBC), including pts with brain metastases (BM), who have received 1 or more prior anti-HER2-based regimens in the metastatic setting. Ado-trastuzumab emtansine (T-DM1), approved for tx of pts with HER2+ MBC after Tras and a taxane, has led to significant improvements in progression-free survival (PFS) and overall survival (OS). Still, further improvements are needed, including pts with active BM. A phase 1b trial evaluated TUC (300 mg PO BID) with T-DM1 in 50 pts with HER2+ MBC who received prior tx with Tras and a taxane (Borges 2018). Common AEs included nausea (72%), diarrhea (60%), and fatigue (56%); mostly grade 1/2. Median PFS was 8.2 months and the objective response rate (ORR) in pts with measurable disease (n=34) was 47%. Sixty percent of pts treated with TUC + T-DM1 had BM at baseline and showed a brain specific response rate (RECISTv1.1) of 36% in pts with measurable BM. This encouraging clinical activity, including in pts with BM, provides rationale for a randomized trial to further evaluate this combination.
Trial design - HER2CLIMB-02 is a randomized, double-blind, placebo-controlled phase 3 study to evaluate efficacy and safety of TUC + T-DM1 in pts with unresectable locally advanced or metastatic HER2+ breast cancer; ~460 pts will be randomized 1:1 to receive 21-day cycles of TUC (300 mg PO BID) or placebo with T-DM1 (3.6 mg/kg IV). Pts must have had prior tx with Tras and a taxane in any setting, be ≥18 yrs, with an ECOG ≤1 and histologically confirmed HER2+ MBC. Prior tx with any investigational antiHER2 or anti-EGFR agent or HER2 TKI is not permitted. Prior pertuzumab tx is allowed, but not required. Baseline brain MRIs are required for all pts; pts with stable, progressing, or untreated BM not requiring immediate local therapy are eligible. While on tx, radiographic disease evaluations (RECISTv1.1) will occur every 6 weeks for the first 24 weeks, and then every 9 weeks. The primary endpoint is PFS per investigator, with OS and ORR as key secondary endpoints. Enrollment is ongoing in the US (NCT03975647) and planned for Canada, the EU, and the Asia/Pacific region.

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS7-65**

# Triple negative breast cancer prospective registry in middle East and Africa (TRIPOLI) study: Interim analysis of the patients' characteristics

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***Background:*****Globally, triple-negative breast cancer (TNBC) is responsible for approximately 15% of all invasive Breast cancer and has been typically associated with poor prognosis. Some retrospective studies have suggested a relatively higher incidence of TNBC in the Middle East and North African Arab countries. Nevertheless, there is complete lack of prospective data, on TNBC in the region, including clinico-pathologic characteristics, treatment patterns and disease outcomes. The TRIPOLI study aims to bridge this information gap.*****Methods:*****TRIPOLI is an ongoing prospective multinational, disease registry, designed to recruit 700 newly diagnosed TNBC patients, from 15 institutions within 9 Arab countries: Egypt, Jordon, Morocco, Kingdom of Saudi Arabia, Lebanon, Oman, Kuwait, Qatar and Iraq. This interim analysis includes the patients' characteristics and treatment approaches of the first 449 cases included in the study from December 2017 to September 2019.*****Results:*****All the 449 TNBC patients were females, with a median age of 49 years (range 23.8 - 93.6 years). Premenopausal status was reported in 54.7%, while a positive family history of BC was stated in 25.2% of these cases. 0.2% of patients were below normal (BMI<18.5), 17.2% had normal weight (18.5≤BMI<25), and 30.5% were overweight (25≤BMI<30). Obesity (BMI ≥ 30) was present in 52% of these patients, while a parity of ≥3 children was present in 254 patients (59.8%) Sixty-six patients (14.7%) had tumours smaller than 2cm. 159 patients (35.4%) had node negative disease. The majority of patients had invasive duct carcinoma (87.1%) with 5 patients (1.1%) grade I, 181 (40.3%) grade II and 234 (52.1%) grade III tumours (29 (6.5%) had unknown histological grade). Thirty-four patients (7.6%) presented with stage I disease, 203 patients (45.2%) with stage II, 161 patients (35.9%) with stage III and 50 patients (11.1%) presented with stage IV disease.Out of the 387 patients with non-metastatic disease who started treatment, 217 patients (56.1%) had upfront surgery and 170 patients (43.9%) started with neoadjuvant chemotherapy. Compared to patients > 40 years, patients ≤ 40 years were less likely to be obese (39.4% versus 60.6%; p=0.002), more likely to have grade III tumours (62.3% versus 53.5%; p=0.116), more likely to have T3 or T4 tumours (41.4% versus 32.7%; p=0.038).*****Conclusion:*****In this interim analysis, Arab women with TNBC had high parity (≥ 3) and high BMI, compared to existing literature based on western population. High tumor grade, younger age and advanced stages at presentation are in line with similar world-wide reports. Younger women in the Arab region (≤40 years) presented with poor prognostic features, which will be further elucidated in subsequent reports.**

**2020 San Antonio Breast Cancer Symposium®**

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# Pilot study for the use of a booklet for breast cancer patients who receive radiation therapy at national cancer institute of Mexico

**Daniel Rivera-Sanchez, Luz M Gutierrez-Zacarias, Juan A Torres-Dominguez, Paulina Guerra-Vazquez and Juan E Bargallo-Rocha. Instituto Nacional de Cancerologia, Mexico City, Mexico**

**Background One of the most used treatments for breast cancer is radiation therapy (RT) which is a standard treatment after breast conserving surgery because it is associated with a reduction of about 50% of local recurrences; after mastectomy RT improves loco-regional control and breast cancer mortality especially with positive lymph nodes.Most of the patients show themselves worried when they find out they will receive RT as part of their treatment, experiencing fear and anxiety since the first consultation and before the RT starts, because they do not have adequate information about RT. Even if the information is given, this could be ununderstandable, unclear, with medical technicism or do not accomplish the patient´s expectatives. Most of the time this information is provided verbally despite the fact it being known that up to half of the patients prefer written information to have it and refer to it later as needed.**
**Currently at the National Cancer Institute of Mexico (INCan), breast cancer patients who need RT, receive only verbal information during the initial consultation by the radiation oncologist, we do not have printed material to complement the information and satisfy patient's needs.**
**Material and Methods We performed a booklet with written information about the whole process of RT, which has general concepts, detailed information of each part of the treatment, adverse effects and self-care. We performed a pilot study with 38 breast cancer patients receiving RT. The aim was to evaluate the guide content. We asked them to read it and after we evaluated the booklet content with a mixed questionnaire of 5 elements to know the patient's opinion. Satisfaction with the information provided was evaluated using a subscale of the BREAST-Q questionnaire to quantify the results.**
**Results Thirty eight patients were interviewed, with an average of 50 years (29-72) diagnosed between 2016 to 2019, all patients had formal education; 18.4% were first time RT patients, 7.9% were during treatment and 73.7% were at the follow up consults, were I, II, III and IV Clinical Stage (23.7%, 31.6%, 10.5% and 10.5% respectively); for 100% of the patients the booklet had clear, adequate, enough, precise and easy to understand information, within the commentaries they said: "Works like a guide", "Detail explained like a consult, explain my difficulties", "Totally clear"; 6 (15.8%) would like to add another information like nutrition tip; related to precise moment for receive the booklet 34 (89.5%) prefer prior first consult in RT service, 3 (7.9%) prefer to have the booklet after RT consult and 1 (2.6%) patient said that the best moment to receive it was during the treatment. Most patients considered RT's booklet as complete, well explained and helped them to understand all the process. During the evaluation of Satisfaction with the information provided by Radiation Oncologist (SIRO) we obtained 77% (37-100) in global satisfaction.**
**ConclusionOur booklet could be used to ameliorate the effective communication and as a complementary tool for patients who are going to receive RT and will allow us to improve the quality of care, upgrading the satisfaction with the information for the patients.**

Publication Number: OT-28-02

# Phase II randomized trial of neoadjuvant trastuzumab and pertuzumab with either palbociclib plus letrozole or paclitaxel for postmenopausal women with estrogen receptor-positive / HER2-positive breast cancer - The TOUCH trial

Laura Biganzoli, Etienne Brain, Luca Malorni, Andrea Gombos, Ursula Hasler-Strub, Claudio Zamagni, Camille Chakiba, Heidi Roschitzki-Voser and Meredith M Regan. International Breast Cancer Study Group and TOUCH Investigators, Bern, Switzerland

Background: HER2 blockade in combination with chemotherapy (CT) remains the treatment of choice for patients with HER2+ early breast cancer (BC), irrespective of estrogen receptor (ER) status. Patients with ER+/HER2+ early BC may benefit from HER2 blockade in combination with endocrine therapy (ET) and potentially also new targeted agents. Recent data have elucidated cyclin-dependent kinases 4 and 6 (CDK4/6) as key therapeutic targets acting downstream of both ER and HER2 pathways suggesting CDK4/6 inhibitors like palbociclib may be ideal partners for ET in this context. Pre-clinical and clinical data suggest that a gene signature of functional loss of retinoblastoma (RBsig) might predict sensitivity to CT versus CDK4/6 inhibition in ER+/HER2+ early BC.
The TOUCH hypothesis is that neoadjuvant therapy with palbociclib + ET + dual HER2 blockade with trastuzumab and pertuzumab may be more active in postmenopausal patients with ER+/HER2+ RBsig LOW early BC while those with RBsig HIGH may require CT. This will be formally tested in the primary objective, exploring the interaction between the RBsig status (HIG or LOW) and treatment activity, assessed by pathological complete response (pCR), of palbociclib+letrozole versus paclitaxel when given with trastuzumab+pertuzumab for ER+/HER2+ primary breast cancer.
The study was initially targeting older patients due to the particular appealing of CT de-escalation in this population. Due to the increasing interest for CT de-escalation and the mounting evidence of the potential benefit of such ET combination optimization, TOUCH has been recently amended to extend accrual to postmenopausal women.
Trial design: TOUCH is an open-label, multicenter, randomized phase II neoadjuvant trial in postmenopausal patients with ER+/HER2+ primary BC. Eligible patients will be randomized (1:1) to dual HER2 blockade (5 doses trastuzumab + pertuzumab) plus either palbociclib (125 mg/d po; 21 of 28d x 4 cycles) and letrozole (daily x 16 weeks), or paclitaxel (80 mg/m$^2$ iv, d1,8,15 q28 days x 4 cycles), before surgery. RBsig (HIGH vs LOW) will be determined centrally on mandatory pre-treatment biopsies. Patients ≥65 years will receive a baseline geriatric assessment including G8, Instrumental Activity of Daily Living (IADL) and Charlson Comorbidity Index. The primary objective is to explore the interaction between RBsig and treatment activity assessed by pathological complete response (pCR) at time of surgery.
Exact logistic regression will test RBsig by treatment interaction (2-sided a=.05) and estimate odds ratios (OR) for treatment effect on pCR according to RBsig status. The sample size provides 86% power, assuming an overall pCR rate of 26%, 50% RBsig LOW, and OR=2.4 vs OR=0.11 for RBsig LOW vs HIGH.
Accrual: The trial will recruit 144 patients from approximately 45 Centers in Belgium, France, Italy and Switzerland. The first patient was enrolled in April 2019. Accrual as of mid-June 2020 was 25 patients.
The TOUCH trial (IBCSG 55-17) is sponsored and coordinated by IBCSG with financial support from Pfizer and Roche. The trial is conducted in collaboration with Unicancer GERICO and SAKK.
NCT03644186

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# VICKI: A Phase Ib/II, randomized, placebo-controlled, study of venetoclax plus ado-trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-positive locally advanced (LA) or metastatic breast cancer (MBC)

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Background ~15-20% of primary, invasive breast cancer (BC) overexpresses HER2 and, despite survival improvements, there remains an unmet need for further progress. The antibody-drug conjugate T-DM1 is approved for HER2-positive LA and/or MBC that has previously been treated with trastuzumab and a taxane (separately or in combination), and as adjuvant therapy for HER2-positive early BC, where there is residual invasive disease after neoadjuvant taxane and trastuzumab- or HER2-based treatment. Venetoclax (GDC-0199/ABT-199), an oral, selective small-molecule inhibitor of the antiapoptotic protein BCL-2, is approved for treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, and acute myeloid leukemia. BCL-2 may play a key role in HER2-positive BC, and venetoclax has shown promising activity in estrogen receptor-positive, BCL-2-positive MBC. We describe VICKI (Venetoclax in Combination with Kadcyla), a Phase Ib/II, randomized, double-blind, placebo-controlled, study of venetoclax plus T-DM1 in previously treated HER2-positive LA/MBC (NCT04298918).

Trial design

The study comprises a Phase Ib stage (dose escalation and expansion cohorts) and a randomized Phase II stage. Phase II will be initiated following identification of the recommended Phase II dose of venetoclax in Phase Ib (400 mg or 800 mg). Pts will be randomized 1:1 to T-DM1 (intravenous 3.6 mg/kg q3w) plus venetoclax or placebo. Randomization will be stratified per BCL-2 status (BCL-2 high vs. low), visceral disease (Yes vs. No), and HER2 immunohistochemistry (IHC) 3+ status (Yes vs. No).

Eligibility

Adult pts with HER2-positive (IHC 3+ or IHC 2+/*in situ* hybridization-positive), previously treated, unresectable, histologically or cytologically confirmed invasive LA/MBC are eligible. Pts will have measurable disease per RECIST v1.1 and an Eastern Cooperative Oncology Group performance status of 0 or 1. Pts in Phase II will have BCL-2 expression status by IHC (≥50% of pts BCL-2 high) and will not have received prior treatment with T-DM1, venetoclax, or anti-HER2 drug conjugates.

Aims

The Phase II co-primary efficacy endpoints will be objective response rate (ORR) and progression-free survival (PFS) per RECIST v1.1 (both investigator-assessed). Secondary and exploratory efficacy endpoints will include duration of response, overall survival, clinical benefit rate, and patient-reported outcomes. Non-efficacy endpoints will be pharmacokinetics, immunogenicity, biomarkers, and safety.

Statistical methods

In Phase II, the primary efficacy populations will include all randomized pts according to their assigned treatment arm (intention-to-treat). A point estimate and 95% CI for ORR and the difference in ORR between treatment groups will be calculated using the normal approximation to the binomial distribution. PFS will be defined as time from randomization to the first occurrence of disease progression or death from any cause. Kaplan-Meier methodology will be used to estimate median PFS. An interim analysis is planned when ~56 PFS events have occurred. Primary efficacy analysis will occur when 161 pts have had a PFS event. Cox proportional-hazards models, stratified by the stratification factors, will be used to estimate the hazard ratio with 95% CI. Safety will be analyzed per treatment received in pts who received any study treatment (safety population).

Accrual

Target accrual is ~226-284 pts at 145 sites globally (Phase Ib dose escalation: 6-24 pts; Phase Ib expansion cohorts: ~20-40 pts; Phase II: 220 pts). Accrual is ongoing.

Contact information

For more information or to refer a patient, email global-roche-genentech-trials@gene.com or call 1-888-662-6728 (USA only).

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# Real-world clinical outcomes of patients with BRCA-mutated (BRCAm) HER2-negative metastatic breast cancer: A CancerLinQ® study

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Background: Limited epidemiological data exist on the real-world outcomes in patients with BRCA-mutated (BRCAm), HER2− metastatic breast cancer (mBC). This study describes clinical outcomes in this population according to germline BRCA mutation (gBRCAm) and hormone receptor (HR) status. Methods: Patients diagnosed with HER2− mBC between January 1, 2010 and December 31, 2018 were retrospectively selected from the American Society of Clinical Oncology (ASCO)'s CancerLinQ Discovery® database. The primary objective was to describe, as a surrogate for progression-free survival, the time to first subsequent therapy or death (TFST; whichever came first), calculated from date of mBC diagnosis, according to gBRCAm status (gBRCAm, gBRCA wild-type [gBRCAwt] or unknown gBRCA [gBRCAu]) and HR status (+/−). TFST was also calculated from first-line systemic therapy initiation. The secondary objective was to describe overall survival (OS), calculated from date of mBC diagnosis. Kaplan-Meier medians and 95% confidence intervals (CIs) were estimated. Results: 3744 patients with HER2− mBC were identified (gBRCAwt, n=460; gBRCAm, n=83; gBRCAu, n=3201); 2738 patients were HR+. Median (Q1, Q3) age was 63.0 (54.0, 73.0) years. Median (95% CI) TFST (months), calculated from date of mBC diagnosis, was 9.2 (8.6, 9.9) in HR+ patients, 5.4 (5.1, 6.0) in HR− patients, and 7.1 (5.0, 9.2), 6.9 (6.1, 8.1) and 8.4 (7.9, 9.1) in gBRCAm, gBRCAwt and gBRCAu cohorts, respectively. Median (95% CI) OS (months) was 34.30 (32.70, 36.40) in HR+ patients, 12.0 (11.1, 13.3) in HR− patients, and 31.5 (23.1, 42.8), 34.7 (28.9, 44.5), 27.6 (26.1, 29.5) in gBRCAm, gBRCAwt and gBRCAu cohorts, respectively. Median TFST and OS stratified by both HR and BRCA mutation status are shown in Table 1.

Table 1. Median TFST and OS

| Cohort | TFST, n (events)[a,b] | Median TFST from mBC diagnosis, months (95% CI) | Median TFST from first-line treatment initiation, months (95% CI) | OS, n (events)[a] | Median OS, months(95% CI) |
|---|---|---|---|---|---|
| gBRCAm, HR+ (n=47) | 45 (40) | 7.7 (5.0, 11.2) | 6.6 (3.2, 9.0) | 47 (21) | 41.1 (31.5, NR) |
| gBRCAm, HR−(n=29) | 20 (19) | 5.4 (3.9, 12.4) | 3.1 (2.2, 8.9) | 29 (18) | 13.7 (11.1, NR) |
| gBRCAwt, HR+ (n=296) | 277 (234) | 8.3 (6.6, 10.2) | 6.5 (5.7, 8.7) | 296 (128) | 55.1 (43.5, 65.5) |
| gBRCAwt, HR−(n=130) | 113 (101) | 5.6 (4.7, 6.6) | 4.1 (3.4, 5.2) | 130 (91) | 14.4 (10.7, 17.0) |
| gBRCAu, HR+ (n=2395) | 2174 (1949) | 9.4 (8.7, 10.1) | 7.3 (6.9, 8.0) | 2395 (1431) | 33.0 (31.3, 34.8) |
| gBRCAu, HR−(n=609) | 466 (425) | 5.4 (5.0, 6.2) | 4.2 (3.7, 4.6) | 609 (448) | 11.7 (10.3, 12.8) |

[a]n refers to the number of patients at risk.[b]For patients with no indication of a further line of therapy or death, TFST was censored at the last activity date.CI, confidence interval; gBRCAm, germline BRCA-mutated; gBRCAu, unknown germline BRCA mutation; gBRCAwt, germline BRCA wild-type; HR, hormone receptor; NR, not reached; OS, overall survival; TFST, time to first subsequent therapy or death. Conclusions: When stratified by HR status, median TFST and OS were broadly similar for patients with mBC, regardless of BRCA mutation status, as captured in the CancerLinQ Discovery® database. Outcomes may have been affected by class of first-line treatment received in a time preceding poly (ADP-ribose) polymerase inhibitor introduction as a targeted treatment for BRCAm patients. Further studies will be required to support these findings. Funding: This study was funded by AstraZeneca.

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# Information needs, media use, and utilization of an online resource to support how young women with metastatic breast cancer evaluate breast cancer media reports

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**Background. Breast cancer is the most commonly diagnosed cancer among women ages 18-39. Young Breast Cancer Survivors (YBCS) face different prognoses, disease characteristics, treatment options, and short- and long-term outcomes from their older counterparts. Women with metastatic breast cancer (mBC) face additional burdens. Median survival time for mBC ranges from 1 - 4 years, often spent in continual treatment. In 2013, the estimated prevalence of mBC was 138,622, including approximately 20,000 women younger than 50 years. YBCS and patients with mBC have distinct needs for information, resources and support. Health information in the media often does not address their concerns, is misleading, or is confusing regarding which information is clinically relevant. Flaws include ignoring side effects, failing to discuss alternative options, exaggerating effectiveness, and under-emphasizing risk. This can affect health care decisions.**

**In response, in 2014 FORCE developed "eXamining the Relevance of Articles for You " (XRAY), a platform to review breast cancer topics reported in the media. XRAY explains the science in plain language, provides patients with a clinical relevance rating, connects patients to guidelines, and corrects misinformation or misreporting by the media. In the fifth year of XRAY implementation, FORCE conducted a national survey on information seeking and sharing of YBCS and women with mBC. The survey asked respondents, "Has your breast cancer progressed, recurred, or metastasized since your initial diagnosis?" The current report presents a summary and discussion of these respondents' survey results.**

**Methods. FORCE launched the online survey nationally, recruiting participants through a targeted media campaign launched through a network of 50 organizations. Eligible participants were women between ages 18 and 45 years who had a history of breast cancer or test results indicating genetic risk for breast cancer. Analysts calculated response frequencies and percentages for each survey item.**

**Results. A total of 135 survey respondents indicated that their breast cancer had progressed, recurred, or metastasized since their initial diagnosis. Women with mBC were more likely than the whole participant sample to have looked up information about chemotherapy, radiation therapy, tumor marker tests, treatment side effects, survivorship and long-term health outcomes, and quality of life with cancer. They were less interested in information about breast cancer screening, risk for other cancers, risk-reducing mastectomy, and risk-reducing ovary removal.**

**A majority of the mBC sample used at least some type of media to look up health information at least monthly. Most respondents indicated that they had shared and discussed media reports with their healthcare providers and that the discussion had impacted health-related decisions. More than three-fourths of respondents indicated interest in information about all components of research and reporting quality evaluated by XRAY.**

**Discussion. Results confirm that a tailored XRAY portal for people with mBC will help to serve this population. Results also suggest that FORCE could benefit from working with organizations that specialize in serving people with mBC to reach this population, disseminate XRAY reviews, and obtain input on content and format of XRAY for mBC.**

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# Budget impact of Ontruzant for the treatment of breast cancer and gastric cancer in the United States

