Independent validation of the HER2DX genomic test in HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab +/- pertuzumab (TCH/TCHP): a correlative analysis from a multicenter academic study.

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Background: HER2DX (Prat et al. EBiomedicine 2022) is a 27-gene prognostic (risk-score) and predictive (pathological complete response [pCR]-score) assay in early-stage HER2+ breast cancer based on clinical data and the expression of 4 gene signatures (immune, proliferation, luminal differentiation and HER2 amplicon). Here, we aim to evaluate, for the first time, the ability of HER2DX to predict pCR following neoadjuvant TCH or TCHP in HER2+ disease. Methods: Standardized HER2DX was performed in a central lab on baseline pre-treatment FFPE tumor biopsies from the GOM-HGUGM-2018-05 study in Spain, a consecutive retrospective series of patients (pts) with newly diagnosed stage I-III HER2+ breast cancer eligible for neoadjuvant therapy. Pts received standard 6 cycles of docetaxel, carboplatin and trastuzumab (TCH) or TCH with pertuzumab (TCHP) regimens. Primary aim was to test the ability of HER2DX pCR score to predict pCR (ypT0/is ypN0). Secondary objectives were to test the ability of HER2DX pCR score to predict pCR independently of clinical-pathological variables and the PAM50 subtype (HER2-enriched versus not), and to evaluate the association of HER2DX pCR score with the HER2DX risk-score. Logistic regression and receiver-operator curve (ROC) analysis were assessed. Statistical analyses were performed in R code 4.0.5. Results: HER2DX was evaluated in 155 pts (97%) enrolled in the study with available RNA (as of June 2022). Mean age of pts was 50 (range 22-74) and 55.2% of pts (n=85) were pre-menopausal. Clinical T2-4 disease represented 77.4% of cases (n=120), clinical node-positive disease (cN1-3) represented 63.9% of cases (n=99), and 68.0% of tumors (n=105) were hormone receptor-positive. The overall pCR rate was 57.4% (95% confidence interval [CI] 50-65): 52.2% (95% CI 40-64) with TCH (n=67) and 61.4% (95% CI 50-72) with TCHP (n=88). The proportion of HER2DX low-, medium- and high-pCR groups was 34.2%, 34.8% and 31.0%, respectively. HER2DX pCR score (as a continuous variable from 0 to 100) was significantly associated with pCR (odd ratio [OR]=1.03, p=5.91e-07). The pCR rates in HER2DX pCR-high and pCR-low groups were 75.0% and 28.0% (OR=7.6, 95% CI 3.2-19.1, p=7.14e-06), respectively. In pts treated with TCHP, the pCR rates in HER2DX pCR-high and pCR-low groups were 85.7% and 27.3% (OR=16.0, 95% CI 4.3-59.01, p=3.2e-05), respectively. The AUC ROC of HER2DX pCR score (as a continuous variable) and pCR status was 0.746 (in all pts) and 0.812 (in pts treated with TCHP). HER2DX pCR score was significantly associated with pCR independently of hormone receptor status, Ki67, age, menopausal status, pertuzumab use, clinical stage and PAM50 HER2-enriched subtype. The proportion of HER2DX low- and high-risk of relapse disease was 32.0% and 68.0%, respectively. The correlation of HER2DX pCR score and HER2DX risk-score was weak (coefficient=-0.17), as previously described. Proportion of cases according to both HER2DX scores and absolute
difference of pCR rates between TCHP and TCH in each combined group is shown in Table. Conclusion: The HER2DX genomic test predicts pCR following neoadjuvant TCH or TCHP regimens independently of clinical-pathological variables and intrinsic subtype. The combination of both HER2DX scores might help better tailor systemic therapy in patients with newly diagnosed stage I-III HER2+ breast cancer.

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Stromal tumor infiltrating lymphocytes and pathological complete response in patients with inflammatory breast cancer treated with neoadjuvant chemotherapy

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Background: Inflammatory breast cancer (IBC) is a rare (1-5%), but aggressive form of breast cancer (BC), accounting for ~10% of BC mortality. In early setting (M0), standard of care is neoadjuvant chemotherapy (NACT), followed by surgery. Nevertheless, outcome is still relatively poor. Pathological complete response (pCR) after NACT is prognostic in BC in general, and can be predicted by a high percentage of stromal tumor infiltrating lymphocytes (sTIL) in the primary tumor. The predictive value of sTIL in IBC has only been sporadically investigated, often in smaller series. Our aim was to determine which variables, including sTIL, are associated with pCR and to determine the prognostic value of pCR in IBC in a large multicentric, retrospective cohort.

Patients & Methods: We included patients with IBC treated with NACT +/- anti-Human Epidermal growth factor Receptor 2 (HER2) therapy, followed by surgery from 10/1996 to 10/2021 in 7 different European hospitals. Clinicopathological variables were collected and central pathological review was performed, including sTIL scoring. This study focused on M0 cases. Considered clinicopathological variables were: age, histology, tumor grade, estrogen receptor status (ER), HER2 status, focality (unifocal vs not), and baseline locoregional nodal status (Table 1). Associations between pCR, clinicopathological variables and sTIL were assessed using Firth’s logistic regression models: Model 1 was adjusted for center, Model 2 additionally included all variables of interest. Similarly, linear regression was used to investigate the association between sTIL and clinicopathological features. Univariable and multivariable Cox regression was used to evaluate the role of pCR on disease free survival (DFS), distant recurrence free survival (DRFS) and overall survival (OS). DFS and DRFS were analyzed considering death without the respective event as competing risk.

Results: 494 patients were included. The distribution according to receptor status was: ER-/HER2- (24.3%), ER+/HER2- (34.4%), ER+/HER2+ (13%) and ER-/HER2+ (20.2%). pCR rate was 26% and per receptor status: ER-/HER2- (28%), ER+/HER2- (10%), ER+/HER2+ (42%) and ER-/HER2+ (45%). pCR was associated with grade (G3 vs G1/2, OR = 2.79 (1.70 - 4.74), p < .001), ER-status (positive vs negative, OR = 0.39 (0.26 - 0.60), p < .001) and HER2 status (positive vs negative, OR = 3.74 (2.43 - 5.81), p < .001) in Model 1. Only the association with HER2 status remained significant in Model 2 (OR = 5.34 (2.83 - 10.47), p < .001). sTIL was scored for 385 patients. Median sTIL was 5.3% [IQR 2.0%;16.7%] and according to receptor status: ER-/HER2- (10%), ER+/HER2- (2.5%), ER+/HER2+ (6.7%) and ER-/HER2+ (8.3%). Higher sTIL was associated with NST (p = .032), grade 3 (p = .015), and ER-negativity (p = .007) in Model 1. This was no longer significant in Model 2, but the direction of the trends was preserved. sTIL was associated with pCR (5% increment, OR = 1.13 (1.05 - 1.22), p = .002), but no longer after adjustment. No association between pCR and sTIL was found stratifying by receptor status. The median FU was 9.4 years and multivariable Cox regression models revealed that ER+ and HER2+ status and achieving pCR were significantly associated with
better DFS, DRFS, and OS (Table1). Conclusion: Our results indicate that patients with HER2+ tumors have a higher probability of achieving pCR and that pCR has an independent prognostic role in IBC. This is the largest IBC study with centrally scored sTIL, demonstrating that sTIL is associated with pCR but its role as an independent predictor of pCR is still not certain.
C-C Chemokine Receptor 2-positive Monocytic Myeloid-Derived Suppressor Cells Predicts Chemotherapeutic Responses of Metastatic Lesions of Breast Cancer Patients

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Anti-tumoral T cell immunity is counterbalanced by several types of immunosuppressive cells such as Myeloid-Derived Suppressor Cells (MDSC). Circulating MDSC levels correlate with poor prognosis and metastatic progression of breast cancer patients. However, the value of MDSC in predicting chemotherapeutic treatment responses in metastatic lesions is not clearly understood. We performed a prospective cohort clinical study to measure MDSC before and after chemotherapy in metastatic breast cancer patients (N=64). Multicolor flow cytometry was used to quantitate two major subtypes, i.e. monocytic (M-, HLA-DRlow/-CD45+CD11b+CD15-CD14+) and polymorphonuclear (PMN-, CD45+CD11b+CD33+CD15+ CD14-) MDSC, and one additional subtype, C-C chemokine receptor 2 (CCR2)-positive M-MDSC in the fresh peripheral blood mononuclear cells. PMN-MDSC and CCR2+ M-MDSC, but not M-MDSC, were significantly increased after chemotherapy. Subsequently, we divided the patients by two groups (therapy-sensitive vs. -resistant groups) by treatment responses. Treatment-resistant patients had significantly increased CCR2+ M-MDSC. Unsupervised clustering of patients based on MDSCs populations dichotomized patients PMN-MDSC high or M-MDSC high groups. M-MDSC high patients had increased bone and lymph node metastasis. In addition, CCR2+ M-MDSC levels correlated with progression-free survival (P< 0.05). Altogether, our results showed that CCR2+ M-MDSC levels potentially predict the therapeutic responses in the metastatic lesions of breast cancer patients.
12/9/2022
7:00 AM - 8:15 AM
Poster Session 6
Validation of an Optical Imaging Platform to Identify Metabolic Vulnerabilities in Chemo-Resistant and Sensitive Tumors