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**OBJECTIVES: Breast cancer is estimated to have the highest incidence among all cancers in the United States (US) in 2020. In turn, the incidence of gastric cancer is ranked fifteenth among all cancers in the US. Targeted therapies, such as trastuzumab, have drastically improved clinical outcomes for patients with over-expressive human epidermal growth factor receptor 2 (HER2+) in early-stage breast cancer (EBC) and metastatic breast cancer (MBC) as well as metastatic gastric cancer (MGC). However, due to the high cost of treatment and eligible patient population size, originator trastuzumab has caused patient affordability challenges and represents a high budget burden on payers. The objective of this study is to assess the potential financial impact associated with the use of intravenous (IV) trastuzumab biosimilar Ontruzant compared to the originator, in patients with HER2+ EBC, MBC and MGC from the US healthcare payer perspective. METHODS: A budget impact model with a 5-year time horizon was developed to compare costs ($; 2020) under scenarios with and without the entry of Ontruzant to a healthcare plan. Only direct costs were considered following a payer perspective. Drug acquisition costs were estimated based on the published wholesale acquisition cost (WAC) price. The target population consisted of incident HER2+ patients eligible to receive trastuzumab IV or subcutaneous. Epidemiological data were obtained from SEER database and Epic Oncology. Predictions on trastuzumab market share and Ontruzant uptake were based on internal market research. The model calculated the budget impact of Ontruzant by indication and across all indications. RESULTS: In a hypothetical healthcare plan with one million members, the number of incident patients treated with the trastuzumab class was estimated to range from 107 in year 1 to 100 in year 5 in HER2+ EBC and 17 to 16 in HER2+ MBC. About ten new patients with HER2+ MGC were estimated to be treated with trastuzumab or biosimilars each year in year 1 to 5. The market uptake of Ontruzant with the trastuzumab class was assumed 50% in year 1 and rising over time to 90% in year 5, which led to a total budget saving of $13,534,498 in EBC and MBC and $459,331 in MGC over the 5-year period for the healthcare plan. The model yielded an average saving of $1,859, $2,073 and $766 per treated member per month in EBC, MBC and MGC, respectively. The cost saving was mainly driven by the lower drug acquisition cost of Ontruzant compared to originator trastuzumab, as well as potential reduction of vial wastage due to the availability of Ontruzant multi-dose vials. CONCLUSIONS: Adding Ontruzant to the formulary for treatment of HER2+ breast cancer and gastric cancer and creating mechanisms to encourage providers to utilize Ontruzant instead of the reference branded agent, could lead to substantial cost-savings for the US healthcare payers; and consequently, improve access to treatments for the patients.**

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# Breast cancer subtype differences according to race/ethnicity

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**Background:Breast cancer incidence and mortality rate differ across racial/ethnic population in the US, little is known about Asian and Pacific Island subpopulations. For the Asian subgroups (Japanese, Chinese, Korean, Filipino, Vietnamese, etc.) in the U.S., overall incidence has increased over recent decades. From 2012-2016 Hawai'i incidence rates were significantly higher than the US overall for breast cancer, although cancer mortality rates in Hawai'i were significantly lower than the US overall for breast cancer. Significant disparities in breast cancer incidence and mortality exist, with Native Hawaiian and Filipino women particularly affected. Native Hawaiian women have the highest incidence and also have a 50% higher risk of breast cancer mortality compared to White women. In addition, there are dramatic racial/ethnic differences in mortality rates in the state, with Native Hawaiians having the highest mortality rates compared to all other major racial/ethnic groups.**

**Methods:We examined unique breast cancer cases in a major health system in Hawai'i from 2013-2019 according to race/ethnicity. We found statically significant differences in breast cancer subtype according to race/ethnicity and menopausal status.**

**Results:In 561 premenopausal breast cancer cases, we found that Native Hawaiians were less likely to have triple negative breast cancer (OR 0.2, p=0.02) and Japanese were less likely to have triple positive breast cancer (OR 0.17, p=0.002) compared to other race/ethnicities. In 1,954 postmenopausal breast cancer cases, we found that Filipino women were more likely to have hormone negative/HER2 positive breast cancer (OR 2.38, p=0.006) compared to other race/ethnicities.**

**Table 1-Breast cancer subtype according to race/ethnicity in premenopausal women**

**Table 2-Breast cancer subtype according to race/ethnicity in postmenopausal women**

**Summary:Although behavioral, environmental, social, economic, and biological factors have been shown to influence risk and survival for breast cancer, they do not entirely explain the**

**differences observed across populations. These findings show the need to characterize the underlying differences in breast tumor biology of breast cancer patients from different racial/ethnic groups to better understand known health disparities. Our hypothesis is that molecular characteristics are key contributors to the disparities in disease outcome across the different racial/ethnic groups. We have previously shown the importance of the tumor microenvironment differences in racial/ethnic groups in our population.**

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# Neratinib and tepotinib combination in advanced breast cancer and inflammatory breast cancer patients with abnormal HER2 and c-Met pathway activity as measured by the CELsignia signaling pathway activity test

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**Background: While HER2 targeted therapeutics have significantly improved outcomes of patients with HER2 overexpressed advanced breast cancer (ABC), c-Met pathway activation serves as a resistance mechanism in about 60% of patients. Neratinib is an irreversible tyrosine kinase inhibitor of the ErbB family of receptors (EGFR, HER2, and HER4) and tepotinib is a tyrosine kinase inhibitor of c-Met. From live extracted cells from patient biopsies, the CELsignia Pathway Activity Test measures in real-time ErbB and c-Met signaling activity and the dynamic response to pathway inhibition by targeted therapy ex vivo. The CELsignia test may identify patients with ABC who would benefit from the combination of neratinib and tepotinib regardless of the molecular breast cancer subtype. Trial Design: We designed a phase Ib/II multi-center, non-randomized, open-label study of combination of neratinib with tepotinib in patients with advanced breast cancer including those with inflammatory breast cancer. The study sites include UT MD Anderson Cancer Center, City of Hope, and The Ohio State University Cancer Center. Four dose levels of neratinib, and two dose levels of tepotinib will be studied in phase Ib to determine the maximum tolerated dose (MTD). Phase II portion of the study will test the early efficacy of neratinib and tepotinib combination in patients with HER2-/HR+ ABC with abnormal HER2 and c-Met signaling activity determined by the CELsignia test. Eligibility: All patients with IBC/ABC will be eligible for the phase Ib. Eligible patients must have measurable metastatic disease per RECIST v1.1 or unresectable disease amenable for biopsy and have had at >1 line of systemic therapy for advanced disease. Patients will have an Eastern Cooperative Oncology Group performance status of 0 to 2. For the phase II component, patients must have hyperactive HER2 and c-Met signaling determined by CELsignia test. Aims: The primary objective of the phase Ib component is to determine the MTD of the combination in previously treated IBC/ABC of any molecular subtype. The primary objective of the phase II component is to determine the overall response rate (ORR) in patients with HER2-/HR+ ABC who have a positive CELsignia test result (described in the Eligibility). Secondary objectives include progression free and overall survival, clinical benefit rate, duration of response, and safety and tolerability. Exploratory objectives will be to assess HER2 and c-Met driven signaling pathways as either hyperactive or abnormally active by CELsignia test. Statistical Methods: The phase I study will be conducted using a Bayesian optimal interval (BOIN) design to establish the MTD and the recommended phase II dose and assess early efficacy of the combination with a maximum of 21 patients. Two dose levels of tepotinib, and four dose levels of neratinib will be studied. The phase II study will assess the ORR using Bayesian optimal phase 2 (BOP2) design to rule out a 10% ORR in favor of a 30% target ORR, with a power of 80% and two-sided 5% significance level. Accrual: Once MTD is determined, up to 29 evaluable CELsignia test positive subjects will be enrolled to the phase II component of the study and an interim analysis will be performed when the total number of enrolled patients reaches 15. We hope to complete the accrual of patients by July 2022 and to schedule the last patient visit by July 2023. Contact information: For more information or to refer a patient, email blim@mdanderson.org, eahobbs@mdanderson.org**

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# Racial disparities within basal-type breast cancer: Clinical and molecular features of African American and Caucasian obese patients

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**Background: African American breast cancer patients (AA) are diagnosed at a younger age and present more frequently with triple-negative/Basal tumors than Caucasian American patients (CA). High prevalence of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome in AA may confound attempts to evaluate the influence of race on gene expression. Previously we showed that differentially expressed genes (DEGs) between AA and CA within the Basal subtype were related to metabolism, translation, and cell signaling pathways (Nunes et al. 2019). However, AA had higher obesity and T2DM rates than CA, and we were unable to distinguish between the influence of metabolic factors and race. In the current analysis, we aim to dissect these factors by comparing clinical and molecular features of Basal-type breast tumors in obese AA and CA.**

**Methods: The prospective, observational FLEX Registry (NCT03053193) includes stage I-III breast cancer patients who receive 70-gene signature (MammaPrint, MP)/80-gene signature (BluePrint, BP) testing and consent to full transcriptome and clinical data collection. This interim substudy included 50 AA and 96 CA (n=146), enrolled from 2017 to present, all obese by body mass index (BMI, ≥30) and whose tumors were MP High Risk and BP Basal subtype. AA were significantly younger (mean, 55 years) than CA (mean, 60 years, p=0.02); thus, an age distribution-matched subset (n=49 AA, n=49 CA) was added for comparison. Gene expression data were quantile normalized using R limma package; DEGs were compared between groups in the following: (1) all AA (n=50) and CA (n=96), (2) AA and 3 random selections of CA (n=50 pairs), and (3) age-matched AA and CA (n=49 pairs).**

**Results: Clinical factors, including tumor stage, nodal stage, and T2DM status were similar between AA and CA, regardless of age-matching. Most tumors were T1/2 (83% AA, 88% CA) and negative for nodal involvement (77% AA, 68% CA). 94% of tumors from AA and 74% of tumors from CA were grade 3 (p=0.17). Notably, 32% of tumors from AA and 46% of tumors from CA were ER+ by immunohistochemistry. Age-matched AA and CA had a 20% rate of T2DM. 152 DEGs were significant (adjusted p<0.05) in at least one comparison, with 115 genes more highly expressed in AA and 37 genes more highly expressed in CA. Across all comparisons, 6 genes were consistently more highly expressed in AA: *PSPH*, *NOTCH2NL*, *POLR1A,* AC069240.1, *ORAI1*, and *RPS26P10*. Except *ORAI1*, these genes were also found in the previous comparison between Basal-type AA and CA, and the current analysis confirmed 11/16 DEGs previously reported (Nunes et al. 2019). Genes more highly expressed in AA are associated with transcription, angiogenesis, and Notch signaling pathways, as well as breast cancer aggressiveness and treatment resistance.**

**Conclusions: Higher prevalence of obesity/T2DM in AA has been proposed as a key factor to explain racial disparities in breast cancer incidence and prognosis, but the current results suggest that race may influence DEGs more than differences in tumor subtype, age, or metabolic factors. This comparison also emphasizes the importance of matched clinical features for DEG analysis and suggests disparities in AA beyond those attributable to clinical differences within the population. DEGs in AA suggest upregulation of Notch-associated aggressiveness, which may be particularly relevant under hypoxic conditions (e.g., obesity), and pathways associated with stemness, metastasis, and chemotherapy resistance. Notch pathway also interacts with key oncogenic pathways, and future studies will reveal the molecular networks underlying racial disparity in AA and CA breast cancer patients.**

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# Findings from the BonE heAlth eduCatiOn needs assessment (BEACON) study: A survey of bone metastatic breast cancer patients at risk for skeletal-related events

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**PURPOSE Nearly 40% of patients with bone metastases from breast cancer experience a skeletal-related event (SRE) such as fracture, spinal cord compression, bone surgery, or radiation to bone, within 1 year of diagnosis (1). Bone-targeting agents (BTAs) significantly reduce the risk of SREs, but real-world data indicates that only 58% (Commercial) and 67% (Medicare) of eligible metastatic breast cancer patients receive treatment with a BTA (2, 3). We surveyed U.S. patients with bone metastases from breast cancer to ascertain their awareness regarding bone health, to describe the source and amount of bone health education received, and to identify potential gaps in bone health education. METHODS The BonE heAlth eduCatiOn Needs assessment (BEACON) survey was developed through a collaboration between GRYT Health Inc. and Amgen Inc. The online survey consisted of treatment-related questions, cancer-related bone health educational questions, and open-ended questions. U.S. adult patients who consented to participate, with self-reported bone metastasis from breast cancer, were recruited using a unique IRB-approved direct-to-patient approach pioneered by GRYT Health, which incorporates digital outreach, advocacy partnerships, and virtual app and conference-based communication. RESULTS Seventy-four breast cancer patients with bone metastasis completed the online survey. Thirty-eight (51%) had experienced at least one SRE, defined as bone fracture (n=19; 26%), spinal cord compression (n=11; 15%), or radiation (n=28; 38%) or surgery (n=9; 12%) on a bone. While the majority of patients were aware that bones are more fragile in individuals with cancer (n=48; 65%) and that treatments are available to help prevent broken bones caused by cancer (n=50; 68%), fewer understood that bones are more fragile after receiving chemotherapy (n=20; 27%) and radiation (n=28; 38%), or that lifestyle changes can help to prevent broken bones (n=23; 31%). Similarly, when asked about bone protection, the majority of patients had knowledge about calcium and/or vitamin D supplements (n=55; 74%) and BTAs (n=53; 72%), but only 24% had knowledge of lifestyles changes as a bone health protection strategy (n=18). Oncologist and nurses were the most commonly reported HCPs to provide cancer-related bone health information. Patient-reported satisfaction with the amount of bone cancer education was “low” or “moderate” (n=46; 62%); “low” satisfaction was more common in patients not receiving a BTA (n=6/13; 46%) compared to those currently receiving a BTA (n=17/61; 28%). More than half of patients reported receiving either no bone health information (n=8; 11%) or less information than desired (n=35; 47%). CONCLUSION Despite potential limitations in patient recall and population selection biases, there appears to exist important gaps in knowledge and education related to bone health and SRE prevention among metastatic breast cancer patients. Patient- and provider-oriented interventions that increase opportunities for communication and education on bone health may help ensure optimal SRE prevention strategies including appropriate BTA use.**

**REFERENCES 1. Clemons M, Gelmon KA, Pritchard KI, Paterson AH. *Curr Oncol* 2012 Oct; 19(5):259-268. 2. Hernandez RK, Adhia A, Wade SW, et al. *Clin Epidemiol* 2015 Jul; 7:335-345. 3. McGrath LJ, Overman RA, Reams D, et al. *Clin Epidemiol* 2018 Sep; 10:1349-1358.**

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# Solti-1718 NEREA trial: Neratinib in hormone receptor (HR)-positive/HER2-negative HER2-Enriched (HER2-E) advanced breast cancer (BC)

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**Background: HR+/HER2-negative BC represent ~70% of all newly diagnosed breast tumors. BC is a clinically and biologically heterogenous disease where intrinsic subtypes play a role(1-3). Non-luminal subtypes within HR+/HER2-negative disease do not benefit at the same extent from standard of care treatments as the luminal subtypes(1). Thus, other strategies are needed. HER2-E subtype represents approximately 6.6-11.0% of HR+/HER2-negative tumors and is enriched in twice as many cases in metastatic tumors. According to EGF30008 trial, HER2-E advance BC patients despite presenting poor outcomes across treatments, showed more benefit from anti-HER2 therapy. SOLTI-1718 NEREA aims to evaluate whether EGFR/ERBB2 axis inhibition by neratinib improves efficacy in terms of progression-free survival (PFS) in patients with advanced HR+/HER2-negative disease resistant to an endocrine treatment (ET). Methods: SOLTI-1718 NEREA is an open-label, single arm, multicenter and multinational phase II clinical trial following a Simon's 2-stage design with one interim and one final efficacy analysis. Locally advanced or metastatic HER2-E, HR+/HER2-negative BC patients who had recurrence or progression while receiving previous ET will be included. Treatment schedule will consist on neratinib 240 mg daily in combination with ET, with either exemestane, fulvestrant or tamoxifen. All patients will take prophylactic loperamide with an established dosing scheme during the first cycle and on demand in subsequent cycles. Tumor assessments will be performed at baseline and every 8 weeks during the first year, and every 12 weeks thereafter. Interim analysis will be performed after 33 patients are evaluable. If 15 to 27 patients achieved a PFS at 6 months (PFS6), the trial will continue to second stage, otherwise it will be stopped for futility (<15) or efficacy (≥28). A total of 56 evaluable patients will be included in stage I and II. The primary objective is to assess the efficacy of neratinib in combination with ET in HER2-E, HR+/HER2-negative patients in terms of PFS6 by local assessment by the investigator using RECIST v.1.1. Secondary endpoints include clinical benefit rate at 6 months, overall response rate, duration of response, time to response and incidence, duration and severity of adverse events. The Spanish national competent authority approved the study on April 8th 2020. The study will enroll patients in 15 sites in Spain and 3 sites in Portugal. Recruitment will start on July 2020.** **We thank PUMA BIOTECHNOLOGY, INC for their provision of Neratinib and financial contribution to the study.** **References: 1. Finn R, Liu Y, Martin M, Rugo H, Dieras V, Im S-A, et al. Abstract P2-09-10: Comprehensive gene expression biomarker analysis of CDK 4/6 and endocrine pathways from the PALOMA-2 study. Cancer Res. 2018;78:P2-09-10. 2. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375:1925-36. 3. Prat A, Brase JC, Cheng Y, Nuciforo P, Paré L, Pascual T, et al. PAM50 intrinsic subtype in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) treated with exemestane (EXE) in combination with everolimus (EVE) or placebo (PBO): A correlative analysis of the phase III BOLERO-2 trial. European Journal of Cancer. 2018;92:S117-8.**

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**Identifying barriers and facilitators to scalp cooling use through a national survey of the awareness, practice patterns, and attitudes of oncologists toward scalp cooling**

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**Background: Over the past decade, there has been a growing body of literature supporting the use of scalp cooling therapy (SCT), or "cold caps", for reducing hair loss due to chemotherapy. Despite guidelines supporting its use in certain malignancies, and while uptake of SCT has increased across the United States, its use is still not wide spread. While literature has examined the reasons driving patient use of SCT, there is less known about factors influencing physician preferences regarding use of SCT. We hypothesized that degree of physician knowledge of scalp cooling and availability of SCT may contribute to lower patient use of SCT. Oncologists' knowledge, practice patterns and attitudes regarding SCT were examined in this study. Methods: Our 33-question survey was distributed through ASCO's Research Survey Pool to a nationally representative, random sample of 600 physicians and advanced practice providers in medical oncology, surgical oncology, gynecology, and urology, in February 2020. Reminders were sent every 1-2 weeks and the survey closed in June 2020. Main outcome measures included oncologists knowledge of SCT, reported initiating conversations about SCT with patients, and degree of support for the use of SCT. The survey also investigators barriers to their support of SCT and scalp cooling options offered at their facilities. The respondents were a representative mix of provider designation, cancers treated, practice setting (academic v private practice), years in practice, and practice area (urban v suburban v rural). Results:158 oncologists provided responses (158/600, response rate= 26.3%). Only 1.9% had no knowledge of scalp cooling, whereas 45.2% were aware of scalp cooling but were not very familiar with it, and the remaining 52.9% were very familiar with it. While 60% of providers reported being in favor of scalp cooling always/most of the time, only 25.8% initiated discussions about SCT always/most of the time. Providers who reported being very familiar with SCT were significantly more likely to initiate a discussion about SCT all or most of the time with their patients and to be in favor of SCT, compared to those who were not very familiar with SCT (46.3% v 2.9% P= <.0001; 76.8% v 44.3 P=<.0001). Providers who had read literature about SCT in the past two years were also significantly more likely to initiate a discussion about SCT all or most of the time with their patients and be in favor of SCT compared with those who had not read literature in the past two years (38% v 3.9% p value=<.0001;72.0% v 42.3% p value=<.0001). Physicians who worked at institutions that offered machine scalp cooling were more likely to initiate conversations with patients about scalp cooling and be in favor of scalp cooling than those at institutions who do not offer it (49.2%, 11.8% p value <.0001; 78% v 51.6% p value .0001). Financial strain for the patient was the number one physician-reported reason for not initiating SCT conversations with their patients, and for not being in favor of scalp cooling. Conclusion: We found that physician lack of familiarity with scalp cooling was correlated with lower likelihood of discussing or recommending SCT with patients. Providers more familiar with scalp cooling, either through experience, exposure to current literature, or working at an institution that provides machines, were more likely to initiate conversations with patients on scalp cooling and to support the use of SCT. These findings suggest that provider knowledge of and access to scalp cooling therapy significantly influences the advice given to patients with regard to SCT. This study of a nationally representative sample of oncologists has identified provider-specific barriers to broader implementation of SCT.**

2020 San Antonio Breast Cancer Symposium®

Publication Number: PS7-69

# Molecular profiles and clinical-pathological features of Asian early-stage breast cancer patients

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**Background/Objective:** Breast cancer incidence in Asian populations has increased in recent years, and variation in prognosis and tumor subtypes indicates that further study is warranted to characterize these differences and identify actionable targets. Patients of Asian ancestry are underrepresented in US registries, and few studies have characterized molecular profiles for these patients. In the current analysis, we assess clinical, pathological, and molecular profiles from self-reported Asian breast cancer patients (AS), in comparison with age-matched Caucasian (CA) and African American patients (AA), to evaluate the influence of Asian ancestry on differential gene expression in breast tumors.

**Methods:** This meta-analysis included cohorts of self-reported AS, CA, and AA with early-stage, invasive breast cancer (EBC) prospectively enrolled in the US from 2011 to 2020 in FLEX (NCT03053193), MINT (NCT01501487), or IMPACt (NCT02670577) trials. AS were significantly younger (mean, 55 years) than CA (mean, 61 years, p<0.001) or AA (mean, 59 years, p=0.005); thus, an age-matched subset was selected for analyses. 70-gene signature (MammaPrint, MP), 80-gene signature (BluePrint, BP), and clinical-pathological features were compared among age-matched AS (n=103), CA (n=103), and AA (n=100). Whole-genome expression data were quantile normalized using R limma package, and differentially expressed genes (DEGs) were compared among AS (n=90), CA (n=102), and AA (n=96). DEGs with adjusted p-value <0.05 and $\log_2$ fold change > ± 0.5 were considered significant.

**Results:** AS tumors were classified as 59% MP HR, compared with 44% HR in age-matched CA (p=0.08) and 64% HR in age-matched AA (p=0.17). AS had a significantly lower rate of obesity (16%, body mass index ≥30) compared with CA (41%) and AA (67%) (p<0.001). Tumors of AS were predominantly ductal carcinoma (84%), T1 (59%), grade 1 or 2 (70%), lymph-node negative (69%), ER+ (95%), and HER2-negative (89%). Distribution of ER, PR, and HER2 pathology and BP subtypes for AS were similar to CA but significantly different from AA (Table). Histologic tumor type, tumor grade, tumor stage, nodal stage, menopausal status, and frequency of Type 2 diabetes mellitus were not significantly different between AS and CA or AA. Whole-genome expression comparisons revealed 19 significant DEGs between AS and CA, and 45 significant DEGs between AS and AA. Immune-related genes, primarily those involved with B cell responses and signaling, were more highly expressed in AS compared with CA. Expression of genes related to cell-cycle pathways was greater in AS compared with AA.

**Conclusions:** AS were significantly younger and more often pre/peri-menopausal at diagnosis compared with CA and AA, consistent with the literature. Most clinical-pathological factors were similar between age-matched groups, except for the obesity rate, which was significantly lower in AS than in CA or AA. Although not significant, AS had EBC that was more often MP HR than CA and less often HR than AA; studies with larger patient groups will help confirm these trends. The current analysis revealed different underlying gene expression pathways in AS compared with other ethnic groups, which may result in differential clinical outcomes. As genomic profiling data are not widely available for Asian American EBC patients, further analyses are warranted to elucidate these outcomes and identify appropriate therapeutic strategies.

| Pathology and Genomic Results*(unknowns excluded)* | Asian (n=103) | Caucasian (n=103) | African American (n=100) | p-valueAS vs. CA | p-value AS vs. AA |
|---|---|---|---|---|---|
| ER status (IHC) | | | | | |
| ER Positive | 69 (94.5%) | 89 (98.9%) | 73 (80.2%) | 0.125 | 0.010 |
| ER Negative | 4 (5.5%) | 1 (1.1%) | 18 (19.8%) | | |
| PR status (IHC) | | | | | |
| PR Positive | 64 (87.7%) | 81 (90%) | 63 (69.2%) | 0.411 | 0.006 |
| PR Negative | 9 (12.3%) | 9 (10%) | 28 (30.8%) | | |
| HER2 (IHC/FISH) | | | | | |
| HER2 Positive | 3 (4.2%) | 3 (3.4%) | 13 (14.3%) | 0.172 | 0.017 |
| HER2 Negative | 64 (88.9%) | 85 (95.5%) | 77 (84.6%) | | |
| Equivocal | 5 (6.9%) | 1 (1.1%) | 1 (1.1%) | | |
| MP/BP results | | | | | |
| Luminal A | 39 (40.6%) | 51 (53.7%) | 28 (30.4%) | 0.232 | 0.043 |
| Luminal B | 45 (46.9%) | 38 (40.0%) | 42 (45.7%) | | |
| HER2 (MP HR) | 7 (7.3%) | 4 (4.2%) | 5 (5.4%) | | |
| Basal (MP HR) | 5 (5.2%) | 2 (2.1%) | 17 (18.5%) | | |

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# A phase 1, first in human study of adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor in subjects with HER2 overexpressing solid tumors

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**Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies, but not in those with solid tumors. Macrophages are actively recruited into and more abundantly present in the tumor microenvironment (TME) as compared to T cells. Tumor- associated macrophages (TAMs), typically evince immunosuppressive behavior, but when engineered to be proinflammatory, may be an ideal vector to administer adoptive cellular therapy in solid tumors. Furthermore, insertion of a CAR confers on the macrophages the ability to selectively recognize and phagocytose antigen overexpressing cancer cells. CAR macrophages can also potentially interact with, stimulate, and present neoantigens to T cells. Human Epidermal Growth Factor Receptor 2 (HER2) is overexpressed in many cancers, including but not limited to breast and gastroesophageal cancers (Table 1). CT-0508 is a cell product comprised of autologous monocyte-derived pro-inflammatory macrophages expressing an anti-HER2 CAR. In vitro and in vivo studies have shown that CT-0508 leads to cancer cell phagocytosis sparing normal cells, decreased tumor burden and prolonged survival. CT-0508 cells were safe in a semi-immunocompetent mouse model of human HER2 overexpressing ovarian cancer. This is a FIH Phase 1 study to evaluate safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of investigational product CT-0508 on approximately 18 subjects with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2 who have failed available therapies including anti-HER2 therapies when indicated.Filgrastim, will be used to mobilize autologous hematopoietic progenitor cells for monocyte collection by apheresis. CT-0508 cell product will be manufactured, prepared and cryopreserved. Group 1 will receive CT-0508 infusion split over D1, 3 and 5. Subjects will be continually assessed for acute and cumulative toxicity. Dose limiting toxicities will be observed and addressed by a Safety Review Committee. Group 2 will receive the full CT-0508 infusion on D1. Pre and post treatment biopsies and blood samples will be collected to investigate correlates of trafficking, persistence, TME modulation, immune response and safety.**

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# The effect of using adjuvant aromatase inhibitors on cognitive functions in postmenopausal women with hormone receptor-positive breast cancer

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Background:Aromatase inhibitors (AIs) are used for the adjuvant treatment of early breast cancer. Although generally well-tolerated, they have some adverse effects. Because of AIs are used long term in adjuvant treatment, side effects are also very important. Preclinical and a little clinic data indicate that estrogens exert neurotrophic and neuroprotective actions in the brain. So estrogen appears to play an important role in cognitive function and memory. We know that AIs reduce circulating estrogen to very low levels. For this reason, there has been concern that these agents may have a negative effect on cognitive functions. However, this situation is still unclear. The purpose of our study is to evaluate the relationship between duration of treatment and cognitive functions in patients with breast cancer who use AIs in adjuvant therapy.

Methods:Patients diagnosed with breast cancer who use AIs as adjuvant treatment and followed up at the Akdeniz University Medical Oncology Clinic were included. The patients were surveyed for demographic characteristics. Montreal Cognitive Assessment (MoCA) and Standardized Mini-Mental State Examination (SMMT) tests were applied to patients by the same investigator to evaluate their cognitive functions. The total scores of the tests and the orientation, naming, short-time memory, visuospatial functions-executive functions, attention, abstract thinking, language which are the MoCA subscales were evaluated separately. In the Turkish population, the normal range of the MoCA and SMMT tests are 21-30 points and 24-30 points, respectively. Patients were grouped as 0-6, 6-12, 12-24, 24-36, 36 and more months according to the duration of AIs using time. 200 patient's data were analyzed with SPSS package program. This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethnics Committee and was conducted in accordance with declaration of Helsinki.

Results:The median follow-up time was 55.5 months. The median duration of AIs treatment was 36.5 months. The mean age of patients was 61.3 years-old. There was no relationship between duration of treatment and MoCA and SMMT scores which indicates cognitive functions (p>0.05). In addition, no statistically relationship was found in the evaluation of MoCA subscales (p>0.05). As expected, the total MoCA and SMMT scores were affected by

factors such as age, education level, and employment status. Interestingly, although it was not our main purpose, a causal relationship between the presence of hypertension and cognitive decline was shown in our study (p: 0.004). A statistically strong correlation was found between the MoCA and SMMT scores. So, our data are reliable. The duration of treatment with AIs and MoCA and SMMT scores of the patients were given in Table 1.

Conclusions:As a result, despite conflicting results in the literature, we showed with 200 patients that adjuvant treatment with AIs does not affect cognitive functions in post-menopausal hormone receptor-positive breast cancer patients.

Table 1: Relationship between the duration of treatment with AIs and MoCA and SMMT scores

| Duration of AI | n | MoCA*Mean±SD | MoCAMed (min-max) | SMMT**Mean±SD | SMMTMed (min-max) |
|---|---|---|---|---|---|
| 0-6 m | 23 | 19,7±5,2 | 21 (10-26) | 25±4 | 25 (15-30) |
| 6-12 m | 24 | 20,7±5,4 | 21,5 (8-28) | 24,7±3,6 | 24 (16-30) |
| 12-24 m | 14 | 18,2±4,1 | 18,5 (13-27) | 24,3±4 | 25 (13-29) |
| 24-36 m | 29 | 20,3±4,9 | 20 (11-29) | 24,1±3,2 | 25 (17-30) |
| 36 m and more | 110 | 20,3±4,5 | 21 (8-29) | 25±3,2 | 25 (14-30) |
| Total | 200 | 20.1±4,7 | 21 (8-29) | 24,8±3,4 | 25 (13-30) |

AI: Aromatase inhibitors, m: Mounths, n: Number, MoCA: Montreal Cognitive Assessment, SMMT: Standardized Mini-Mental State Examination, SD: Standart Deviation, Med: Median*p: 0.550 **p:0.533

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# Uptake of screening and risk reducing recommendations among women with hereditary breast and ovarian cancer syndrome evaluated at a large urban comprehensive cancer center

**Maria Levitin, Hadeel Assad, Hyejeong Jang, Wei Chen, Nancie Petrucelli and Michael Simon. Karmanos Cancer Institute, Detroit, MI**

**Background: Carriers of pathogenic variants in *BRCA1* and *BRCA2* have an elevated lifetime risk of breast, ovarian and other cancers. Current NCCN guidelines recommend specific screening for early cancer detection and risk reducing surgeries. Previous studies investigating the choices women make following the identification of pathogenic germline *BRCA1* or *BRCA2* variants reveal racial disparities in uptake of recommendations with black patients having lower rates of risk-reducing surgical procedures. We report on screening and prevention practices among 128 women identified with a pathogenic *BRCA1* or *BRCA2* variant at a large, urban comprehensive cancer center in Detroit, Michigan to evaluate racial differences in compliance with screening and prevention practices and to identify potential barriers to guideline-recommended care.**

**Methods: The study population included women evaluated for genetic counseling and testing at the Karmanos Cancer Institute (KCI) from January 1, 2000 through December 31, 2017, who tested positive for a pathogenic variant in *BRCA1* or *BRCA2*. A 54-item mail or telephone-based questionnaire was used to measure sociodemographics, medical history, cancer screening and risk reducing surgery, and cancer worries and fears. The primary and secondary outcomes were rate of risk reducing salpingo-oophorectomy (RRSO) and risk reducing mastectomy (RRM). Univariable logistic regression analyses were performed to identify potential predictors of RRSO and RRM, including race, personal cancer history, age at survey, time interval since *BRCA1* or *BRCA2* diagnosis, education, income, marital status and family history of a pathologic BRCA variant. P values less than 0.05 were considered statistically significant.**

**Results: Of 374 women with pathogenic *BRCA1* or *BRCA2* variants during the study period, 129 (35%) completed the study survey (75 written, 54 telephone) with one ineligible. Of the 128 *BRCA1* or *BRCA2* carriers, 94 (73%) and 76 (59%) underwent RRSO and RRM, respectively and 13 (38%) and 10 (19%) planned to complete those procedures in the future. The rate of RRSO was 72% for white and 71% for black carriers. Black women tended to be less likely to have RRM compared to white women, but this difference did not reach statistical significance (OR 0.5 [95% CI 0.17 - 1.43], p = 0.193). Women who had RRM were 3 times more likely to have RRSO (and vice versa) (OR = 3.28, p = 0.004). With each increasing year of age at the time of genetic counseling, the odds of RRSO increased by 6% (OR = 1.06, p = <0.001). The odds of having had RRM increased with the time interval between genetic diagnosis and the survey by 9% (OR = 1.09, p = 0.043) for each elapsed year. The occurrence of new breast or ovarian cancer since genetic testing had no impact on RRSO, however participants who developed a new ovarian cancer had higher odds of having RRM (OR = 2.63, p = 0.01). There was no association between rate of RRSO or RRM with education level, annual household income, marital status or family history of pathologic BRCA variant.**

**Conclusion: There was no racial difference in the rate of RRSO or RRM between white and black carriers of pathogenic *BRCA1* or *BRCA2* variants. Further multivariable models will assess predictors of risk reducing surgeries and will include assessment of screening practices as well as cancer worries and fears.**

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# Tenacity: A phase 2, multicenter, open-label, single-arm study of AL101 monotherapy in patients with notch-activated triple negative breast cancer

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**Background: There is an urgent need to identify new therapeutic strategies for triple-negative breast cancer (TNBC), a sub-type associated with poor prognosis. The Notch pathway is activated during mammary gland development and has been implicated as a key driver in breast cancer (Collu, 2007). The frequency of Notch mutations or gene rearrangements was reported at 5 to 16% in TNBC tumors and over-expression of Notch was associated with worse overall survival (Robinson, 2011; Stoeck, 2014; Wang, 2015). AL101 is a potent and selective inhibitor of gamma secretase-mediated Notch signaling. In preclinical models, AL101 exerts its antitumor activity through direct inhibition of cell proliferation and indirectly via inhibition of tumor angiogenesis. In TNBC patient-derived xenograft (PDX) tumor models, the presence of activating Notch mutations/fusions correlated with robust response to AL101 monotherapy (ASCO 2019, Abstr 1064). AL101 has been studied in three Phase 1 studies in more than 200 subjects with various cancers (ASCO 2018, Abstr 2515) and is currently being studied in a Phase 2 study for patients with Adenoid Cystic Carcinoma with Notch activating mutations (ACCURACY- NCT03691207). Preliminary data reported from this trial showed clear signs of clinical activity along with a favorable safety profile (ESMO 2019, Abstr 3568). Trial design: The TENACITY study is an open-label, international, multicenter, single arm Phase 2, Simon two-stage optimal design for targeted therapy study of AL101 monotherapy in subjects with Notch-activated recurrent or metastatic TNBC who have received ≤ 3 lines of prior therapy. Patients with stable, asymptomatic CNS metastases are eligible. Notch activation will be determined by Next Generation Sequencing (NGS) of tumor DNA/RNA to detect somatic mutations and gene rearrangements. Target enrollment is 67 subjects. The design will include a lead-in cohort of 6 subjects to ascertain safety of AL101, 6 mg weekly (QW). After the 6th subject completes 4 weeks of therapy, safety will be assessed and subsequent dosage of AL101 will be determined (continue at 6 mg QW versus reduction to 4 mg QW). The primary endpoint is overall response rate (ORR), based on RECIST v1.1 as assessed by the treating investigator. The study design has 80% power with type I error level of 5% to detect an ORR of 23%. Key Secondary endpoints include progression free survival, clinical benefit rate, duration of response, overall survival and quality of life. Study will open to enrollment in July 2020. For further information on this trial, email chen.d@ayalapharma.com or visit clinicaltrials.gov (NCT04461600).**

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# Breast cancer fast-track programme to shorten time between initial symptoms, diagnosis and initiation of treatment. 10 years update

Maria Teresa Martinez, Santiago Moragon, Soraya Simon, Belen Ortega, Jose Vicente Monton-Bueno, Jorge Navarro, Ana Sanmartin, Ana Julve, Elvira Buch, Octavio Burgues, Cristina Hernando, Juan Miguel Cejalvo, Ana Lluch, Begona Bermejo, Andres Cervantes and Isabel Chirivella. Hospital Clinico Universitario of Valencia, Valencia, Spain

Background: Breast cancer (BC) is one of the most serious health problems worldwide. The implementation of screening programs as well as advances in diagnosis and therapeutics have achieved an increase in survival. However, there are patients who do not benefit from screening programs: very young or older than 69 years old patients and interval cancers.The main aim of this breast cancer fast-track program (BCFP) is to reduce the time from the onset of breast cancer signs and symptoms until the beginning of treatment.
· Methods: The programme began in June 2009; we hereby present data from the first ten years (June 2009-June 2019) in the Clinico-Malvarrosa Health Department in Valencia, Spain. Breast surgeons, primary care (PC) physicians, radiologists who are experts in breast cancer and oncology coordinators regularly met to discuss suspected cases of BC, and initially set guidelines with the criteria to be used by PC physicians in order to refer patients to BCFP. On the same day that the PC physician identified a patient with suspected BC, an index card was sent to the oncology coordinator, who reviewed these cases and referred those meeting previously defined criteria to either breast surgeons or breast radiologists.
· Results: 1849 proposals were sent to the hospital from which 1778 patients came to the first visit at the specialist. 312 (16.9%) referred cases were diagnosed with BC. 206 (66%) women were diagnosed of BC in the age range in which screening with mammography is not recommended in our general population (between 45-69 years old). 296 patients had a localized BC (94%) and 16 (6%) an advanced BC. The median time from submission of a proposal until the specialist assessment was 13 days for diagnosed patients, 2 days from the first visit to histopathological diagnosis, and 29 days from the histopathological diagnosis until a treatment is initiated (either oncological or surgical). It took a median of 18 days to confirm the absence of BC in 1466 patients with initial suspicion of it.
• Conclusions: Our data show that the time interval between patient referral by the PC physician to the specialist, diagnosis of breast cancer, and start of therapy can be reduced. We optimized existing resources with no additional costs associated with the implementation of this programme.

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Keywords: Breast Cancer, Clinical Guidelines, Early diagnosis

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# KEYLYNK-009: A phase 2/3, open-label, randomized study of pembrolizumab plus olaparib vs pembrolizumab plus chemotherapy after induction with first-line pembrolizumab plus chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC)

**Hope Rugo[1], Antonio Llombart-Cussac[2], Fabrice Andre[3], Mark E. Robson[4], Shigehira Saji[5], Nadia Harbeck[6], Peter Schmid[7], David Cescon[8], Jin Seok Ahn[9], Rita Nanda[10], Li Fan[11], Jaime Alberto Mejia[11], Vassiliki Karantza[11] and Aditya Bardia[12]. [1]University of California San Francisco Comprehensive Cancer Center, San Francisco, California, CA;[2]Hospital Arnau de Vilanova, Valencia, Spain[3]Faculte de Medicine Paris-Sud XI, Gustave Roussy, Villejuif, France[4]Memorial Sloan Kettering Cancer Center, New York, NY;[5]Fukushima Medical University, Fukushima, Japan[6]Breast Center, Ludwig-Maximilian University of Munich (LMU), Munich, Germany[7]Barts Cancer Institute, London, United Kingdom[8]University of Toronto, Toronto, ON, Canada[9]Sungkyunkwan University College of Medicine, Seoul, Korea, Republic of[10]The University of Chicago, Chicago, IL;[11]Merck & Co., Inc., Kenilworth, NJ;[12]Massachusetts General Hospital, Harvard Medical School, Boston, MA**

**Background: Combination therapy with immunotherapy + chemotherapy is a promising approach for first-line treatment of locally recurrent, inoperable TNBC or metastatic TNBC (mTNBC). However, an unmet need exists for effective and tolerable maintenance regimens in mTNBC to sustain clinical benefit after induction therapy and avoid potential toxicity or resistance to prolonged chemotherapy. The poly (ADP-ribose) polymerase (PARP) inhibitor olaparib has shown efficacy in the maintenance setting for platinum-sensitive ovarian cancer, and the high prevalence of *BRCA* mutations (or "BRCAness") in TNBC may make these tumors particularly sensitive to DNA-damaging agents. Moreover, evidence suggests that combination therapy with olaparib and the PD-1 inhibitor pembrolizumab may provide clinical benefit greater than treatment with either single-agent. KEYLYNK-009 (NCT04191135) is a phase 2/3, open-label, randomized study of pembrolizumab + olaparib or pembrolizumab + chemotherapy after induction with first-line pembrolizumab + chemotherapy in patients with locally recurrent, inoperable TNBC or mTNBC.Methods: This 2-in-1 study design will enroll ~317 patients in phase 2; if a planned efficacy boundary is met, ~615 additional patients will be enrolled in phase 3. Patients eligible for induction therapy must have measurable, locally recurrent, inoperable TNBC that cannot be treated with curative intent or mTNBC previously untreated with chemotherapy in the metastatic setting. All patients will receive up to 6 cycles of induction therapy with pembrolizumab 200 mg Q3W + chemotherapy (carboplatin AUC 2 + gemcitabine 1000 mg/m$^2$ on days 1 and 8 Q3W). Patients eligible for postinduction treatment must achieve complete or partial response or maintain stable disease during induction after 4-6 treatment cycles, with ECOG PS 0/1 and no persistent grade >1 toxicities related to induction therapy (excluding alopecia, hemoglobin ≥9.0 g/dL, grade 2 hyper-/hypothyroidism, or grade 2 hyperglycemia). These patients will be randomized 1:1 to receive pembrolizumab 200 mg Q3W + olaparib 300 mg twice daily or continue pembrolizumab + chemotherapy (same as induction regimen). Olaparib and chemotherapy may continue until progression or unacceptable toxicity; pembrolizumab may continue for ≤35 cycles (including induction), unacceptable toxicity, or progression. Phase 3 dual primary endpoints are PFS per RECIST version 1.1 by blinded independent central review and OS. Secondary endpoints are OS and PFS in patients with *BRCA* mutation, health-related quality of life, and safety. PFS and OS will be estimated using the Kaplan-Meier method, treatment differences will be assessed using a stratified log-rank test, and HRs and 95% CIs will be assessed using a stratified Cox proportional hazard model with Efron's method of tie handling. AEs are monitored until 30 days (90 days for serious AEs) after treatment discontinuation per NCI CTCAE version 5.0. Patient enrollment is ongoing with a total planned enrollment of 932 patients. Contact Hope S. Rugo at hope.rugo@ucsf.edu for additional information.**

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# Fertility preservation in breast cancer patients

Sonia Baulies, Maxim Izquierdo, Marta Devesa, Ignacio Rodriguez, Francesc Tresserra and Rafael Fabregas. Hospital Universitari Quiron Dexeus, Barcelona, Spain

Fertility preservation in breast cancer patients. Aims. - Study in breast cancer patients whether fertility preservation (FP) can affect the onset of the oncological treatment and the pathological response in those patients who underwent neoadjuvant chemotherapy (NAC). Methods. - Patients with breast cancer who underwent fertility preservation and NAC are matched 1:2.45 to non-FP controls by age and date al diagnosis and are studied: -Timing between the diagnosis of breast cancer and the onset of oncological treatment was performed. The following variables were chosen: 1.- Confirmation (pathologic result), 2.- FP visit, 3.- Onset FP, 4.- Final FP, 5. - Onset oncological treatment. The periods analyzed (median in days) were: 1.- Period of FP visit (AP result-FP visit), 2.- Period of FP (FP beginning -FP ending), 3.- Period of onset of oncological treatment (FP ending-onset of oncological treatment), 4.- Overall period (AP result-onset of oncological treatment). - Studying the pathological complete response (Miller Payne scale) among patients with FP compare to non-FP control group was also performed.Results. - 20 patients with FP and NAC are studied between 2010-2019 and were compared to 49 non-FP patients. The median age at diagnosis was 36 years (28-39). The oncological characteristics of the patients are shown in Table 1.The time analysis in FP group was: 1.- Period of FP visit was 4 days (1-26), 2.- the period of FP (start of the stimulation treatment until the recovery of the oocytes) 12 days (7-20), 3.- the Period of onset of oncological treatment 7 days (1-27). The overall period took 26 days (18-51) compared to 17.5 days (1-60) in non-FP group (NS).
Pathological complete response (Miller Payne 5): The pathological complete response was 80% (16/20) in FP group versus 40.8% (20/49) in non-FP group. Analyzed by tumor subtype in FP group, a MP5 was achieved in 72.7% luminal tumor (8/11), 75% positive-HER2 (3/4), 100% triple negative (5/5) versus 19% luminal tumor (4/21), 41.6% (5/12) positive-HER2 and 68.7% triple negative (11/16) in non-FP group. Conclusion. - FP does not delay the onset of oncological treatment and our data do not suggest an adverse impact of FP on pathological complete response to NAC.