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Less than 20% of Triple Negative Breast Cancer (TNBC) patients experience long-term responses to mainstay chemotherapy, as tumors develop chemo-resistance. While combinations of chemotherapies and targeted therapies show potential improvements in TNBC clinical outcomes, patient stratification and prediction of treatment response is critical. Spatio-temporal metabolic reprogramming holds promise as a biomarker of therapy response as resistant tumor subpopulations utilize alternate metabolic pathways to escape therapy, enter minimum residual disease (MRD) and recur. Currently, there are limited tools to temporally evaluate heterogeneous changes along distinct metabolic axes in vivo at a spatial resolution capable of resolving vulnerabilities of residual tumor subpopulations. Here, we utilized an optical imaging-based platform to identify in vivo, longitudinal differences in metabolic reprogramming between a resistant and sensitive tumor model at high resolutions along three metabolic axes of TNBC chemoresistance (oxidative phosphorylation, glycolysis, and fatty acid oxidation). Xenografts were established by orthotopic cell injection and mice were treated with Paclitaxel (PTX), a commonly used chemotherapeutic drug in TNBC treatment, under a conventional maximum dose density regimen once the tumor reached a volume ~150mm3. MDA-MB-231 xenografts were resistant to PTX, defined as an initial response to PTX, a period of minimal residual disease, and a resurgence in tumor volume at ~60 days post drug withdrawal (n=3). HCC-1806 xenografts were sensitive to PTX, defined as an initial response to PTX in all mice and a complete cure in 7/10 mice. A separate cohort of mice for each tumor line was implanted with window chambers and imaged longitudinally at distinct stages of the tumor’s lifecycle with previously validated fluorophores 2-NBDG, TMRE, and Bodipy to directly report on glucose uptake, mitochondrial membrane potential, or fatty acid uptake, respectively. Wide field fluorescence imaging of MDA-MB-231 mice showed a significant increase in TMRE as early as two days after the 3rd PTX dose (n=5, p< 0.05), a significant decrease in 2-NBDG as early as two days after the 5th PTX dose (n=5, p< 0.05) and no significant changes in bodipy uptake. This increase in non-glucose-driven mitochondrial respiration was sustained during
MRD. An increase in heterogeneity of TMRE uptake was seen during disease regression, MRD, and recurrence (n=5, p<0.05). HCC-1806 tumors showed increased glucose uptake, decreased fatty acid uptake, and no significant changes in mitochondrial membrane potential during acute treatment. Metabolic changes were transient, with no significant changes in probe uptakes after drug withdrawal and during MRD. Unlike the MDA-MB-231 tumors, no significant changes in the heterogeneity of TMRE uptake were seen following paclitaxel withdrawal in HCC-1806 tumors (n=5, p>0.05). Our results point towards a metabolic switch from glycolysis to non-glucose, non-fat-driven mitochondrial respiration in MDA-MB-231 mice, possibly suggesting amino acid catabolism as a fuel during MRD. In the sensitive HCC-1806 line, we observed changes in glucose and fatty acid uptake during acute treatment, but no significant changes in metabolism during MRD. Consistent with the literature, our results point toward an increase in metabolic plasticity and heterogeneity in a chemo-resistant model compared to a chemo-sensitive one. Together, our results show the potential of using metabolic changes following therapy as a biomarker of therapy response, while highlighting the importance of tracking the change (or lack of change) in metabolism longitudinally. We aim to use this system to visualize and exploit early, in vivo metabolic vulnerabilities of disease regression that accompany local and distal recurrences.

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Introduction:
MammaPrint, a 70-gene assay used to predict breast cancer recurrence, is typically obtained on the surgical specimen to guide the use of adjuvant chemotherapy. However, MammaPrint results obtained at the time of diagnosis on core biopsy specimen could allow consideration of neoadjuvant chemotherapy (NAC), particularly for tumors that may not traditionally be considered for NAC such as invasive lobular carcinoma (ILC). We hypothesized that MammaPrint scores correlate with pathologic complete response (pCR) and can predict NAC response independent of histology type.