Table 1. Oncological patient’s characteristics

| Patient’s characteristics | Cases (%) (range) | |
|---|---|---|
| | FP group | Non-FP group |
| N (patients) | 20 (100) | 49 (100) |
| Median age (years) | 36 (28-39) | 38 (29-41) |
| Tumor stage | | |
| -T1c | 3 (15) | 6 (12.2) |
| -T2 | 16 (80) | 37 (75.6) |
| -T3 | 1 (5) | 6 (12.2) |
| Lymph node involvement | | |
| -Positive | 8 (40) | 21 (42.8) |
| -Negative | 12 (60) | 28 (57.2) |
| Tumor Histology: | | |
| -IDC | 15 (83.3) | 46 (93.8) |
| -ILC | 3 (16.7) | 3 (6.2) |
| -NA | 2 | |
| Hormone Receptors | | |
| -Positive | 14 (70) | 30 (61.3) |
| -Negative | 6 (30) | 19 (38.7) |
| HER2 | | |
| -Positive | 4 (20) | 12 (24.5) |
| -Negative | 16 (80) | 37 (75.5) |
| Tumor subtype | | |
| -Luminal | 11 (55) | 21 (42.8) |
| -HER2+ | 4 (20) | 12 (24.5) |
| -Triple negative | 5 (25) | 16 (32.7) |

**2020 San Antonio Breast Cancer Symposium®**

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# Phase II study of talazoparib, a PARP inhibitor, in somatic *BRCA1/2* mutant metastatic breast cancer

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**Background: PARP inhibitors are currently approved for the treatment of germline *BRCA1/2* mutant metastatic breast cancer, and have been shown to improve outcomes and patient quality of life. However, germline *BRCA1/2* mutations are observed in 5-10% of breast cancer, limiting the applicability of this well-tolerated therapy. We previously identified that a proportion of patients have somatic *BRCA1/2* mutations detected by cell-free DNA (cfDNA), in the absence of germline *BRCA1/2* mutations, and have demonstrated that a PARP inhibitor has therapeutic efficacy in a circulating tumor cell-line developed from a patient with a somatic *BRCA1* mutation (Vidula, CCR, 2020). We hypothesize that PARP inhibitors may be effective in somatic *BRCA1/2* mutant metastatic breast cancer identified via cfDNA.**

**Trial Design: In this phase II investigator initiated single-arm clinical trial, 30 patients with pathogenic somatic *BRCA1/2* mutations detected by cfDNA in the absence of a known germline *BRCA1/2* mutation will be treated with talazoparib, a PARP inhibitor, until development of disease progression or unacceptable toxicity. Patients will undergo serial imaging with CT chest, abdomen, and pelvis and bone scan every 12 weeks, and cfDNA collection every 4 weeks.**

**Eligibility criteria: Patients with metastatic breast cancer that is triple-negative (with receipt of at least 1 prior line of chemotherapy) or hormone receptor positive, HER2 negative (with receipt of at least 1 prior line of hormone therapy or considered inappropriate for hormone therapy) are eligible. Patients must not have received a PARP inhibitor and must not have a germline *BRCA1/2* mutation. Any number of prior lines of therapy are allowed. The somatic *BRCA1/2* mutation detected in cfDNA must be an established pathogenic variant. Adequate organ function is also required.**

**Specific Aims: 1. To determine progression-free survival (PFS) by RECIST 1.1 (Primary endpoint), 2. Objective response rate, 3. Safety and tolerability by NCI CTCAE v 5.0, 4. Serial changes in *BRCA1/2* mutant allelic frequency in cfDNA, and compare pre- and post-treatment cfDNA results with treatment (Exploratory aim).**

**Statistical Methods: Patients are being enrolled in a two-stage design, which provides 80% power to demonstrate that the study treatment is associated with “success” (PFS > 12 weeks) in □53% patients (4% alpha).**

**Accrual: Patients are being screened for enrollment at the Massachusetts General Hospital. This study is also opening at other sites in the U.S. including the University of California San Francisco. (NCT03990896)**

**Funding: This study is funded by Pfizer ASPIRE award and Conquer Cancer Foundation of ASCO Career Development Award.** **Contact information: Neelima Vidula, MD, Massachusetts General Hospital, nvidula@mgh.harvard.edu**

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**Publication Number: PS7-72**

**Will it work? Opportunities for physicians and employers to assist breast cancer patients in addressing non-medical barriers to care**

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**Background: Advances in cancer treatments have improved the prognosis for many people and enabled some to work during treatment. Although physicians have conversations with cancer patients about care preferences, conversations often do not include the impact of treatment on the non-medical aspects of patients' lives. In particular, work disruption has the potential to exacerbate existing hardships and has been proven to be a significant barrier to care and attaining optimal wellbeing. For many patients, returning to work is viewed as a key milestone. This study evaluated the impact of breast cancer on work activities, return-to-work decision-making, and the opportunity for employers to accommodate and support employees with cancer. Methods: A cross-sectional survey of patients served by Patient Advocate Foundation in 2018-2019. Descriptive statistics were calculated using frequencies for categorical variables. Results: Of 677 breast cancer patients surveyed, >6-months of treatment-related work absence was experienced by 53%; 32% utilized FMLA; 32% short-term disability; 40% unpaid leave. One fifth retired early; 23% reduced hours worked; 8% changed careers and 66% discussed treatment impact with HR. Almost two-thirds of employers (60%) made reasonable adjustments to work duties; 68% were supportive during the entire illness. Half (51%) of the patients reported that their provider initiated a conversation about the impact of treatment on their ability to work; 54% considered work impact when deciding on their first treatment; and 53% reported that their treatment 'always' or frequently' reduced their ability to work. Work disruption had a negative impact on monthly income; 68% of patients stating that it had 'a lot of impact' and 46% reported lost wages >$750. Survey respondents were 65% Caucasian, 20% African American, and 15% Other or Undisclosed. Nearly half (44%) were <55 years old, and 77% reported income <$48,000. Two thirds (63%) reported full time employment, 73% age <60 years and half reported stage 0-2 (49%) at time of diagnosis; 47% were employer insured. Discussion: Patients with cancer struggle to afford needed medical care alongside daily financial obligations due to rising healthcare costs. It is important for provider care conversation to expand beyond just the decision around clinical care. Employers were reported to be supportive and flexible about return to work and most cancer survivors in this study were satisfied with their employers' responses to their needs. The large percentage of patients that did not discuss the impact of cancer treatment on work activities may indicate their reluctance to have these conversations with HR and highlight how the threat of reduced financial status may change treatment decisions. Conclusions: Health system-level solutions will require person-centered policies focused on expanding shared decision making by integrating what matters to patients in the context of their lived experience with illness. Care conversations must incorporate all aspects of the patient's situation and preferences to ensure the alignment of treatment, personal and financial goals. It is imperative that clinicians recognize and discuss the impact of treatment choices on a patient's ability to work, as employment changes place patients at increased risk for negative financial impact. Similarly, employers should develop and implement worksite wellness policies that encourage (and protect) patients facing changes in health that impact work and support flex scheduling for persons with chronic conditions. The adoption of such policy could minimize the need for extensive time off or loss of job. This in turn could avert lost wages, lost productivity, and early retirement of employees, as well as potentially decreasing the costs associated with employee turnover.**

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# A phase II study to evaluate the efficacy and safety of pembrolizumab plus carboplatin in BRCA-related metastatic breast cancer: PEMBRACA trial

**Laura Cortesi[1], Marta Venturelli[1], Federica Caggia[1], Luigi Marcheselli[1], Annita Gozzi[1], Alberto Zambelli[2], Valentina Guarneri[3], Antonino Musolino[4], Elena Fiorio[5], Giancarlo Bisagni[6], Andrea Rocca[7], Valentina Arcangeli[8], Elisabetta De Matteis[9], Sergio Rizzo[10] and Andrea Michelotti[11]. [1]Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy[2]Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy[3]University of Padova, Padova, Italy[4]University Hospital of Parma, Parma, Italy[5]Azienda Ospedaliero Universitaria Integrata, Verona, Italy[6]Azienda USL-IRCCS, Reggio Emilia, Italy[7]Scientific Institute Romagnolo for the Study and Treatment of Cancer (IRST) IRCCS, Meldola, Italy[8]Ospedale Infermi, Rimini, Italy[9]Vito Fazzi Hospital, Lecce, Italy[10]University of Palermo, Palermo, Italy[11]Azienda Ospedaliero Universitaria Pisana, Pisa, Italy**

**Background**
**Considering the high proportion of tumor-infiltrating lymphocytes (TILs) in BRCA-related breast cancer, we expect that PD-1 pathway is highly expressed and PD-1 antagonist pembrolizumab could provide clinical activity in this kind of tumor. Furthermore, BRCA-related breast cancers are known to be more sensitive to platinum-derived drugs. Thus the association between Pembrolizumab and Carboplatin in metastatic BRCA-related breast cancer seems to be active in this setting of patients. This study will evaluate the safety and the efficacy of Pembrolizumab associated with Carboplatin in BRCA mutated or with unknown mutations metastatic breast cancer patients.**
**Study and Statistical DesignThis is a national multicenter two-stage single arm phase II study, enrolling BRCA mutated or with unknown mutations metastatic breast cancer patients. The sample size has been estimated by using the two-stage Simon's design. In the first stage, 20 subjects will be enrolled. If, after first stage ≤11 responses (r1) will be observed, accrual will terminate and the experimental regimen will be rejected. Otherwise if 12 or more responses will be seen then the accrual will continue to the second stage of an additional 33 subjects (total, 53 subjects). At the second stage if 33 or less responses out of 53 subjects will be observed the treatment will be rejected. With the null hypothesis (p0) being equal 0.55 with a type I (alfa) error of 0.10 (10%) and a type II (beta) error of 0.20 (power=80%) and the alternative hypothesis (p1) is 0.70, (response rate 70%), we expect to reach an overall response rate (ORR) ≥ 70% by the combination of Pembrolizumab plus Carboplatin. We also expect to reach a median Time to Progression (TTP) and Overall Survival (OS) of five and fifteen months respectively. The Disease Control Rate (DCR) will be expected as ≥ 80% by the combination of Pembrolizumab plus Carboplatin**
**Study TreatmentCarboplatin at area under the time-concentration curve 6 (AUC 6) intravenously once every 3 weeks in combination with Pembrolizumab 200 mg intravenously every 3 weeks will be administered for six courses and then only Pembrolizumab alone will continue until occurrence of unacceptable toxicities or disease progression.**
**Eligibility CriteriaIn order to be eligible for participation in this trial, the subject, aged ≥ 18 years, must have metastatic confirmed breast cancer, with a disease progression by radiological techniques within 12 months prior to signing informed consent, and a documented mutation in *BRCA1* or *BRCA2* genes that is predicted to be deleterious or suspected deleterious or with unknown significance. The subject must have measurable disease based on RECIST 1.1 and have a performance status of 0 or 1 on the *Eastern Cooperative Oncology Group (*ECOG) Performance Scale. Prior chemotherapy with anthracyclines and taxanes has to be administered in neoadjuvant or adjuvant setting. In case of luminal tumors hormonal treatments for advanced disease can be administered before. The life expectancy must be greater than 3 months and the subject must demonstrate adequate organ function by screening labs performed within 10 days of treatment initiation.**
**Objectives and HypothesisThe primary end-point will be the ORR, evaluated according to RECIST criteria. Secondary objectives will be the TTP, the duration of response (DOR ), the DCR, and the OS. The safety of the combination will be evaluated according to the worst toxicity grade reported throughout the whole treatment period.The Exploratory Objective will be the evaluation of ORR, TTP, DOR, and DCR based on irRECIST. Biological parameters of CD8/TILs and PD-L1 will be considered in the metastatic biopsy.**
**Target AccrualThe first subject was enrolled in January 2019 and recruitment is ongoing. Enrollment of the first 20 subjects is expected to complete in Q2 2021.**

**2020 San Antonio Breast Cancer Symposium®**

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**Late presentation and suboptimal treatment of breast cancer among Syrian refugees. A call for systematic international action**

**Hikmat Abdel-Razeq, Faris Tamimi, Maryam El-Atrash, Baha' Sharaf, Razan Mansour and Rawan Mustafa. King Hussein Cancer Center, Amman, Jordan**

**Introduction: The Syrian crisis, started in 2011, has had a profound impact on the entire region. Jordan, a low-middle income country with limited resources is ranked first in the region in relation to the number of refugees hosted. The latest national census reported over a million Syrian refugee in the country. Lack of sufficient funding, from either the host country or international refugee aid organizations, may lead to suboptimal treatment of cancer patients. The total number of Syrian cancer patients registered at King Hussein Cancer Center (KHCC) hospital-based cancer registry was 510 patients. Local and regional funds covered the treatment of almost two thirds of these patients. In this study, we report on patterns of presentation and management of Syrian patients with breast cancer treated and followed at our institution. Patients and methods: This is a retrospective data collection of Syrian refugees who presented to our institution with a diagnosis of breast cancer from January 2011 to December 2019. Adult patients aged 18 year or older with pathologically-confirmed diagnosis of breast cancer were required to have at least one medical encounter. Data was collected from the electronic medical records for eligible patients. Management was compared against our approved clinical practice guidelines (CPG). Results: During the study period, a total of 147 adult Syrian refugee patients with breast cancer had at least one medical encounter at our institution. All were females and median age (range) at diagnosis was 47 (21-84) years. Thirty-four (23.1%) patients did not complete the work up and missed subsequent visits and will be excluded from analysis. The remaining 113 patient had biopsy proven invasive (n=110) or ductal carcinoma in situ (n=3) and continued their treatment and follow up; 39 (34.5%) had early stage disease, 48 (42.5%) locally advanced and 26 (23.0%) presented with metastatic disease. Estrogen receptors (ER) were positive in 75 (66.4%) patients while 63 (55.8%) had positive progesterone receptor (PR). HER2 positive disease was documented in 31 (27.4%) while 18 (15.9%) patients had triple negative disease. Eighty (70.8%) patients underwent surgery, 60 (75.0%) were at KHCC. The median time from first encounter to surgery for those who underwent upfront surgery was 2 months. Breast conserving surgery (BCS) was done for 27 (45.0%). However, only 11 (35.4%) of the 31 patients eligible for breast reconstruction underwent such procedure. Adjuvant radiation was given to 49 (77.7%) of 63 candidate patients and some were delayed. Systemic treatment with chemotherapy was given to 103 patients; as neoadjuvant (n=37, 35.9%), adjuvant (n=45, 43.7%) and palliative (n= 21, 20.4%). Among the 31 patients with HER2-positive disease, only 11 (35.5%) patients received it. Additionally, only 3 (30.0%) of 10 patients who were candidates for CDK4/6 inhibitors received it. Genetic Testing and counselling were also suboptimal, only 8 (12.3%) of 65 candidate patients underwent genetic testing. Across all needed treatment, 37 (32.7%) patients had significant deviations when judged against our institutional CPGs. Conclusions: Syrian refugees with breast cancer had late presentation and more advanced-stage disease. They are more likely to receive delayed and suboptimal surgeries, genetic counseling and systemic therapy highlighting the urgent need for international systematic approach for cancer care among such unprivileged population.**

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# Associations and spectrum of genetic mutations in younger patients with breast carcinoma and additional malignancies

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Background: The development of cancer is understood to be a series of molecular events causing uncontrollable cell growth and malignant behavior. Primary breast carcinoma is associated with a number of molecular alterations that may also be implicated in the molecular deregulation underlying other malignancies. In addition, underlying germline genetic mutations have been clearly associated with the development of breast carcinoma (BC) in young patients. Increased risks for the development of additional malignancies following or preceding breast cancer have been reported, however, specific associations and genetic mutations remain unclear, especially in young patients.Materials and methods: Our patient cohort consisted of young women (<!--=40 years of age) at our institution who were diagnosed with BC between May 2009 to May 2018. Retrospective review of electronic medical records was performed in order to identify the occurrence of a second neoplasm either before or after a BC diagnosis and germline genetic alterations were recorded.Results: 13 out of 437 young women were diagnosed with either a second malignancy or high-grade dysplasia. The clinico-pathologic characteristics of these patients are summarized in the Table 1. There was almost an equal distribution of these neoplasms occurring either before or after the diagnosis of BC. 6 tumors were diagnosed 10 months to 7 years after the diagnosis of BC, whereas 5 tumors diagnosed 1 month to 20 years earlier. Interestingly, only 2 cases were concurrently diagnosed and both of these were malignant phyllodes tumors of the breast.On studying the pathologic characteristics of the breast tumors in young patients with a second malignancy, the majority of these cancers were either grade 1 or grade 2 (10/13) while 3/13 were grade 3 carcinomas. Additionally, 10/13 of the cases were positive for estrogen receptor and negative for HER2, 2 cases were triple negative, and hormone receptor status was unknown in one case. 10/13 carcinomas were treated with mastectomy and the remaining 3 by lumpectomy. Lymph nodes were examined in 9 cases and one or more lymph nodes were found to be positive in 3 cases. Germline mutations panel (limited or complete) were available in 12 cases. Germline genetic alterations were found in three of the patients (3/12), as summarized in the Table 1. These included BRCA1 (2/12) and PTEN (1/12). Although variant of uncertain significance (VUS) mutations were also recognized in other genes e.g. ATM (1/12), SMAD4 (1/12) and MSH2 (1/12), those were not included in our analysis due to lack of current knowledge regarding their clinical significance.Additionally, 51 benign neoplasms were also diagnosed (e.g. benign nevi, thyroid adenomas, benign ovarian neoplasms, etc.). Nearly half (20/51) involved the female genital tract (uterus, cervix, or ovaries), 17 the skin and soft tissues, 4 the gastrointestinal tract, 8 the thyroid, and 1 the brain.Conclusions: Young women with BC are likely to have an underlying genetic predisposition for the development of BC and other malignancies. Although BRCA1 was the most common mutation observed, germline mutations of other genes were also seen. Therefore, genetic counselling, testing, and increased surveillance are extremely useful tools in managing the development of other associated malignancies in young women with BC.

Table 1: Summary of clinico-pathologic characteristics of BC with second malignancies

| No. | Type of carcinoma | Grade | Prognostic markers | Associated in-situ carcinoma | Age at diagnosis | Secondary diagnosis | Timeline of second diagnosis | Initial management of BC | Lymph node status | Genetic testing results |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Invasive lobular carcinoma | 1 | Unknown | Lobular carcinoma in situ | 39 | Malignant phyllodes tumor | Concurrent | Mastectomy | Negative | Unknown |
| 2. | Invasive ductal carcinoma | 3 | Triple negative | Ductal carcinoma in situ | 36 | Squamous cell carcinoma, esophagus | 7 years later | Mastectomy | Negative | BRCA1+ |
| 3. | Invasive ductal carcinoma | 3 | Triple negative | None | 38 | High grade serous carcinoma, ovary | 5 years later | Mastectomy | One lymph node positive | BRCA1+ |
| 4. | Invasive ductal carcinoma with mucinous features | 1 | Estrogen receptor+/Progesterone receptor+/HER2- | Ductal carcinoma in situ | 33 | Gastrointestinal stromal tumor, jejunum | 7 years later | Mastectomy | Negative | Negative |
| 5. | Invasive ductal carcinoma | 2 | Estrogen receptor+/Progesterone receptor+/HER2- | Lobular carcinoma in situ | 31 | Malignant phyllodes tumor | 7 years earlier | Mastectomy | Negative | Negative |
| 6. | Invasive ductal carcinoma | 2 | Estrogen receptor+/Progesterone receptor-/HER2- | Ductal carcinoma in situ | 37 | Complex endometrial hyperplasia with atypia and leiomyoma with Fumarate hydratase features | 6 years later | Mastectomy | Not performed | Negative |
| 7. | Invasive ductal carcinoma | 2 | Estrogen receptor+/Progesterone receptor+/HER2- | None | 36 | Hodgkin disease | 20 years earlier | Mastectomy | Negative | Negative |
| 8. | Invasive ductal carcinoma | 3 | Estrogen receptor+/Progesterone receptor+/HER2- | Ductal carcinoma in situ | 29 | High grade squamous intraepithelial lesion | 1 year earlier | Mastectomy | One lymph node positive | Negative |
| 9. | Invasive ductal carcinoma | 2 | Estrogen receptor+/Progesterone receptor+/HER2- | Ductal carcinoma in situ | 36 | High grade squamous intraepithelial lesion | 1.5 year later | Mastectomy | One lymph node positive | Negative |
| 10. | Invasive ductal carcinoma | 2 | Estrogen receptor+/Progesterone receptor+/HER2- | Ductal carcinoma in situ | 36 | High grade squamous intraepithelial lesion | 1 month earlier | Lumpectomy | Negative | Negative |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **11.** | **Invasive ductal carcinoma** | **1** | **Estrogen receptor+/Progesterone receptor+/HER2-** | **Ductal carcinoma in situ** | **38** | **Endometrioid adenocarcinoma** | **10 months later** | **Lumpectomy** | **Not performed** | **Cowden syndrome (PTEN gene)** |
| **12.** | **Invasive mucinous carcinoma** | **1** | **Estrogen receptor+/Progesterone receptor+/HER2-** | **Ductal carcinoma in situ** | **41** | **Papillary thyroid carcinoma** | **14 years earlier** | **Lumpectomy** | **Not performed** | **Negative** |
| **13.** | **Invasive tubular carcinoma** | **1** | **Estrogen receptor+/Progesterone receptor+/HER2-** | **Ductal carcinoma in situ** | **37** | **Malignant phyllodes tumor** | **Concurrent** | **Mastectomy** | **Negative** | **Negative** |

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# A phase 2, open-label study of bintrafusp alfa monotherapy in patients with *HMGA2*-expressing triple-negative breast cancer

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**Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with few targeted treatment options and a poor prognosis. Despite approvals of the anti-PD-L1 monoclonal antibody (mAb) atezolizumab in combination with *nab*-paclitaxel for unresectable, locally advanced/metastatic TNBC that expresses PD-L1 (tumor-infiltrating immune cells ≥1% of tumor area), many recent studies of other anti-PD-(L)1 therapies in advanced TNBC have shown limited efficacy, likely due to intrinsic therapeutic resistance. Transforming growth factor β (TGF-β), which promotes cancer progression by inducing angiogenesis, fibrosis, and epithelial-mesenchymal transition (EMT), may attenuate the efficacy of or promote resistance to anti-PD-(L)1 therapies. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. In a cohort of 33 patients with heavily pretreated, advanced TNBC that progressed during/after first-line therapy, bintrafusp alfa was safe and resulted in antitumor activity (NCT02517398). Exploratory biomarker analysis showed that high mobility group AT-hook 2 (*HMGA2*) expression was 32-fold higher in tumor samples from patients who experienced disease control than from patients who had progressive disease in that cohort. Elevated expression of HMGA2, a protein associated with TGF-β signaling and a known regulator of EMT, is associated with metastasis and poor survival in breast cancer. We present the study design of a phase 2 trial to evaluate the efficacy and safety of bintrafusp alfa in patients with pretreated metastatic TNBC that expresses high levels of *HMGA2*. Trial Design: This phase 2, multicenter, open-label study will evaluate bintrafusp alfa monotherapy in patients with *HMGA2*-expressing TNBC that progressed on ≥1 line of systemic therapy for their metastatic disease. Patients will receive bintrafusp alfa 1200 mg every 2 weeks until confirmed progression, unacceptable toxicity, or trial withdrawal. Eligibility Criteria: Patients must have histologically confirmed TNBC defined by ASCO-CAP guidelines (estrogen receptor: immunohistochemistry [IHC] <1%; progesterone receptor: IHC <1%; human epidermal growth factor receptor 2: in situ hybridization nonamplified or IHC 0/1), high tumor *HMGA2* expression, ECOG performance status ≤1, and measurable disease by RECIST 1.1. Patients must have experienced disease progression while receiving the most recent therapy prior to enrollment. *HMGA2* expression will be centrally determined on archival or fresh tumor tissue by RT-PCR. Prescreening for *HMGA2* expression while receiving preceding treatment is allowed; a fresh tumor biopsy prior to study entry may be requested for exploratory biomarker analysis. Patients with prior exposure to immunotherapy are not eligible. Specific Aims: The primary endpoint is independent review committee-assessed objective response rate per RECIST 1.1. Key secondary endpoints include safety, duration of response, durable response rate, progression-free survival, and overall survival. Additional exploratory biomarker characteristics will also be investigated. Statistical Methods: Descriptive statistics, including mean, median, standard deviation, and range, will be used to characterize continuous variables. Frequency counts and percentages will be used to characterize categorical variables. Accrual: Planned enrollment is 29 patients.** **Contact Information: Leisha A. Emens, MD, PhD Email: emensla@upmc.edu**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS7-75**

# Why do women experience a delay to chemotherapy? A qualitative analysis

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**Background: (Neo) Adjuvant chemotherapy decreases the risk of recurrence and improves overall survival among breast cancer patients, however, delays in chemotherapy initiation are associated with adverse outcomes. While the determinants of such delays are not clearly understood, delays are more likely to occur in those: with additional comorbidities, belonging to a low social economic status, without a partner, enrolled in public health insurance, or who identify as Latino/Hispanic or Black/African Americans. The causes of disparities in the delivery of care among breast cancer patients are complex and include interrelated social, economic, cultural, environmental, and health system factors. The goal of Project Start was to conduct a qualitative investigation to assess and identify the multilevel factors contributing to the barriers and facilitators of initiating chemotherapy in the context of breast cancer treatment.**

**Methods: We enrolled English or Spanish speaking women, ≥18 years, diagnosed with primary invasive breast cancer who experienced a ≥ 60 days delay to chemotherapy initiation, whether adjuvant or neoadjuvant (determined from the date of surgery or the date of histopathologic diagnosis). Participants were identified through electronic medical record review and approached in clinic to participate. Semi-structured interviews were conducted in-person or over the phone to explore participants' perceptions about individual, community, and system level barriers and facilitators contributing to starting chemotherapy. Interviews were audio-recorded, transcribed verbatim, and coded using the *Sort and Sift, Think and Shift* qualitative approach to identify concepts and topics within and across transcripts. Participants completed brief questionnaires collecting sociodemographic characteristics, health literacy and numeracy, physician trust, and social support to supplement the qualitative data. Quantitative data were summarized using descriptive statistics.**

**Results: Seventeen participants completed semi-structured interviews and questionnaires (mean age 49.9 years; range 30-70 years). Participants identified as: Latina (n=7); Black (n=2); and non-Latina White (n=8). Most completed interviews in English (n=15) and over half had lower educational attainment (i.e., middle school, high school, associate's degree; n=10). While the interview included questions addressing chemotherapy delays, explicit insight into chemotherapy delay was rare among participants. When discussing their process to chemotherapy, participants described barriers and facilitators at the patient, family, medical, and community levels contributing to their timeline to start chemotherapy. At the patient level, participants discussed their fear and anxiety, the command over their diagnosis, and the importance of playing an active role in treatment. Within the family realm, participants described their family roles (e.g., caregiving, income), treatment costs, and the need for emotional support (e.g., not shutting family members out). Participants sought out and relied heavily on support from their communities (e.g., churches, other patients, survivors). Finally, patients described their reliance on the medical team for information, the trust needed to navigate their treatment process, and the challenge of managing information associated with their treatment.**

**Conclusions: Women expressed the importance of managing individual stressors, family roles and support, medical information, and community support. Activating women to be engaged in the treatment process at multiple levels appeared to facilitate initiating chemotherapy. Multilevel interventions that engage the patient, family, medical team, and community may provide the supports to enable the initiation of timely chemotherapy.**

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# Irene study: Phase 2 study of incmga00012 (retifanlimab)and the oncolytic virus pelareorep in metastatic triple negative breast cancer

**Mridula George[1], Nicole Williams[2], Maryam Lustberg[2], Coral Omene[1], Nancy Chan[1], Nisha Ohri[1], Maria Kowzun[1], Lindsay Potdevin[1], Firas Eladoumikdachi[1], Shicha Kumar[1], Robert Wesolowski[2], Grey Wilkinson[3], Danielle Tang[1], Sinae Kim[4], Shridar Ganesan[1], Bruce Haffty[1] and Deborah Toppmeyer[1]. [1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ;[2]Ohio State University Comprehensive Cancer Center, Columbus, OH;[3]Oncolytics Biotech, Calvary, AB, Canada[4]Rutgers School of Public Health, New Brunswick, NJ**

**Background: Triple negative breast cancer (TNBC) is an aggressive subtype accounting for 15% of all breast cancer cases. It is characterized by larger tumor size, higher grade, early peak of recurrence, and a worse 5-year overall survival rate compared to other breast cancer subtypes. Chemotherapy serves as the backbone for the treatment of metastatic TNBC. Treatment with immunotherapy in combination with Abraxane, a taxane-based chemotherapy, is of benefit only in PD-L1 positive tumors, which represents a minority of the patients. Pelareorep, a proprietary isolate of the unmodified, replication competent reovirus type 3 Dearing (T3D), has been shown to upregulate PD-L1 expression in tumor and inflammatory cells and downregulate intra-tumoral regulatory T-cells in the tumor microenvironment in pre-clinical and early clinical studies. Retifanlimab is a PD-1 inhibitor currently in development. The rationale for this clinical study is that the administration of pelareorep will prime the tumor microenvironment for enhanced tumor response to PD-1 inhibitor retifanlimab.Trial design: This is a phase II multi-site single-arm clinical trial to study the combination of PD-1 inhibitor retifanlimab and the oncolytic virus Pelareorep in metastatic triple negative breast cancer who have progressed on chemotherapy. Eligible patients will receive pelareorep $4.5x10^{10}$ $TCID_{50}$ /day IV, on Days 1, 2, 15 and 16 and retifanlimab 500mg IV on day 3 of every 28-day cycle until disease progression or unacceptable toxicity. Patient will be monitored clinically and radiologically for response to treatment. Tumor tissue, stool and blood samples will be collected while on treatment to evaluate changes in PD-L1 expression, gut microbiome and inflammatory cells induced by the study drugs. (ClinicalTrials.gov Identifier: NCT04445844) Eligibility criteria: Eligible patients will include premenopausal/postmenopausal women with metastatic TNBC who have previously received 1-2 prior lines of chemotherapy in the metastatic setting. ECOG PFS 0-2. Specific aims: Primary endpoint will be objective response rate (ORR) and safety, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0. The secondary end-points will be progression free survival (PFS), overall survival (OS) and duration of response (DOR) and quality of life measures using EORTC QLQ-C30. Statistical methods: Simon's optimal 2-stage design will be used to calculate sample size. In the first stage, 14 patients will be accrued. If there are 1 or fewer responses in these 14 patients, the study will be stopped. Otherwise, 11 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 4 or more responses are observed in 25 patients. The first 6 patients will be enrolled in a staggering interval for the safety run-in phase of the study. Accrual: The study will enroll up to 25 patients at Rutgers Cancer Institute of New Jersey and Ohio State University Comprehensive Cancer Center Contact information: Mridula George, MD Email: mridula@cinj.rutgers.edu**

**2020 San Antonio Breast Cancer Symposium®**

**Publication Number: PS7-76**

# Association between metabolic syndrome and immunohistochemical profile at breast cancer diagnosis in postmenopausal women

**Andre Hideo Motoki, Daniel de AraujoBrito Buttros, Ana LuisaCamolezi Gaspar, Eduardo Carvalho Pessoa, Benedito de Sousa Almeida Filho, Jorge Nahas Neto, Heloisa de Luca Vespoli and Eliana AguiarPetri Nahas. Faculdade de Medicina de Botucatu, Botucatu, Brazil**

**Objective: To evaluate the association between metabolic syndrome (MetS) and the immunohistochemical profile of breast cancer (BC) in postmenopausal women.Methods: This cross-sectional cohort study included 189 women, aged 45-75 years and amenorrhea > 12 months, with newly diagnosed BC and no previous cancer treatment. Clinical, anthropometric and biochemical (total cholesterol, HDL, LDL, triglycerides, and glucose) data were collected, as well as data on BC (histopathology, grade, tumor stage, lymph node metastasis hormone status (estrogen receptor, ER; progesterone receptor, PR; human epidermal growth factor receptor 2, HER-2), and epithelial proliferative activity (Ki-67). Tumors were divided into five subtypes: luminal A, luminal B HER-2 negative, luminal B HER-2 positive, non-luminal HER-2, and triple negative. Women with three or more of the following criteria were diagnosed with MetS: waist circumference ≥ 88 cm; triglycerides ≥ 150 mg/dL; HDL-cholesterol < 50 mg/dL; blood pressure ≥ 130/85 mmHg; glucose ≥ 100 mg/dL. The Student t-test, gamma distribution (asymmetric variables), chi-square test, and logistic regression (odds ratio, OR) were used for statistical analysis.Results: Sixty-three (33.3%) of the 189 patients had MetS at the time of diagnosis. The mean age, time since menopause and BMI were 59.0 ± 10.6 years, 11.4 ± 9.6 years and 28.5 ± 5.5 kg/m$^2$, respectively, without difference between women with and without MetS (control). Women with MetS had a higher frequency of tumors ≤ 2 cm than women without MetS (49.2% vs 31.8%) (p=0.038). There were no differences in histological grade, staging, or axillary lymph node metastasis (p>0.05). The proportion of PR-positive (p=0.006), HER-2-negative (p=0.034), and luminal B HER-2-negative tumors was higher among patients with MetS (p=0.038) compared to women without MetS (79.4% vs 61.8%, 89.9% vs 78.6% and 44.5% vs 27.8%, respectively). Multivariate analysis adjusted for age, time at menopause and BMI showed a higher risk for luminal B HER-2-negative tumors among women with MetS (OR 2.00, 95% CI 1.03-3.89), obese patients (OR 2.03, 95% CI 1.06-3.90), and women with abdominal obesity (OR 1.96, 95% CI 1.01-4.03). The other BC subtypes were not associated with MetS or its components.Conclusion: In postmenopausal women with newly diagnosed BC, the presence of MetS was associated with a more favorable immunohistochemical profile of BC, such as a smaller tumor size, PR-positive and HER-2-negative status, and the luminal B tumor subtype.**

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# Combination ipatasertib and atezolizumab to prevent recurrence in triple negative breast cancer(TNBC): A phase II single arm trial

**Elizabeth Mittendorf[1], Sara Tolaney[1], Paul Wileyto[2], Michelle DeMeo[1], Hope Rugo[3], Rita Nanda[4], Ingrid Mayer[5], Ben Park[5], Heather MacArthur[6] and Angela DeMichelle[2]. [1]Dana-Farber/ Brigham and Womens Cancer Center, Boston, MA;[2]University of Pennsylvania, Philadelphia, PA;[3]University of California San Francisco, San Francisco, CA;[4]University of Chicago, Chicago, IL;[5]Vanderbilt University, Nashville, TN;[6]Cedars Sinai Medical Center, Los Angeles, CA**

**Background: TNBC patients with residual disease after neoadjuvant chemotherapy (NAC) have high recurrence rates. Targetable mechanisms likely responsible for NAC resistance must therefore be identified to identify new therapeutic options. Alterations in the PI3K/mTOR pathway as well as expression of the immune checkpoint PD-L1 have emerged as potential targets, with significant frequency of alteration in TNBC. Importantly, the AKT inhibitor ipatasertib (ipat) and the anti-PD-L1 antibody atezolizumab (atezo) have demonstrated activity against TNBC. Recent data suggests that the presence of circulating tumor cell-free DNA (cfDNA) following NAC correlates with residual disease and a higher recurrence risk. We have hypothesized that combination therapy with ipat and atezo will target micrometastatic disease, as determined by the presence of cfDNA after NAC, in TNBC patients. Trial design:Open label single-arm phase II study to evaluate combination therapy with ipat and atezo, in TNBC patients with detectable cfDNA after completion of NAC, definitive surgery, and adjuvant radiation and/or chemotherapy. Eligible patients will receive: atezo [840mg IV days 1 and 15 and ipat [400 mg orally daily on days 1-21, followed by one week off] in a 28-day cycle for 6 cycles; cfDNA will be evaluated after 3 and 6 cycles. Biomarkers including PD-L1 expression on tumor cells or infiltrating immune cells in the primary tumor or PD-L1 expression on circulating tumor cells will be assessed. Eligibility criteria:Patients ≥ 18 yrs of age with pathologically confirmed residual invasive TNBC (ER and PR negative defined as <10% of cells expressing ER/PR by local assessment; HER2 negative according to ASCO/CAP guidelines) following NAC with evidence of cfDNA after completion of all local and systemic neoadjuvant and adjuvant therapy. Patients must enroll within 12 months of last therapy (definitive breast surgery, radiation and/or all intended adjuvant therapy). Prior treatment with immunotherapeutic agents is allowed. Specific aims:The primary objective is to evaluate the efficacy of 6 cycles of ipat + atezo in reducing micrometastatic disease (detectable cfDNA) in patients with residual breast and/or axillary disease after NAC and completion of all locoregional and/or systemic adjuvant therapy. Secondary objectives include: evaluating efficacy of ipat + atezo in reducing micrometastatic disease after 3 cycles; determining the recurrence risk after treatment with ipat + atezo; and determining the safety and tolerability of the combination. Correlative objectives include determining whether: 1) pretreatment circulating markers (mutations or copy number changes in PTEN/PI3K/AKT) are associated with response; 2) PD-L1 expression on tumor cells or infiltrating tumor cells in the primary tumor is associated with response; 3) PD-L1 expression on circulating tumor cells has utility as a pharmacodynamic biomarker; and 4) stool microbiome profiles are associated with response and/or survival. As an exploratory objective, patient attitudes and experience surrounding testing for tumor cfDNA and, for those testing positive, participation in a trial targeting cfDNA, will be assessed. Statistical methods:The primary objective is to determine the response rate defined as the proportion of patients with detectable cfDNA who become undetectable. We anticipate that 30% of patients screened will be tumor cfDNA-positive, thus anticipate screening ~ 120 patients to enroll 40. With 40 patients enrolled (assuming a one-sided alpha of 0.05), we will have 80% power to detect a 19.0% (81% positive versus 93% positive) clearance rate using a one-sample binomial exact test. Target Accrual:40 patients Contact:A. DeMichele (angela.demichele@pennmedicine.upenn,edu) Clinicaltrials.gov #: NCT04434040**

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# Phase Ib/II trial of copanlisib in combination with trastuzumab and pertuzumab after induction treatment of HER2 positive metastatic breast cancer with *PIK3CA* mutation or *PTEN* mutation

**Senthil Damodaran[1], Rashmi K Murthy[1], Maliha Nusrat[2], Babita Saigal[1], Samantha C Trager[1], Debu Tripathy[1] and Funda Meric-Bernstam[1].**
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**Background:The PI3K/Akt/mTOR pathway is a critical regulator of cell growth, survival, and metabolism in cancer. Its activation plays an important role in resistance to chemotherapy and HER2 targeted therapy. *PIK3CA* activating mutations and *PTEN* loss were reported in 30% and 16% of BOLERO-1 and 32% and 12% of BOLERO-3 patients, respectively. Exploratory analyses suggested that the addition of everolimus to trastuzumab and chemotherapy improved progression free survival (PFS) in patients with *PIK3CA* mutations and *PTEN* loss. In the phase III CLEOPATRA trial, while the combination of pertuzumab (P) plus trastuzumab (H) plus docetaxel (T) as compared with trastuzumab (H) plus docetaxel (T), significantly prolonged PFS (18.5 vs 12.4 months) for first-line treatment for HER2-positive (+ve) metastatic breast cancer (MBC), longer median PFS was observed in patients with wildtype versus mutated *PIK3CA* in both the control (13.8 v 8.6 months) and pertuzumab groups (21.8 v 12.5 months). Copanlisib is a highly selective, class 1 pan-PI3K inhibitor with predominant activity against both the δ and α isoforms. It is currently FDA approved for the treatment of adults with relapsed follicular lymphoma. This study hypothesizes that the addition of copanlisib to dual HER2 targeted therapy after first line induction treatment will improve clinical outcomes in HER2 positive MBC patients with *PIK3CA* or *PTEN* genomic alterations. Trial Design: This is a randomized, two- arm, open label, phase-2 study to evaluate the clinical activity of copanlisib added to HP maintenance after induction with THP in HER2 +ve MBC patients with *PIK3CA* mutations or *PTEN* loss. A safety run-in cohort (phase 1B) will be performed. Copanlisib will be administered weekly on D1, D8 of a 21-day cycle. Eligibility criteriaHER2 +ve MBC based on ASCO-CAP criteria (HER2 status based on metastatic tissue)• Activating mutations in *PIK3CA,* or *PTEN* loss• ECOG performance status ≤1• Normal organ and marrow function• Within 8 weeks of completion of first-line induction therapy with THP (Phase-2). Any prior treatment provided eligible to receive THP induction (Phase-1B) Specific aimsTo assess the benefit of adding copanlisib to HP in HER2+ve MBC patients with *PIK3CA* mutations or *PTEN* loss after induction treatment (Phase-2)• To determine safety and recommended phase 2 dose (RP2D) of copanlisib, HP combination in HER2 MBC patients (Phase-1B)• To correlate PFS and OS with the triplet combination with the number of induction cycles, hormone receptor status, and PTEN loss by IHC• To identify potential predictive and prognostic biomarkers for copanlisib activity Statistical methodsThe primary objective of the phase-1B portion is to determine the RP2D for the combination of copanlisib, trastuzumab, and pertuzumab. Phase 1 portion will use a 3+3 dose de-escalation design. The primary objective of the phase 2 portion is to determine a difference in PFS with the addition of copanlisib to HP maintenance after induction. Projected median PFS in control group is 8 months and 16 months in the experimental arm. We aim to detect a HR of 0.50 with power of 0.90 with 1-sided alpha of 0.1. With a sample size of 82, 12 months post-accrual follow-up, and accrual rate of 5 patients per month, the study duration is 30 months. To have 82 evaluable patients with a 15% drop-out rate, we would need to enroll 96 patients. A Wieand rule futility interim analysis will be conducted when half of the total of 54 required PFS events are observed.**

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# Pathological response after neoadjuvant chemotherapy and long-term outcomes among very young women with HER2 negative breast cancer

**Fernando Valencia[1], Jorge Laboriano[2], Luis A. Chirinos[3] and Henry L. Gomez[2]. [1]Vallesur - AUNA, Arequipa, Peru[2]INEN, Lima, Peru[3]Universidad Cientifica del Sur - Facultad de Medicina Humana, Lima, Peru**

**Purpose: To describe the pathological response rates (according to the MD Anderson RCB score) achieved by patients with 35 years old or younger, with HER2 negative breast cancer, who received neoadjuvant chemotherapy (NAC) and long term outcomes according to the response. Methods: A retrospective review of 526 medical records of women aged less than or equal to 35 years at diagnosis between 2009 and 2014 at INEN in Lima-Peru, who received NAC for invasive breast cancer, was performed. HER2 positive patients were excluded because of a lack of access to neoadjuvant anti-HER2 therapy during this period in our hospital. Descriptive statistics were used to describe baseline characteristics. OS was calculated from the date of diagnosis to death or last follow-up and presented as Kaplan-Meier curves. The comparison among patients who achieved pCR (RCB-0) and those with residual disease, was based on a log-rank test. Results: Seventy women (One with synchronous bilateral disease) were selected according to selection criteria, median age: 31.7 years old (IQR: 30.0-33.2). Hormone receptor-positive: 38 (53.5%). Clinical stage: IIA: 13(18.3%), IIB: 8(11.3%), IIIA: 25(35.2%), IIIB: 21 (29.6%) and IIIC: 4 (5.6%). Type of NAC: Anthracyclines 6 (8.6%), Anthracyclines and taxanes 55 (78.6%), Platin 5 (7.1%), Taxanes 4 (5.7%). Type of surgery: Conservative 16 (22.5%), radical 50 (70.4%), toilet 5 (7.0%). Type of pathological response RCB-0: 9(12.7%), RCB-I: 2(2.8%), RCB-II:29(40.8%), RCB-III: 24(33.8%), non-pCR: 7(9.9%). With a median follow-up of 46.5m, 5y OS: 100/100/79.3/45.8% according to RCB-0/I/II/III respectively (p=0.004). Conclusions: "Very young" women reach fewer pCR rates than reported for "young" and older women. Even so, RCB-0 can be considered as a biomarker of excellent prognosis and could be used as a surrogate biomarker to evaluate the efficacy of neoadjuvant therapy even in very young women who receive NAC.**

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# Trends in BRCA testing among patients diagnosed with breast cancer -a retrospective analysis of a United States commercial claims database from the PRIOR-1 study

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**Background The use of BRCA testing to guide the course of breast cancer treatment has evolved in the last 5 years; however, little is known about the use of BRCA testing in a real-world setting. This study assessed the trend in prevalence of BRCA testing and sociodemographic and clinical predictors of receiving a BRCA test among newly diagnosed patients with breast cancer. Methods This was a retrospective study conducted using the Optum Clinformatics Datamart database. Patients newly diagnosed with breast cancer, continuously enrolled in a health plan for ≥6 months before and after diagnosis were included in the study. Claims for BRCA testing were identified after diagnosis using HCPCS, ICD-9/10 procedure, and LOINC codes. The prevalence of BRCA testing was calculated for patients diagnosed in each year from 2012-2017. Multivariable logistic regression was used to assess predictors of BRCA testing controlling for sociodemographic and clinical factors. Results From a total of 81,774 breast cancer patients included, 13,529 (16.5%) received a BRCA test after diagnosis. The prevalence of BRCA testing increased from 1,721 (11.5%) in 2012 to 2,384 (17.1%) in 2013 and remained stable over time until 2017 [2,191, (18.5%)]. Of patients receiving a BRCA test, 11,688 (86%) were tested within 1 year of diagnosis. The median time to receive a BRCA test from diagnosis was 29 days (mean: 172.7 days). Results from logistic regression indicated that diagnosis at a younger age (e.g., 18-44 years versus ≥75 years, odds ratio [OR] = 25.3), diagnosis in recent years (e.g., 2017 versus 2012, OR =1.94), having a point of service versus health maintenance organization plan type (OR = 1.10), presence of metastasis (OR = 1.62), and family history of cancer (OR = 4.98) significantly (*P*<0.05) increased odds for receiving a BRCA test. Female gender (OR = 0.28), living in regions other than West (e.g. South, OR = 0.86), having commercial insurance versus Medicare Advantage (OR = 0.96), Charlson comorbidity index score of ≥3 vs 0 (OR= 0.83) were significantly (*P*<0.05) associated with lower odds of receiving a BRCA test. Conclusions Prevalence of BRCA testing among breast cancer patients increased initially in 2013 and remained stable over time until 2017. Several demographic and clinical factors were associated with the use of BRCA testing among breast cancer patients.**

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# Solti-1507 A phase ib study of ipatasertib and anti-her2 therapy in her2-positive advanced breast cancer with pik3ca mutation (ipather)

**Mafalda Oliveira[1], Patricia Villagrasa[2], Eva Ciruelos[3], Joaquin Gavila[4], Alexandra Cortegoso[5], Fernando Henao[6], Estela Vega[7], Javier S. Bofill[8], Vanesa Quiroga[9], Laura Garcia-Estevez[10], Serafin Morales[11], Pablo Tolosa[12], Pamela Celiz[2], Xavier Gonzalez Farre[13] and Cristina Saura[1]. [1]Vall d' Hebron University Hospital / Vall d'Hebron Institute of Oncology / SOLTI Breast Cancer Research Group, Barcelona, Spain[2]SOLTI Breast Cancer Research Group, Barcelona, Spain[3]Hospital 12 de Octubre / SOLTI Breast Cancer Research Group, Madrid, Spain[4]Instituto Valenciano de Oncologia / SOLTI Breast Cancer Research Group, Barcelona, Spain[5]Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain[6]Hospital Virgen de Macarena, Sevilla, Spain[7]Centro Integral Oncologico Clara Campal, Madrid, Spain[8]Hospital Virgen del Rocio, Sevilla, Spain[9]Badalona-Applied Research Group in Oncology (B-ARGO Group), Catalan Institute of Oncology, Barcelona, Spain[10]Hospital MD Anderson Cancer Center, Madrid, Spain[11]Hospital Universitario Arnau de Vilanova, Lleida, Spain[12]Hospital 12 de Octubre, Madrid, Spain[13]SOLTI Breast Cancer Research Group / Institut Oncologic Dr. Rosell, Barcelona, Spain**

**Background The combination of trastuzumab, pertuzumab (HP) and a taxane increases progression-free survival (PFS) and overall survival (OS) in patients with HER2-positive (HER2+) advanced breast cancer (BC). *PIK3CA* mutations can occur in 30-35% of HER2+ tumors, independently of hormone receptor (HR) status. In an exploratory analysis from CLEOPATRA, patients with a tumor harboring a *PIK3CA* mutation (mut) had a shorter PFS. The AKT inhibitor ipatasertib (IPAT) blocks the PI3K/AKT pathway and has activity in PI3K/AKT-altered tumors. We hypothesize that ipatasertib + HP is safe and can be beneficial in patients with *PIK3CA*mut HER2+ BC. Trial design This is an open-label, single arm, phase Ib study to evaluate the safety and preliminary efficacy of IPAT plus HP (+/- endocrine therapy [ET]) in patients with *PIK3CA* mut HER2+ BC. Key inclusion criteria include the presence of locally advanced/unresectable or metastatic HER2+ BC with a *PIK3CA* mut (detected in tissue or plasma ctDNA); candidates to receive maintenance HP (+/- ET) after taxane discontinuation in first line setting for a reason different to progressive disease; male and female (pre and postmenopausal status); adequate performance status (ECOG 0-1); and adequate bone marrow, cardiac and hepatic function. Key exclusion criteria include: active or progressive brain metastases; diabetes mellitus requiring insulin, and prior exposure to an AKT inhibitor. The primary endpoint is to define the maximum tolerated dose (MTD) and the recommended phase 2 dose of the combination. MTD is defined as the highest dose level at which ≤1 of 6 subjects experience a dose-limiting toxicity (DLT) during the first 28 days of treatment. Grade ≥3 diarrhea for more than 72 hours or Grade ≥2 diarrhea for more than 5 days are considered DLTs amongst others. Secondary endpoints include objective response rate, duration of response, clinical benefit rate and PFS. Exploratory objectives include identification of molecular biomarkers of response to treatment both in ctDNA (Amplicon-seq) and tumor tissue (Breast Cancer 360 panel), as well as to characterize the pharmacokinetics of study drugs. Given the low risk for overlapping toxicities, full doses of IPAT (400mg orally once daily D1-21 q28d) and standard dose HP will be used in the first cohort. Dose reductions of IPAT (300mg and 200mg) are allowed if the full dose exceeds MTD. Loperamide is given as prophylaxis for diarrhea. In HR-positive tumors, ET may be started after the DLT period. Approximately 25 evaluable patients in a given dose level will be required to assess the safety of the combination of IPAT plus HP. Patients are currently being screened for *PIK3CA* mutations at 7 sites in Spain. The first patient was enrolled in March 2020 and the recruitment is ongoing. This study is sponsored by SOLTI and financially supported by Roche. For further information on this trial, visit ClinicalTrials.gov (NCT04253561)**

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# Clinicopathological characteristics of male breast cancer in Japan from the national clinical database

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Background: Male breast cancer is a rare cancer. According to the Japanese Breast Cancer Society's Breast Cancer Registry, there were 613 cases of male breast cancer in 2016. It is only 0.6% of all cases of breast cancer incidence. Because of its rarity, there have been no comprehensive studies on characteristics of male breast cancer in Japan. Therefore, there has been few specific treatments developed for male breast cancer. In this study, we investigated the prevalence and clinicopathological characteristics of male breast cancer in Japan, using the most reliable domestic data, the National Clinical Database (NCD). NCD is a database that collects medical information on diseases, treatments, and surgeries in Japan. In collaboration and cooperation with academic societies and academic organizations, NCD maintain and manage the collected data. The data are used in domestic research to evaluate the standards of medical care and support clinical research. This study conducted with a collaboration with NCD and the registration committee of Japan Breast Cancer Society. Materials and Methods: Clinicopathological data were collected from all breast cancer patients in NCD between 2012 and 2018. We compared the male and female breast cancer patients on age, stage, surgical technique, estrogen receptor (ER) status, progesterone receptor (PgR) status, HER2 expression, family history, comorbidities, and systemic treatment history. Results: 3,780 male and 590,636 female breast cancers were enrolled in the study. The median age was 71 years for men (56-87 years, 5-95 percentile) and 61 years for women (40-83 years). The clinical stage in males was 7.2% in stage 0, 36.3% in stage I, 33.4% in stage II, 12.4% in stage III, 1.4% in Stage IV and 4.5% in unknown, respectively. In females, 13.0%, 41.6%, 31.4%, 6.6%, 1.3% and 2.3%, respectively. Breast conserving surgery (BCS) was performed for 14.6% in men 46.2% in women. BCS rate in men is more frequent in Japan compared to in western countries (Ann Oncol. 2018 Feb 1;29(2):405-417). Hormone receptor-positive (HR+; ER+ and/or PgR+) HER2-negative (HER2-) was 88%, HR+HER2-positive (HER2+) was 8%, HR-HER2+ was 1% and HR-HER2- was 3% in men. 74%, 10%, 6% and 10% in women, respectively. The distribution of subtypes in men is similar to western countries. Comorbidity was reported in 42.3% of men and 66.8% of women. Hypertension, diabetes, cardiac disorder and cerebrovascular disorder were more common in men. Conclusion: Male breast cancer is 0.6% of all breast cancer in Japan. Stage III and HR+ is more frequent in male and its tendency is similar to data from western countries. BCS is underwent more frequent in Japan than in western countries.

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# Phase III study of GDC-0077 or placebo (pbo) with palbociclib (P) + fulvestrant (F) in patients with *PIK3CA*-mutant/hormone receptor-positive/HER2-negative locally advanced or metastatic breast cancer (HR+/HER2- LA/MBC)

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**Background**
HR+/HER2- BC is the most common BC subtype, and adjuvant endocrine therapies (ET) are an integral part of its management; however, ~30% of patients still relapse. Development of ET resistance remains a challenge in HR+/HER2- BC; aberrant phosphoinositide 3-kinase (PI3K) signaling contributes to ET resistance and *PIK3CA* mutations occur in ~40% of HR+/HER2- BCs. Current research has led to the development of new targeted therapies, including CDK4/6 inhibitors and PI3K inhibitors (alpelisib). Preclinical models have demonstrated synergy between CDK4/6 inhibitors and PI3K inhibitors, with PI3K inhibitors blocking CDK4/6 inhibitor resistance development. GDC-0077 is a potent, selective PI3Kα inhibitor and a mutant p110α-degrader with anti-tumor activity alone and in combination with ET + P in *PIK3CA*-mutant preclinical models. An ongoing phase I trial showed that GDC-0077 + P + F could be combined at maximum doses. INAVO120 is a phase III, randomized, double-blind, pbo-controlled study that will assess efficacy and safety of GDC-0077/pbo + P + F in patients with *PIK3CA*-mutant/HR+/HER2- LA/MBC (NCT04191499).
**Trial design**
Patients are randomized 1:1 to GDC-0077 (9 mg orally; once daily [QD] continuously on a 28-day cycle) + P (125 mg orally; QD, days 1-21 of each 28-day cycle) + F (500 mg intramuscularly every 28 days with a loading dose in Cycle 1) or pbo + P + F. Circulating tumor DNA or tumor tissue must be positive for a *PIK3CA* mutation.
**Eligibility**
Patients whose disease progressed during/within 12 months of adjuvant ET completion, and who have not received prior systemic therapy for LA/MBC.
**Aims**
The primary endpoint is investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors v1.1. Secondary endpoints include objective response rate (ORR); best overall response (BoR); duration of response (DoR); clinical benefit rate (CBR); overall survival (OS); safety; patient-reported outcomes; and pharmacokinetics.
**Statistical methods**
Patients are stratified by visceral disease, primary vs secondary resistance, and geographic region. For the primary PFS analysis, the treatment arms will be compared using a two-sided stratified log-rank test. The treatment effect will be quantified via a hazard ratio, computed from a stratified Cox proportional-hazards regression, including a 95% confidence interval. Median PFS will be estimated using Kaplan-Meier methodology.
**Accrual**
Target enrollment is 400 patients at ~210 sites globally. The study is open for enrollment and, as of 06/04/2020, eight patients have been enrolled.
**Contact information** For more information or to refer a patient, email global.rochegenentechtrials@roche.com or call 1-888-662-6728 (USA only).
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# Ribociclib-endocrine therapy (ET) combination versus chemotherapy as 1st line treatment in patients (pts) with visceral metastatic breast cancer (BC). A multicenter, randomized phase III trial: SAKK 21/18

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**Background: Pts with hormone receptor (HR)-positive/HER2-negative BC and visceral metastases have a worse outcome. Despite international guidelines recommending first line ET, many oncologists prefer to treat these pts primarily with chemotherapy, expecting a faster response. Combination of CDK4/6 inhibitors with ET was shown to be superior to ET alone, in terms of progression free survival (PFS), overall survival (OS), response rate and time to response, while maintaining QoL. The value of an initial period of chemotherapy followed by ET maintenance+/-CDK4/6i versus upfront ET+CDK4/6i is unknown, particularly in a population with visceral disease and mainly luminal B tumors, usually less endocrine sensitive.Trial design:As cancer response and QoL are the main parameters leading the decision of the oncologists, a composite endpoint "QoL-adjusted early disease control" (QoL-eDC) was developed to assess tumor response (progression-free at 12 weeks) and QoL (no deterioration according to FACT-B). The pts are randomized to: arm A, endocrine therapy (aromatase inhibitor or fulvestrant) with ribociclib; arm B, mono-chemotherapy at the choice of the physician for at least 12 weeks - thereafter, a switch to a maintenance ET+/-ribociclib is allowed.Baseline measurements and procedures: ECG, blood count, liver and renal functions, tumor assessment and QoL form (FACT-B, BPI-SF single item "worst pain"). Tumor and QoL assessments are repeated at baseline, on week 6, 12, then every 12 weeks, and at the end of trial treatment. Translational research: Plasma is collected for ctDNA at baseline, week 12, 24, then every 6 months, and at progression. Fresh tissue is collected at baseline and at progression, when feasible. Eligibility: Postmenopausal women presenting hormone receptor positive(ER ≥ 10%) and HER2-negative BC with measurable visceral disease, according to RECIST v1.1. Exclusion criteria include visceral crisis, previous systemic treatment for metastatic disease, prior adjuvant CDK4/6i, symptomatic and uncontrolled brain metastases, or significant organ dysfunction. Specific aims: Primary endpoint is QoL-eDC. Secondary endpoints are DC at 12 weeks, objective response rate (ORR), time to OR, PFS, time to treatment failure, OS at 3 years, overall change in QoL until 24 months or PD, time to QoL deterioration/improvement, time to pain improvement, and adverse events.Statistical methods:Group sequential two proportions non-inferiority design. Hypotheses for QoL-eDC during the first 12 weeks. H0: difference arm B – arm A is ≥ 12.5% and H1: difference arm B – arm A is < 12.5%. With a significance level of 0.05, a power of 0.8 and one interim analysis a sample size of 190 pts in each arm (total sample size increased to 400 pts for potential excluded pts). Interim analysis: after 95 evaluable pts for the primary endpoint in each arm.Testing: one-sided group-sequential z-test with pooled variance according to the statistical design; categorical variables summarized using frequencies and percentages; modelling binary outcomes by logistic regression; time-to-event medians estimated by Kaplan-Meier method (95% CI); treatment effect on time-to-event endpoints assessed using Cox proportional hazard models with stratification factors as strata.Present accrual and target accrual: Recruitment started Q2, 2019. Recruitment on July 07, 2020: 20/400.22 centers are open for inclusion in Switzerland and 1/8 in Belgium. Study activation process is ongoing in Belgium (8 centers), Italy (15 centers) and Austria (5 centers).Contact: Karin Rothgiesser, SAKK Coordinating Center, Switzerland. karin.rothgiesser@sakk.ch ClinicalTrials.gov Identifier: NCT03905343**

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# Family history (FH) of breast cancer (BC) and associated risk-factors and screening: Analysis of an internet-based risk assessment tool

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BackgroundBreast cancer (BC) is the most common cancer in women worldwide, and a leading cause of death. There are well established risk-factors for BC: Lifestyle factors include smoking, drinking alcohol, obesity, and low physical activity, and biologic factors may include increased exposure to estrogen and specific genetic mutations. The impact of having a family history (FH) of BC on associated risk factors is poorly understood. Results from previous literature suggest that those with FH of BC are more likely to adopt screening behaviors, but do not differ in risk-related behaviors. Because women with a FH of BC have an increased risk of developing BC themselves, we sought to better understand the co-present modifiable risk and screening behaviors associated with both BC and other common cancers. MethodsAn Internet based tool designed to provide personalized information on cancer risk was designed by healthcare providers and made publicly available in 2009 (OncoLink.org). Data from female responders in a convenience sample frame were analyzed as part of this study. All procedures were approved by IRB. Differences between respondents with v. without FH of BC were analyzed using chi-square test. Results15,712 female responses were analyzed; 10,800 (68.7%) had a FH of any cancer, 4578 (29.1%) BC. Median age was 26 (IQR 19-38); 84.4% of respondents were between 18-45; 76.7% were white, 88.3% pre-menopausal, 83.5% from North America, and 76% completed some college. Respondents had an average of 1.88 listed cancers in their FH with 15.89% reporting more than 4 cancers in FH. 248 (1.58%) and 202 (1.29%) reported a FH of BRCA1 and BRCA2, respectively. 3939 reported a FH of just one cancer, with 815 reporting just a FH of BC. Among those with FH of just BC, 20.74% were the respondent's mother, 2.1% sister, and 50.3% grandmother. Those with a FH of BC were more likely to be current smokers and to have a history of secondhand smoke exposure (Table). There was no difference in rates of heavy smoking (1+ packs per day) (Table). Those with a FH of BC were more likely to be current drinkers, but not more likely to be heavy drinkers (7+ per week) (Table). Median BMI in those with FH of BC was higher than in those without; those with FH of BC were also more likely to be overweight or obese, and to exercise less than once per week (Table). Those with FH of BC were more likely to have had menarche before age 12 or to have taken OCPs, but showed no difference in menopause after 50, or rate of taking HRT for 2+ years (Table). They were also more likely to have performed a self-breast exam or to have received one in clinic (Table). Those with a FH of BC were not more likely to engage in common preventive and screening behaviors for cervical cancer, including being vaccinated against HPV or receiving regular pap screening (Table).ConclusionsOur results suggest many with FH of BC have both modifiable and non-modifiable risk factors that increase risk for development of cancer. We found that a FH of BC was associated with increased rates of smoking, drinking, obesity, and sedentary lifestyle when compared to those without FH. Importantly, our results lend further support to previous findings that these individuals are more engaged with BC-related screening behaviors. However, we found that FH of BC did not impact rates of screening for cervical cancer. Future work should explore targeted interventions to reduce risk-increasing behaviors among those with FH of BC.

| | Total | | Pos FH BC | | Neg FH BC | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | RR | AR | Chi-Square p-value |
| Behavioral Risk Factors | | | | | | | | | |
| Any Smoking-Related Risk | 9651 | 61.4% | 2911 | 63.6% | 6740 | 60.5% | 1.05 | 3.1% | < 0.001 |
| Current Smoker | 1715 | 10.9% | 539 | 11.8% | 1176 | 10.6% | 1.11 | 1.2% | 0.03 |
| 1+ Packs Per Day (among smokers) | 363 | 20.8% | 124 | 22.9% | 239 | 19.9% | 1.15 | 3.0% | 0.15 |
| Ever Smoke | 5273 | 33.6% | 1576 | 34.4% | 3697 | 33.2% | 1.04 | 1.2% | 0.14 |
| Ever Quit | 3616 | 23.0% | 1053 | 23.0% | 2563 | 23.0% | 1.00 | 0.0% | 0.98 |
| Secondhand Smoke Exposure | 5165 | 32.9% | 1641 | 35.8% | 3524 | 31.7% | 1.13 | 4.2% | < 0.001 |
| Currently Drinks Alcohol | 7879 | 50.1% | 2408 | 52.6% | 5471 | 49.1% | 1.07 | 3.5% | < 0.001 |
| 7+ Drinks Per Week | 1243 | 15.6% | 388 | 16.0% | 855 | 15.5% | 1.03 | 0.5% | 0.78 |
| Overweight (BMI 25-30) | 3355 | 26.8% | 1009 | 28.3% | 2346 | 26.1% | 1.08 | 2.1% | 0.02 |
| Obese (BMI 30+) | 3170 | 25.7% | 1010 | 28.3% | 2160 | 24.6% | 1.15 | 3.7% | < 0.001 |
| Diet Risk | 11218 | 71.4% | 3357 | 73.3% | 7861 | 70.6% | 1.04 | 2.7% | < 0.001 |
| Exercise <1x per week | 6084 | 38.7% | 1891 | 41.3% | 4193 | 37.7% | 1.10 | 3.6% | < 0.001 |
| Exercise 5+ Times Per Week | 2140 | 13.6% | 568 | 12.4% | 1572 | 14.1% | 0.88 | -1.7% | 0.004 |
| UV Exposure Risk | 5704 | 36.3% | 1781 | 38.9% | 3923 | 35.2% | 1.10 | 3.7% | < 0.001 |
| Tanning Salon | 4550 | 29.0% | 1423 | 31.1% | 3127 | 28.1% | 1.11 | 3.0% | < 0.001 |
| Estrogen Risk Factors | | | | | | | | | |
| Age Menarche Before age 12 | 4899 | 32.4% | 1540 | 34.8% | 3359 | 31.4% | 1.11 | 3.4% | < 0.001 |
| Age Menopause After 50 (if menopausal) | 828 | 44.9% | 241 | 42.4% | 587 | 46.0% | 0.92 | -3.6% | 0.15 |
| Age First Gave Birth > 30 (if gave birth) | 1310 | 20.3% | 399 | 20.7% | 911 | 20.1% | 1.03 | 0.7% | 0.55 |
| Taken 2+ Years of HRT (postmenopausal) | 374 | 20.3% | 126 | 22.2% | 248 | 19.5% | 1.14 | 2.7% | 0.18 |
| Ever Taken OCPs | 10602 | 67.5% | 3202 | 69.9% | 7400 | 66.5% | 1.05 | 3.5% | < 0.001 |
| Preventive and Screening Behaviors | | | | | | | | | |
| Previous Tamoxifen Use | 122 | 0.8% | 58 | 1.3% | 64 | 0.6% | 2.20 | 0.7% | < 0.001 |
| Ever Performed Self Breast Exam | 10561 | 67.2% | 3142 | 68.6% | 7419 | 66.6% | 1.03 | 2.0% | 0.02 |
| Ever Had Clinical Breast Exam | 9286 | 59.1% | 2845 | 62.1% | 6441 | 57.8% | 1.07 | 4.3% | < 0.001 |
| Received HPV Vaccine (those <35 yo) | 4288 | 38.4% | 1207 | 38.5% | 3081 | 38.3% | 1.01 | 0.2% | 0.84 |
| Regular Pap Screening (25-65 yo) | 7046 | 82.1% | 2182 | 82.7% | 4864 | 81.9% | 1.01 | 0.9% | 0.33 |

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# MEDEA: A randomized trial of weight loss to reduce cancer-related fatigue (CRF) among overweight and obese breast cancer (BC) patients

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Rationale: Overweight and obesity are highly prevalent among BC patients and are linked to poorer prognosis and worse patient-reported outcomes (PROs). Weight loss interventions, based on caloric restriction, increased physical activity (PA) and behavioral counselling, are safe and feasible among BC survivors and hold the promise to improve BC-specific outcomes. MEDEA: Motivating to Exercise and Diet, and Educating to healthy behaviors After breast cancer (ClinicalTrials.gov NCT04304924) will evaluate the impact of weight loss on CRF.
Trial design: French multi-center 1:1 randomized controlled trial comparing a 12-month personalized, telephone-based weight loss program + health education intervention vs health education alone in overweight or obese BC patients.
Endpoints and measures: Primary endpoint: difference in self-reported CRF 12 months post-randomization between arms, measured using the EORTC QLQ-C30 CRF subscale. Secondary endpoints: 1) PROs (EORTC QLQ-C30, -B45, -FA12), anxiety and depression (Hospital Anxiety and Depression Scale); 2) weight and body mass index (BMI), diet habits and quality, PA, sleep; 3) cost-effectiveness (number and length of hospital-admissions, all-drug consumption, number and duration of sick leaves). Accelerometer data will be collected to track PA and sleep measures. Qualitative analyses will evaluate patient motivation and satisfaction.
Main eligibility criteria: stage I-II-III BC, primary BC treatment completed within the prior 12 months (definitive surgery, adjuvant chemo-, and/or radio-therapy, if administered), BMI ≥25 kg/m$^2$, ability to walk at least 400 meters at any pace, ECOG PS 0-1, not participating in another weight loss, dietary or PA intervention clinical trial.
Intervention and Control arms: The intervention and health education program are adapted from the BWEL: Breast Cancer WEight Loss study (ClinicalTrials.gov NCT02750826; PI Ligibel JA). The behavior change program is based on the Social Cognitive Theory. Patients in the intervention arm are paired with an individual lifestyle coach, who delivers the intervention through 24 semi-structured telephone calls of 30-60 minutes, supplemented by a detailed participant workbook and scheduled as follows: 1) intensive phase (weeks 1-12), 12 weekly calls; 2) consolidation phase (weeks 13-24), 6 bi-weekly calls; 3) maintenance phase (weeks 25-52), 1 monthly call. Coaches were hired and trained specifically for MEDEA, they are located at a centralized call center and receive support from coordinating nutrition, PA, and behavioral experts. Regular meetings with study team and investigators assure standardized delivery of the intervention and troubleshooting. Intervention goals include weight loss ≥10% of baseline weight, caloric restriction of 500-1000 Kcal/day, increased PA to 150 minutes/week in the initial phase and 225-300 minutes/week in the maintenance phase. Toolbox solutions are offered to tailor the intervention and meet the needs of specific ethnic, socioeconomic or other patient populations with difficulties in achieving intervention goals. All participants in both arms receive a health education program focusing on healthy living.
Accrual: MEDEA will enroll 220 patients overall. Recruitment started in June 2020.
Statistical considerations: The primary analysis of MEDEA will compare the primary endpoint of CRF scores at the 12-month post-randomization time point between arms. The study has 90.0% power at two-sided $\alpha$=0.05 to detect a standardized effect size of 0.40 (sample size inflated for drop outs). For interpreting the clinical significance of effects, 0.2, 0.5 and 0.8 standard deviation effects will be considered as small, moderate, and large (Cohen, 1988). All other measures, time points and analyses will be considered secondary or exploratory.

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# Clinical and pathological features of very early-onset breast cancer and treatment challenges on public health care system at a cancer center in Brazil

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**Background: Even though breast cancer is uncommon in women ≤ age 35, women in this group are more likely to present aggressive cancer subtypes, advanced clinical stage at diagnosis and pathogenic variants (PV) in cancer susceptibility genes. Higher recurrence and mortality rates in very early-onset breast cancer patients may be related to differences in tumor biology, mutation status, clinical or treatment features. Management of those women should comprehend dedicated approach and standard care that are often not available on cancer care centers at low-middle income countries. We aim to describe the clinical and pathological factors associated with very early-onset breast cancer patients and the challenges associated with treatment of those women in a public health facility in Brazil. Methods: Retrospective review of 748 patients diagnosed and treated at the biggest surgical center for breast cancer in Brasilia - Brazil between 2015 and 2020 was performed and 54 patients with cancer diagnosis ≤ age 35 were identified. Pathological and clinical characteristics as well as treatment information were collected from medical and electronic patients' records. Bivariate and multivariate analyzes were performed. Findings: Median age at diagnosis was 31.9 years old (23 to 35). 44% had a positive familial history for HBOC. 20% presented first period <12 years of age and 61% and 53% had first childbirth < 30 years and breastfed for over 6 months, respectively. Only 10% had a BMI index over 30, and 37% were overweight. The distribution of BC stage at diagnosis was I (9.3%), II (51.9%), III (29.6%) and IV (3.7%). The most common were invasive carcinoma of no special type (98%) and malignant phyllodes (2%) and 10.9%, 50.9% and 27.3% were grades 1, 2 and 3, respectively. BC subtypes were as follows: Luminal A 18.5%, Luminal B 31.5%, HER2 positive 24.1% and Triple negative 25.9%. With a mean follow-up of 31.94 months, the overall survival rate was 93%, with a recurrence-free survival rate of 72.1%.Although all patients met the criteria for germline testing, only 25.9% had access, with two BRCA1, four BRCA 2, one CHECK2 and one TP53 PV detected. 27.8% had BCS as surgical treatment and 53.7% e 13% had unilateral and bilateral mastectomy. There was an increased rate of bilateral mastectomy on the last 8 years. 73.6% were treated with neoadjuvant chemotherapy (NC) and mean interval between NC and surgery was 61.1 days (19-370). 63% had radiotherapy and the mean interval between previous treatment (chemotherapy or surgery) and radiotherapy was 93.8 days (56-150). None of the HER2 positive patients were exposed to dual HER2 blockade and there was no adjuvant treatment with T-DM1 or capecitabine when pCR was not achieved. Only 22% of the women with hormone receptor tumors were exposed to ovarian suppression alongside hormone therapy. Of the 54 patients, 27.9% relapsed, 18.6% distant recurrence, 9.3% local. The most common sites of metastasis was bone and liver (6.8% each) followed by lung and central nervous system (3.4% and 1.7%). Conclusions: Previous studies showed that breast cancer is diagnosed at an earlier age among Brazilian patients. BC is often detected when symptomatic and therefore a significant proportion is diagnosed at more advanced clinical stages. These findings alongside the restrict acess to genetic counseling and the delay on treatment in the public healthcare system are a clear indication of the challenges for achieving standard care for those patients and could have a significant impact on survival outcomes. These data combined indicate the need for supportive care program for young women with breast cancer.**

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# A real-world evidence study of treatment patterns among patients with HER2-positive metastatic breast cancer

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**Background**
Historically, the standard-of-care treatments for human epidermal growth factor receptor 2-positive (HER2+) metastatic breast cancer (mBC) have included targeted therapies, such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), which have shown efficacy in clinical trials. Treatment choice and sequencing for patients with HER2+ mBC after first-line therapy have not been well delineated in the US real-world setting.
**Methods**
Patients who received at least two lines of therapy for HER2+ mBC diagnosed from January 2013 - April 2019 were selected from the Flatiron Health electronic health record-derived database. The Flatiron database is nationwide and comprises deidentified patient-level structured and unstructured data curated via technology-enabled abstraction in the US. The index date was the start date of the second line of therapy (2L). Treatment patterns from 2L onward were examined. Baseline information included disease stage at diagnosis and prior treatment for mBC. Duration of therapy was estimated using the Kaplan-Meier method.
**Results**
Among the 1390 patients with HER2+ mBC with a documented 2L therapy, the mean age at the initiation of 2L therapy was 60.4 years. Patients had one (n = 514; 37.0%), two (n = 390; 28.1%), or three or more (n = 461; 33.2%) metastatic sites by the start of 2L therapy. The most common metastatic sites were bone (n = 872; 62.7%), lung (n = 494; 35.5%), liver (n = 473; 34.0%), and brain (n = 223; 16.0%). The majority of patients (n = 1141; 82.1%) had positive hormone receptor status. Nearly half of patients (n = 601; 43.2%) had stage IV disease at their initial breast cancer diagnosis, 289 (20.8%) had stage III, and 277 (19.9%) had stage II. Before 2L therapy, 720 patients (51.8%) received a HER2-targeted combination therapy, 337 (24.2%) received hormone therapy alone, and 209 (15.0%) received HER2-targeted monotherapy. Among all included patients, 481 (34.6%) had two lines of systemic therapy for mBC, 359 (25.8%) had three, and 550 (39.6%) had four or more. Of these patients, 1290 (92.8%) had used a HER2-targeted agent (monotherapy or in combination) in at least one line of therapy, and 1108 (79.7%) had two or more lines of therapy containing a HER2-targeted agent. In 2L, the most frequently prescribed regimens were pertuzumab + trastuzumab + taxane (n = 246; 17.7%), T-DM1 monotherapy (n = 213; 15.3%), and trastuzumab monotherapy (n = 192; 13.8%). Overall, in 2L, 721 (51.9%) of all included patients received HER2-targeted combination therapy, 427 (30.7%) received HER2-targeted monotherapy, 82 (5.9%) received chemotherapy, and 118 (8.5%) received hormone therapy alone. Hormone therapy was combined with chemotherapy or targeted therapy in 622 patients (44.7%). Median (95% CI) duration of 2L therapy was 6 (6-6) months. Among the 909 patients who had third-line (3L) therapy, the most common regimens were T-DM1 (n = 170; 18.7%), pertuzumab + trastuzumab + taxane (n = 77; 8.5%), and hormone therapy alone (n = 59; 6.5%). Overall, in 3L, 446 patients (49.1%) had HER2-targeted combination therapy, 283 (31.1%) had HER2-targeted monotherapy, and 78 (8.6%) had chemotherapy, with hormone therapy added to chemotherapy or targeted therapy in 388 patients (42.7%). Median (95% CI) duration of 3L therapy was 5 (4-6) months.
**Conclusions**
The results of this real-world study of patients receiving care in community-based oncology clinics suggest that treatment patterns in later-line settings are variable, with no clear treatment approach for this patient population and patients often being re-treated with the same HER2-targeted therapies. As additional targeted therapies have recently been approved for HER2+ mBC with improvements in patient outcomes, future examination of the treatment landscape is warranted.

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# Artificial intelligence supporting cancer patients across Europe - the ASCAPE project for breast cancer patients

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Background Many breast cancer patients experience adverse effects of cancer or treatment, which can considerably decrease quality of life (QoL). The current strategy of supporting breast cancer patients does not meet their needs due to the limited personalized-based approach in rehabilitation plan and the lack of healthcare, financial and other resources. ASCAPE (Artificial intelligence Supporting CAncer Patients across Europe) is a collaborative research project involving 15 partners from 7 countries, including academic medical centers, small and medium-sized enterprises, research centers and universities, aiming to leverage the recent advances in Big Data and AI (Artificial Intelligence) to support cancer patients' QoL and health status. Specifically, ASCAPE aims to provide personalized- and AI-based predictions for QoL issues in breast cancer patients as well as suggest potential interventions to their physicians.
Trial design During the first part of the project, large-scale retrospective datasets with breast cancer patients will be analyzed to develop and train AI-based models for specific QoL issues. During the second part of the project, a multicenter prospective longitudinal study is planned. Eligible patients will be followed for one year with validated questionnaires regarding different QoL issues, and wearables that will collect active monitoring data on physical activity, sleep pattern, and heart rate. The collected data will be used to further train and optimize the AI-based models and personalized-based intervention suggestions.Based on the retrospective and prospective data, an ASCAPE-integrated prototype will be developed, enabling personalized- and AI-based predictions and intervention suggestions. This approach will be evaluated at the end of the prospective study regarding patients´ and physicians´ experience as well as health economics.
Eligibility criteria Breast cancer patients planned for curative treatment with surgery with or without oncological therapy or breast cancer patients at least 1 year post-treatment (except endocrine therapy) will be eligible for the prospective study.
Specific aims 1.To develop and optimize AI-based predictions for QoL issues in breast cancer patients as well as potential intervention suggestions.2.To evaluate the AI-based follow-up approach for breast cancer survivors in terms of patients´ experience, physicians´ experience, and health economics.
Statistical methods For discrete QoL outcome variables, ASCAPE will examine the efficiency of classification-based machine learning models trained using decision tree learning algorithms, nearest-neighbors based algorithms, probabilistic learning algorithms, support vector machines and (deep) neural networks. Regressive counterparts of aforementioned methods will be analyzed for numeric QoL outcome variables including also regression specific methods (e.g., ridge regression, lasso regression and elastic net regression). The accuracy of trained models will be estimated relying on standard machine learning validation procedures such as the K-fold cross-validation and leave-one-out cross-validation.
The ASCAPE platform will utilize state-of-the-art explainability techniques to make the machine learning models' predictions transparent and comprehensible for the patient and the physician.Present accrual and target accrual Four retrospective datasets will be used for the first part of the project including approximately 18,000 breast cancer patients. For the prospective study, it is planned to be included about 30 patients monthly during a period of 12 months.
Contact information for people with a specific interest in the trial https://ascape-project.eu/artificial-intelligence-supporting-cancer-patients-across-europe

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# Outcomes and risk factors associated with breast cancer in women aged 35 and under: Single centre retrospective analysis

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**Introduction** Breast cancer is the most common malignancy affecting women under the age of 35 and young age at diagnosis is associated with a poor prognosis. Previous studies have shown that these patients have adverse tumour biology including high grade morphology, lymph node involvement and lack of hormone receptor expression. The aim of this study was to assess the outcomes and risk factors associated with the different subtypes of breast cancer as defined by receptor status in a cohort of young patients in a central London cancer centre. **Methods** Women diagnosed with breast cancer at the age of 35 or younger between 1st January 2010 and 1st June 2020, at Guys and St Thomas' NHS Foundation Trust (GSTT) were identified from the GSTT Breast Cancer Clinical Database. Data on patient demographics, histopathology, treatment, family history of breast or ovarian cancer, recent use of oral contraceptive pill (OCP) and outcome were collected from electronic hospital records. Risk factor data was analysed using chi-squared ($\square^2$) statistical analysis; survival data (Overall survival (OS) and recurrence free survival (RFS)) was assessed using cox-regression analysis and formulation of Kaplan-Meier curves. **Results** We identified 119 patients with a median age of 32.5 years (range 22-35 years). Four were diagnosed with *in situ* carcinoma (3 DCIS, 1 LCIS) and the remainder were invasive cancers. Of the invasive cancers, 54% (n= 62) were ER+HER2-, 23% (n=26) ER-HER2-, 19% (n=22) ER+HER2+ and 4% (n=5) ER-HER2+. The majority of patients presented with stage 1 or 2 disease and a small number presented with metastatic disease, irrespective of subtype. Approximately 23% (n= 28) of patients had taken the OCP and 15% (n=18) of patients were pregnant or breast feeding at the time of diagnosis, with no variation by subtype. ER+HER2+ patients were less likely to have had children (p=0.0008). ER+HER2- patients were more likely than ER-HER2- patients to have a family history of breast cancer (P=0.03), but were less likely to be referred for genetic testing (52% (n=38) vs 81% (n=21)). 11.8% (n=14) were found to have a germline mutation, two occurred with *in situ* cancer (*BRCA2* in the case of LCIS and *TP53* in a case of ER+HER2+ DCIS). Of the ER+HER2- cases that underwent genetic testing 12.5% (n=4) had a germline mutation (2 *BRCA2*, 1 *PALB2*, 1 *CHEK2*) and 38% (n=8) of the ER-HER2-subgroup (6 *BRCA1*, 2 *BRCA2*). With a median follow up of 29 months (range 3.1 to 103.3 months), 23% of ER-HER2-, 10% of ER+HER2- and no HER2+ cases had developed a recurrence (loco-regional or distant). 5-year RFS in ER+HER2- was 79.5% vs. 61.9% in ER-HER2- (HR 2.96, 95%CI 0.95-9.20; p=0.061). Of the ER+HER2- patients that recurred, 83% (n=5) had full ovarian function suppression (OFS) with Goserelin. Mean survival was 36.4 months; 12 out of 115 patients died, the 5-year OS across all subgroups was 76.7%. ER-HER2- patients were more likely to have died (27% (n=7) (HR 5.9 95%CI 1.69-20.46; p=0.005), with a 5-year OS of only 47%. Only 6% (n=4) of ER+HER2- patients died, they had a 5-year OS of 89.3%. Only 5% (n=1) of ER+HER2+ patients died (HR 1.47 95%CI 0.16-13.80; p=0.733) with a 5-year OS of 75%. **Conclusions** Despite optimum treatment, 23% of women under 35 with ER-HER2- breast cancer still died from their disease. In addition, even with this relatively short follow up, there is a subgroup of ER+HER2- patients who presented with a low nodal burden, were treated with full OFS and still recurred. This group of patients would benefit from somatic molecular testing to identify potential treatment targets. The majority of HER2+ patients in this cohort also had ER+ disease which is similar to previous reports of HER2+ breast cancer in young women. However contrary to that report, HER2+ positive patients in our study had a low risk of recurrence, this is likely due to the widespread use of targeted anti-HER2 therapy.

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# Lymphovascular invasion among female patients diagnosed with breast cancer

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**Background The presence of carcinoma cells in either lymphatic vessels, blood vessels or both is defined as lymphovascular invasion (LVI). The presence of LVI is associated with an increased risk of axillary lymph node and distant metastases. LVI is also characterized as one of the significant prognostic factors for the patients diagnosed with breast cancer. Objective The objective of this study is to identify predictors of LVI among female patients diagnosed with breast cancer. Method From the Commission on Cancer's National Cancer Database from 2010 through 2016, we identified 1,220,046 female patients diagnosed with breast cancer and with non-missing value for LVI. Patient demographics, tumor characteristics and biomarkers were analyzed using descriptive statistics. Odds ratios (OR) were computed using stepwise multivariate logistics regression. All statistical analysis was done using SAS version 9.4, SAS institute, Cary, NC and for all statistical tests alpha of 0.05 was used. Results The study population included 78% non-Hispanic white (NHW), 11% non-Hispanic black, (NHB), 5% Hispanic and 6% from 'other' race category. The median age of the patients at the time of diagnosis was 61 years. Of the total patients, only 16 % had LVI. Significant predictors of LVI include race (Hispanic vs NHW, OR=1.03, 1.01-1.06 p=0.008; NHB vs NHW OR=0.91,0.90-0.93, p<0.001; 'Other' vs NHW OR=0.97, 0.95-1.00, p=0.018), insurance status (government vs no-insurance , OR=1.08,1.04-1.11, p<0.001; private vs no-insurance, OR=1.08,1.05-1.12, p<0.001), Charlson-Dayo Index (1 vs none, OR=1.08, 1.06 -1.09, p<0.001, 2 vs none, OR=1.16, 1.12 -1.20, p<0.001, 3 or more vs none, OR=1.16 ,1.10 -1.22, p<0.001), primary sequence (OR=1.03,1.01-1.04, p<001), cancer stage (I vs 0, OR=2.99, 2.86-3.14, p <0.0001, II vs 0, OR=9.40,8.97-9.86 p <0.0001, III vs 0, OR=21.28, 20.25-22.36, p <0.0001, and IV vs 0, OR=15.11,14.32-15.94, p <0.001), ER (OR=1.02, 1.01-1.04 p=0.002), PR (OR=1.03, 1.01-1.05 p=0.002), HER2neu (equivocal vs negative OR=1.14, 1.10-1.18 p <0.001, positive vs negative OR=1.28, 1.26 -1.30, p <0.001), and 10 year increment in age at the time of diagnosis (OR=0.90, 0.89-0.90, p <0.001). Conclusion The predictive factors for LVI includes Hispanic race, government or private insurance, higher Charlson-Dayo scores, primary sequence, cancer stages, ER, PR and HER2neu expression. The chances LVI decreases with increasing age. These finding might provide insights for clinicians for the treatment plan for the patients.**

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# Population based survival of breast cancer in Greater Mumbai, India

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**Introduction:**
Population based survival provides a measure of the efficacy of cancer control in a defined geographical area. The Mumbai Cancer Registry (MCR), India's oldest population based cancer registry (PBCR), was established by the Indian Cancer Society (ICS) in 1963. It covers 603 sq. km. of Greater Mumbai with a population of 146, 51,584 (2015) and over half a century it has consistently provided cancer statistics from its coverage area. Breast cancer is the commonest cancer in women in Mumbai constituting 30% of all female cancers, and is now the most common cancer in women in India (1, 62,468 in 2018), constituting 27.66% of all female cancers. There have been few reports on breast cancer survival from India, and in this study, we report the survival rate of women diagnosed with breast cancer in Greater Mumbai during the years 2009-13.
**Patients and Methods:**
Breast cancer cases registered during the years 2009-13 with the MCR were followed for outcome till 31 Dec 2018. Social investigators visited hospitals, nursing homes, clinics, hospices and laboratory centers for documenting cancer cases. Mortality data was collected from the Vital Statistics Division of the Municipal Corporation. Data and was verified and duplicate cases were deleted. Follow up was conducted with repeated scrutiny of medical records, death certificates issued by the Municipal Corporation, postal and telephone enquiries, house visits and linkage with electoral database. Observed survival was calculated by the Kaplan Meir (1958) method. Expected survival was calculated using the national life-table of India for (Maharashtra) based on Census of India, 2011. Using observed and expected survival, relative survival was calculated by Ederer (1961) method using STATA 12.0. The survival rate was compared to that from other regions of India and with developed countries.
**Results:** Of the 9707 breast cancer cases registered during the period 2009-13, 8031 (83%) cases were included in this study. 1676 (17%) cases were excluded as 469 (5%) had only Death Certificate Information and 1207 (12%) were lost to follow up. The median follow up was 5.1 years (range 8 months - 9 years). The median age was 55 years (range 18 -96 years) with 2725(34%) ≤ 50 years and 5306 (66%) > 50 years. The overall observed survival rates at 1, 3, 5 years were 82.5%, 72.8% and 67.0% respectively and the corresponding figures for relative survival were 83.5%, 75.4%, and 70.9%. Increasing age had an inverse relationship with breast cancer survival. The highest 5-year relative survival was shown by ≤29 age group (74%) and lowest by >70 age group (60%). Those with localised disease at diagnosis had a higher 5-year relative survival rate (84%) compared to 79.7% for direct extension and 20.8% for distant metastasis. The clinical extent of disease and education were significant risk factors affecting survival ($p < 0.001$).
**Conclusion:**The 5-year population-based survival of patients treated in Greater Mumbai during the period 2009-2013, is 70%. This compares favourably with previously reported 5-year survival from Mumbai (51-55.7%) and other Indian registry data (33-55%), but is inferior to that reported in the developed world (84-88 %). The association of survival with educational status and stage at diagnosis highlights the importance of awareness and early detection. Enhanced awareness and detection coupled with easy access to adequate and affordable treatment could help improve breast cancer outcomes.

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# Molecular determinants of racial disparity guide triple-therapy for triple negative breast cancer

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**Background and Aim: Triple-negative breast cancer (TNBC) is a very aggressive subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor expression. Mortality from TNBC is significantly higher in African American (AA) women in comparison to White American (WA) women (5-year relative survival of only 14% for AA in comparison to 36% for WA) even though the incidence rates are lower in AA women. Irrespective of stage at diagnosis, AA-TNBC is more aggressive with higher metastasis and a poorer survival than WA-TNBC; therefore, it is imperative to understand the molecular determinants that drive aggressive progression of AA-TNBC. Overall aim of this study is to decipher the alterations in the molecular circuitry underlying racial disparity in TNBC progression in AA women compared to WA women. Results: AA-TNBC cells (HCC1806 and HCC1569) exhibited increased growth and higher migration potential; higher expression of stemness factors, increased number of mammospheres and higher CD44+/CD49f+ population in comparison to WA-TNBC (Hs578t, BT549, HCC1937 and HCC1187) cells. We analyzed RNA sequencing data of multiple AA and WA TNBC cell lines to query the status self-renewal pathways (Wnt/βCatenin, GLI1/Shh and YAP-TAZ) and observed significantly higher levels of GLI1 in AA-TNBC cell lines while no significant alterations were observed in other pathway components. Further analysis of TCGA dataset revealed a positive correlation between GLI1 and Notch1 in AA-TNBC with a negative correlation in WA-TNBC. Increased expression of components of GLI1 and Notch1 pathway (SHH, Jagged, cleaved-Notch (NICD), Hes1 and FOXM1) were noted in AA-TNBC compared to WA-TNBC cells. AA-TNBC cells showed increased nuclear localization of GLI1 and NICD as compared to WA-TNBC cells. We observed that GLI1 and NICD co-localize and co-immunoprecipitate in AA-TNBC indicating a direct interaction between these two transcription factors. High expression of GLI1 and Notch1 correlated with poor recurrence free survival in TNBC patients. Analyses of clinical samples revealed higher levels of nuclear NICD and GLI1 in AA-TNBC in comparison to WA-TNBC. Concomitant inhibition of GLI1 and Notch1 using respective small molecule inhibitors, GANT61 and DAPT, along with standard chemotherapeutic agents (Doxorubicin and carboplatin) effectively inhibited AA TNBC tumor growth in mice. Also, e*x vivo* analyses of tumor cells showed reduced migration and invasion potential as well as downregulation of CD44+/CD49f+ and ADLH1A1+ population in a synergistic manner. Combined treatment with GANT61+ DAPT+ Carboplatin effectively reduced stem cell frequency of AA-TNBC tumors in *in vivo* limiting dilution assay. Conclusions: In conclusion, these results show that AA-TNBC cells are inherently aggressive with increased growth, migration and stemness potential. We found aberrant activation of GLI1 and Notch pathway and a crosstalk between GLI1 and NICD whose inhibition effectively inhibits AA-TNBC and sensitizes AA-TNBC to standard chemotherapy. Our studies propose a 'triple drug regimen' for AA-TNBC tumors based on its molecular circuitry.**

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# Incidence, treatment and survival of patients with brain metastases at initial metastatic breast cancer diagnosis: A real-world experience in national cancer center, China

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**Background: To characterize the incidence, treatment and survival of patients with brain metastases at initial diagnosis of metastatic breast cancer (MBC) in China. Methods: The China National Cancer Center database was used to identify 2087 MBC patients diagnosed between 2003 to 2015. Clinicopathological features, treatment and survival information were extracted. Multivariable logistic and Cox regression were performed to determine factors predictive of brain metastases at MBC diagnosis and survival, respectively. Results: Brain metastases occurred in ninety patients (4.3%) at MBC diagnosis, and in 27 patients (2.5%), 42 patients (7.2%) and 21 patients (5.2%) with hormone receptor positive, human epidermal growth factor receptor 2 negative (HR+HER2-), HER2-positive and triple negative breast cancer (TNBC), respectively. HER2-positive subtype (OR = 2.38; 95% CI 1.40 -4.04; p <0.0001), TNBC subtype (OR = 1.89; 95% CI 1.02-3.51; p =0.005), and metastases to all three sites of bone, liver and lungs (OR = 3.23; 95% CI 1.52-6.87; p =0.002) were shown to increase the risk of BM at MBC diagnosis. Median survival after BM was 23.7 months. First-line tyrosine kinase inhibitors (TKI) improved survival compared to trastuzumab-based regimen (44.9 vs 35.4 months, p=0.09). Factors that independently decreased BM death risk were ECOG<2, brain metastases only and multidisciplinary treatment. Conclusion: HER2-positive and TNBC subtypes have a higher incidence of BM at initial MBC diagnosis. Brain screening might be considered in patients with HER2-positive or triple-negative diseases or with extensive extracranial metastases. First-line TKI and multidisciplinary treatment helped to extend survival.**

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# Effect of the COVID-19 pandemic on the initial treatment of breast cancer in the Netherlands: A population-based study

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*Introduction* The COVID-19 pandemic led to a significant drop in the incidence of cancer diagnoses in the Netherlands, partially due to the suspension of all national cancer screening programs on 16th March 2020 (week 12). Hospitals were forced to focus on care for COVID-19 patients resulting in limited capacity and down scaling of health care for non-COVID-19 patients. Specific recommendations for breast cancer treatment strategies, such as alterations in sequence, type, and/or frequency, were temporarily implemented from week 12 onwards. The aim of this study was to investigate the impact of the first outbreak on the initial treatment of breast cancer patients.
*Methods* Women older than 18 years, treated within three months following their breast cancer diagnosis during weeks 2-17 2018-2019 (reference period) or weeks 2-17 2020 (COVID-19 period), were selected from the Netherlands Cancer Registry. Weeks 2-17 2020 were split up in four periods, based on the number of breast cancer diagnoses: weeks 2-8, weeks 9-11, weeks 12-13, and weeks 14-17. Average number of breast conserving surgeries (BCS), mastectomies with direct reconstruction (DR), mastectomies without DR, chemotherapy, endocrine therapy or other therapies, given as initial treatment per week, were calculated, stratified by period and by tumor stage. Treatments given to patients diagnosed in the reference period were compared with treatments given to patients diagnosed in the COVID-19 period, using a Mantel-Haenszel test, adjusting for age.
*Results* A total of 16,553 patients were included in the current study. Of these patients 5,504 received their initial treatment in weeks 2-17 2018, 5,641 in weeks 2-17 2019 and 5,408 in weeks 2-17 2020. An increase in the use of endocrine therapy was seen in weeks 12-13 and 14-17 2020 compared to weeks 2-17 2018/2019, especially for patients with stage I cancer (12.3% and 7.7% vs 4.8%) and stage II cancer (25.4% and 17.4% vs 13.4%). In addition, a lower proportion of patients with stage II breast cancer received chemotherapy as first treatment in weeks 12-13 (21.1%) and 14-17 2020 (20.1%) compared to weeks 2-17 2018/2019 (29.8%) (Table).
*Discussion* The COVID-19 pandemic led to a major increase in the use of endocrine therapy following the recommendations, which was mainly used to enable postponing surgery. The lower use of chemotherapy was probably related to the thought to limit hospital visits and the expected higher risk of developing COVID-19 complications due to chemotherapy. Possible long-term effects of changes in initial treatments will be monitored.

Average number (percentage) initial treatments per week, stratified by stage and period

| | Total | Breast conserving surgery | Mastectomy with direct reconstruction | Mastectomy without direct reconstruction | Chemotherapy | Endocrine therapy | Total |
|---|---|---|---|---|---|---|---|
| DCIS | | | | | | | |
| Week 2-17 2018/2019 | 40.6 | 29.5 (72.7) | 4.9 (12.0) | 5.7 (13.9) | 0.1 (0.2) | 0.3 (0.8) | 0.1 (0.2) |
| Week 2-8 2020 | 43.7 | 30.9 (70.6) | 5.0 (11.4) | 7.3 (16.7) | 0.4 (1.0) | 0.1 (0.3) | 0.0 (0.0) |
| Week 9-11 2020 | 38.0 | 27.0 (71.1) | 4.0 (10.5) | 7.0 (18.4) | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) |
| Week 12-13 2020 | 48.0 | 31.5 (65.6) | 7.0 (14.6) | 7.0 (14.6) | 0.0 (0.0) | 2.5 (5.2) ↑ | 0.0 (0.0) |
| Week 14-17 2020 | 28.3 | 19.0 (67.3) | 3.0 (10.6) | 5.8 (20.4) ↑ | 0.0 (0.0) | 0.5 (1.8) | 0.0 (0.0) |
| Stage I | | | | | | | |
| Week 2-17 2018/2019 | 146.2 | 104.5 (71.5) | 10.0 (6.8) | 17.8 (12.2) | 6.2 (4.3) | 7.0 (4.8) | 0.7 (0.5) |
| Week 2-8 2020 | 148.4 | 107.9 (72.7) | 7.0 (4.7) ↓ | 15.3 (10.3) | 10.0 (6.7) ↑ | 7.4 (5.0) | 0.9 (0.6) |
| Week 9-11 2020 | 131.7 | 93.7 (71.1) | 8.0 (6.1) | 14.3 (10.9) | 6.3 (4.8) | 8.0 (6.1) | 1.3 (1.0) |
| Week 12-13 2020 | 163.0 | 107.5 (66.0)[a] | 10.0 (6.1) | 20.0 (12.3)[b] | 4.5 (2.8) | 20.0 (12.3)[c] | 1.0 (0.6) |
| Week 14-17 2020 | 117.3 | 77.0 (65.7) ↓ | 10.8 (9.2) | 16.8 (14.3) | 3.3 (2.8) | 9.0 (7.7) ↑ | 0.5 (0.4) |
| Stage II | | | | | | | |
| Week 2-17 2018/2019 | 114.9 | 37.0 (32.2) | 5.0 (4.3) | 20.8 (18.1) | 34.3 (29.8) | 15.4 (13.4) | 2.5 (2.2) |
| Week 2-8 2020 | 116.1 | 33.4 (28.8) ↓ | 4.1 (3.6) | 18.4 (15.9) | 38.4 (33.1) ↑ | 18.3 (15.7) | 3.4 (3.0) |
| Week 9-11 2020 | 118.7 | 35.7 (30.1) | 5.7 (4.8) | 19.0 (16.0) | 36.0 (30.3) | 20.0 (16.9) | 2.3 (2.0) |
| Week 12-13 2020 | 142.0 | 42.5 (29.9) | 5.5 (3.9) | 26.5 (18.7) | 30.0 (21.1) ↓ | 36.0 (25.4)[d] | 1.5 (1.1) |
| Week 14-17 2020 | 83.3 | 27.5 (33.0) | 5.5 (6.6) | 16.0 (19.2) | 16.8 (20.1) ↓ | 14.5 (17.4)[e] | 3.0 (3.6) |
| Stage III | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Week 2-17 2018/2019** | **31.1** | **2.0 (6.3)** | **0.5 (1.7)** | **5.8 (18.5)** | **16.0 (51.5)** | **5.3 (17.0)** | **1.6 (5.0)** |
| **Week 2-8 2020** | **27.9** | **2.4 (8.7)** | **0.6 (2.1)** | **5.0 (17.9)** | **14.3 (51.3)** | **4.7 (16.9)** | **0.9 (3.1)** |
| **Week 9-11 2020** | **26.7** | **2.0 (7.5)** | **0.3 (1.3)** | **5.7 (21.3)** | **12.7 (47.5)[f]** | **5.7 (21.3)** | **0.3 (1.3)** |
| **Week 12-13 2020** | **38.5** | **2.0 (5.2)** | **0.5 (1.3)** | **7.5 (19.5)** | **19.0 (49.4)** | **8.5 (22.1)** | **1.0 (2.6)** |
| **Week 14-17 2020** | **20.8** | **1.5 (7.2)** | **1.3 (6.0) ↑** | **4.5 (21.7)** | **8.0 (38.6)** | **4.5 (21.7)** | **1.0 (4.8)** |
| **Stage IV** | | | | | | | |
| **Week 2-17 2018/2019** | **15.0** | **0.3 (2.3)** | **0.0 (0.2)** | **0.6 (4.0)** | **5.3 (34.9)** | **6.8 (44.9)** | **2.1 (13.7)** |
| **Week 2-8 2020** | **14.6** | **0.6 (3.9)** | **0.0 (0.0)** | **0.4 (2.9)** | **4.7 (32.4)** | **6.7 (46.1)** | **2.1 (14.7)** |
| **Week 9-11 2020** | **12.0** | **0.0 (0.0)** | **0.0 (0.0)** | **0.0 (0.0)** | **3.3 (27.8)** | **7.0 (58.3)** | **1.3 (11.1)** |
| **Week 12-13 2020** | **19.5** | **1.5 (7.7)** | **0.0 (0.0)** | **2.5 (12.8) ↑** | **6.0 (30.8)** | **7.5 (38.5)** | **2.0 (10.3)** |
| **Week 14-17 2020** | **13.8** | **0.3 (1.8)[g]** | **0.0 (0.0)** | **0.3 (1.8)** | **3.8 (27.3)** | **8.3 (60.0) ↑** | **1.3 (9.1)** |

**Foodnote by table: Weeks 2-17 2020 (the COVID-19 period) were compared to the same weeks in 2018-2019, adjusted for age (<40, 40-50, 50-65, 65-74, >74). A statistically significant: ↑ higher proportion of patients received this therapy, corrected for age; ↓ lower proportion of patients received this therapy, corrected for age; a: lower proportion of patients aged between 50 and 64 years received BCS; b: higher proportion of patients aged 39 or younger received mastectomy without DR; c: higher proportion of patients aged 39 or younger, or aged between 50 and 75 years received endocrine therapy; d: higher proportion of patients aged between 40 and 74 years received endocrine therapy; e: higher proportion of patients aged 74 or younger received endocrine therapy; f: higher proportion of patients aged 39 or younger received chemotherapy; g: higher proportion of patients aged 75 years or older received BCS**

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# The socioeconomic impact of breast cancer in Brazil: An analysis of AMAZONA III cohort study

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**INTRODUCTION**Patients diagnosed with breast cancer (BC) in Brazil are on average 54 years old and the majority (70%) have stage II-III. Age and clinical stage have a negative impact on patient personal life and labor productivity. The socioeconomic status is a fundamental part of the population's health, which includes marital and employment status. Our aim was to analyze the socioeconomic impact of BC diagnosis which is poorly studied in low or middle-income countries.

**METHODS**This is a cross-sectional study including patients from AMAZONA III cohort study. Eligible patients were female aged > 18 years with diagnosis of any stage invasive BC from 2016 to 2018 in 24 participating hospitals in Brazil. The present analysis evaluated the marital and employment status at baseline and at 1-year follow-up after BC diagnosis. Patients with missing data were excluded and women older than 60 years, retirement age in Brazil, were not included in this analysis. A multivariate Poisson regression analysis with robust variance was adjusted to assess which patients' characteristics associated with job loss and relationship status. The characteristics evaluated were age (<= 50 vs. > 50 years), educational level (Illiterate to completed first degree or completed second degree vs. higher), personal income (no income – 2 minimum wages vs. 2 to 5 minimum wages vs. more than 5 minimum wages), clinical-stage (I-III vs. IV), molecular subtype (luminal, HER2 positive vs. triple negative), surgery type (breast conserving surgery vs. any type of mastectomy ), and systemic treatment (chemotherapy vs. hormonal therapy vs. none). The significance level was set at 5%. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

**RESULTS**From a total of 1257 patients with evaluable employment status, 655 patients (52.1%) had working activity at the time of BC diagnosis. After 1 year of follow-up, there was an absolute decrease of 5.3% in patients' employment (52.1% to 46.8%; p= 0.0075). Loss of employment was higher in older patient > 50 years (8.7%), lower educational level (9.9%), those earning 2-5 minimum wages (11.2%), stage I-III (7%), triple negative (6.9%), mastectomy (9.9%) and treatment with hormone therapy (11%). Patients with higher educational level (RR 0.61, 95% CI 0.36-0.94, p=0.0265) were at lower risk of employment loss whereas patients with personal income of more than 2 minimum wages (RR 1.83, 95% CI 1.08-3.10, p=0.0236) and mastectomy (RR 2.16, 95% CI 1.47-3.17, p=0.0015) were at higher risk of being unemployed loss after 1 year of diagnosis. Other factors such as age, clinical stage, BC subtype and treatment were not independently associated with unemployment. A total of 1947 patients had marital status information at baseline. Of those, 1182 (60.7%) were married or in common-law marriage at BC diagnosis. After 1 year of follow-up, 52 (2.7%) of these women loss their relationship (60.7% vs. 58%; p=0.08). Loss of relationships was higher (5.2%) in younger patients (≤ 50 years), lower educational level (4.9%), no income or up to 2 minimum wages (5.4%), stage IV (7.7%), HER2 positive (5.5%), mastectomy (5.4%) and treatment with hormone therapy (5.5%). None of the variables evaluated such as age, educational level, personal income, clinical-stage, molecular subtype, surgery type and systemic treatment, were significantly associated with change of marital status for patients previously married or in common-law marriage.

**CONCLUSION**

The socioeconomic impact of BC diagnosis was minimal at 1-year follow-up in Brazil. Nonetheless personal income and surgery type were associated with higher chance of unemployment whereas no specific variables were related to marital status change. Government social policies specifically for work return remains critical for BC patients in short-term after BC diagnosis.

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# Reproductive breast cancer risk factors and breast tissue composition on benign breast biopsies

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**Background: Reproductive factors related to childbearing are recognized as breast cancer risk factors. Whether any of these factors could influence adult breast tissue composition is unclear. We investigated the associations of reproductive factors with percentage of epithelium, stroma, and fat tissue in benign breast biopsy samples. Methods: This study included 983 cancer-free women with biopsy-confirmed benign breast disease (BBD) within the Nurses' Health Study and Nurses' Health Study II cohorts. Percentage of each tissue type (epithelium stroma, and fat) was measured on whole section images with a deep-learning technique. All tissue measures were log-transformed in all the analyses to improve normality. The data on reproductive variables and other breast cancer risk factors were obtained from biennial questionnaires. Generalized linear regression was used to examine the associations of reproductive factors (parity, age at first birth, breastfeeding, age at menarche and the duration of the interval between menarche and age at first birth) with percentage of tissue types, while adjusting for known breast cancer risk factors.Results: In this study of 983 cancer-free women, 299 (30.4%) had non-proliferative disease, 559 (56.9%) had proliferative disease without atypia, and 125 (12.7%) had atypical hyperplasia, consistent with previously reported distributions of these BBD subtypes. The average proportion of epithelium, stroma, and fat in our study sample was 9.1% (range 0.5-52.2%), 72.4% (range 23.6-99.0%), and 18.5% (range 0-71.3%), respectively. As compared to parous women, nulliparous women had a smaller percentage of epithelium (β= -0.26, 95% confidence interval [CI] -0.41, -0.11) and fat (β= -0.34, 95% CI -0.54, -0.13) and a greater percentage of stroma (β=0.04, 95% CI 0.01, 0.08). Among parous women, number of children was inversely associated with percentage of stroma (β per child= -0.01 (-0.02, -0.00). Duration of breastfeeding of ≥24 months was associated with a reduced proportion of fat (β= -0.30, 95% CI -0.54, -0.06; p-trend=0.04). In a separate analysis restricted to premenopausal women, being nulliparous was associated with a greater proportion of stroma (β=0.06, 95% CI 0.02, 0.10) and smaller proportion of epithelium (β= -0.22, 95% CI -0.38, -0.06) and fat (β= -0.32, 95% CI -0.56,**
**-0.08). Greater parity and older age at first birth were both associated with a greater proportion of epithelium (and a smaller proportion of stroma. The age at menarche and the duration of the interval between age at menarche and first birth were not associated with the proportion of any of the tissue types. Conclusions: Our findings suggest that reproductive factors with a protective effect on breast cancer risk may be associated with a greater proportion of epithelium and a smaller proportion of stroma, potentially suggesting importance of epithelial-stromal interactions. Future studies are warranted to confirm our findings and to elucidate the underlying biological mechanisms.**

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# Influence of physician's lifestyle on the prescription of healthy habits to breast cancer patients (LACOG 1218)

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**BACKGROUND Healthy lifestyle has been shown to have a positive impact on quality of life, risk of recurrence, and overall survival in breast cancer (BC). Physicians play an important role in encouraging their patients to lifestyle modification. Nonetheless, little is known whether physician lifestyle can impact on healthy habits recommendations to BC patients. We aimed to evaluate how physician's lifestyle influences the prescription of healthy habits to BC patients. METHODSLACOG 1218 was an observational, cross-sectional study. An online questionnaire composed of 14 objective questions to evaluate physician lifestyle and prescription of healthy habits to BC patients was developed and circulated by e-mail to breast surgeons, clinical and radiation oncologists who were members of the Brazilian Society of Clinical Oncology (SBOC) and Latin American Cooperative Oncology Group (LACOG) and dedicated to the treatment of BC patients. The primary objective of the study was to evaluate the correlation between the physician lifestyle and the prescription of healthy habits to BC patients. A multivariate Poisson regression analysis was used to assess which factors of physician lifestyle could influence prescription of healthy habits.RESULTSA total of 267 physicians answered the questionnaire from October to November 2018. Of these, 142 (53.2%) were clinical oncologists, 116 (43.5%) were breast surgeons, and 9 (3.4%) were radiation oncologists. Female were 58.4%, 51.8% were older than 50 years and the majority 71.5% worked in private health insurance practice. In terms of physician lifestyle, 228 (85.4%) had healthy eating habits, 236 (88.4%) practiced physical activity and 93 (34.9%) were self-reported with overweight or obese. A total of 143 (46.1%) did not drink alcohol or drunk less than once a month and did not consume more than 5 doses and only 8 (3%) of them were current smoker. Overall, 84.3% of the physicians advised their BC patients on the importance of lifestyle modification. Physicians who did not exercise regularly have a higher chance of not advising for health lifestyle (HR 2.48; 95% CI 1.28 to 4.82, p=0.0265) as opposite to physicians older than 50 years (RR 0.37; CI 95% 0.15 - 0.92; p=0.0118).Obesity treatment and management was performed by 121 (45.3%) of physicians. Being a breast surgeon (RR 1.29; 95% CI 1.02 to 1.63, p=0.0025) or radiation oncologists (RR 1.82; 95% CI 1.43 to 2.31, p=0.0025) were the only factors associated with not performing obesity treatment and management. About 53.4% of physicians referred overweight or obese patients to a dietician and/or endocrinologist. Male gender (RR 1.35; CI 95% 1.03-1.76; p=0.0296), breast surgeons (RR 1.99; CI 95% 1.50-2.64; p=0.0001) and clinical practice in public health system (RR 1.53; CI 95% 1.20-1.96; p=0.0012) were factors associated with not referring patients to dietician and/or endocrinologist as opposed to physicians older than 50 years (RR 0.46; CI 95% 0.28-0.75; p=0.0005).CONCLUSIONIn general physicians treating BC patients have a healthy lifestyle. Physicians who practice physical activity regularly or older than 50 years had more chance to advise lifestyle modification. Only half of BC patients' physicians treat obesity or refer these patients to specialist which in this case may impact BC patient's outcome.**

2020 SABCS De-escalation of Surgical Therapy: What Does the Data Support
DCIS PRO

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Although almost all DCIS is treated as if it would progress to invasion, DCIS represents a heterogeneous disease with a wide range of outcomes according to biology. Long-term outcomes following treatment are at least as favorable as those for some other early stage cancer types such as prostate cancer, for which active surveillance is now routinely offered as a standard of care option. However, active surveillance has not yet been tested in relation to DCIS**.** Worldwide, there are four international trials (LORIS, COMET, LORD, LORETTA) which are evaluating whether DCIS with favorable biologic features may be managed with close monitoring, with treatment only undertaken if there is disease progression. These trials will determine whether there may be some women with low-risk DCIS who do not substantially benefit from treatment and who could thus be safely managed with close surveillance. For active monitoring for DCIS to be safe and feasible, additional work must be done to optimally implement this approach, involving effective communication between patients and their physicians about the risks and benefits of treatment versus surveillance. Importantly, these treatment decisions must take into account patient factors such as risk tolerance, age, and competing causes of mortality. Emerging evidence from epidemiology, clinical trials, and correlative biomarker studies, will permit accurate risk stratification that will be needed to change practice.