Methods:
The National Cancer Database was used to identify patients with AJCC Stage I-III unilateral HR+/HER2- breast cancer with MammaPrint scores treated 2010-2018. Patients were stratified by histology: invasive ductal carcinoma (IDC) and ILC; and by MammaPrint score for 5-year breast cancer recurrence: Low Risk (1%) and High Risk (12%). Descriptive statistics identified clinical and treatment differences between groups. Logistic regression was used to identify factors associated with chemotherapy receipt and sequence. A subset analysis of patients receiving NAC compared pCR rates by MammaPrint score and histology type.

Results:
Of 10,999 patients, 9,351 (85%) were diagnosed with IDC and 1,648 (15%) with ILC. ILC were larger at presentation: 40% of ILC were cT2 or greater vs. 29% of IDC (p< 0.001). However, 90% of patients in both groups had cN0 disease. The majority of ILC were grade II (67% ILC vs. 52% IDC, p< 0.001). High Risk MammaPrint scores were significantly more common in IDC tumors: 44% IDC vs 25% ILC (p< 0.001). Mastectomy and axillary lymph node dissection (ALND) were performed more often for ILC than IDC (unilateral mastectomy 32% vs. 21%, bilateral mastectomy 17% vs. 12%, ALND 29% vs. 24%; all p< 0.001). Conversely, chemotherapy (38% vs. 30%, p< 0.001) and radiation (69% vs. 64%, p< 0.001) were more frequently used to treat IDC than ILC. In the subset analysis of patients who received NAC (n = 715), tumors with High Risk MammaPrint scores had more favorable in-breast and axillary responses than those with Low Risk scores for both ILC and IDC (Table 1). Furthermore, only tumors with High Risk MammaPrint scores achieved an overall pCR: 7% IDC and 5% ILC. There were no significant differences in pCR rates by histology type. On multivariable logistic regression, High Risk MammaPrint score was positively associated with the receipt of NAC (OR 4.3, p< 0.001) and adjuvant chemotherapy (OR 24.8, p< 0.001). NAC, adjuvant chemotherapy, and any chemotherapy were also strongly associated with node-positive disease and tumor size >2cm, but not IDC vs. ILC histology.

Conclusions:
Superior response to NAC was observed in tumors with High Risk MammaPrint score regardless of histology type, indicating a correlation between pCR rates and genomic assay results. Greater use of NAC guided by High Risk MammaPrint score obtained on core needle biopsy may allow patients with invasive breast cancer to undergo less extensive breast and axillary surgery. Further prospective studies using MammaPrint testing on core biopsy specimens could validate these findings in clinical practice.

| Table 1. Response to neoadjuvant chemotherapy by MammaPrint score for patients with invasive breast carcinoma, NCDB 2010-2018 |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Histology** | **Invasive Ductal Carcinoma** | **Invasive Lobular Carcinoma** |
| **MammaPrint Score** | **Low Risk** | **High Risk** | **p-value** | **Low Risk** | **High Risk** | **p-value** |
| **In Breast Response** | | | | | | |
| Downstage | 56 (46.3%) | 225 (49.6%) | <0.001 | 15 (27.8%) | 19 (38.8%) | 0.195 |
| pCR* | 6 (5.0%) | 49 (10.8%) | 0.053 | 1 (1.9%) | 3 (6.1%) | 0.263 |
| **Axillary Response** | | | | | | |
| Downstage | 4 (5.6%) | 62 (25.0%) | 0.340 | 4 (16.7%) | 6 (26.1%) | 0.597 |
| pCR* | 2 (2.8%) | 54 (25.0%) | <0.001 | 3 (12.5%) | 5 (21.7%) | 0.400 |
| **Combined Response** | | | | | | |
| n = 281 | n = 46 |
| pCR* | 0 (0.0%) | 15 (7.1%) | 0.021 | 0 (0.0%) | 1 (4.5%) | 0.291 |

*pCR = pathologic complete response

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Background: In ER+/HER2- breast cancer, several lines of evidence suggest that tumors with high level of tumor-infiltrating lymphocytes (TILs) have a greater chance of obtaining a pathological complete response (pCR) after neoadjuvant chemotherapy. In addition, high 21-gene recurrence score (RS) is associated with an increasing rate of pCR in luminal tumors. We investigated the relationship between TIL and RS in 1,883 patients with early ER+ HER2- breast cancer.

Method: In 1,883 ER+ breast cancer patients with 21-gene assay, TIL level was evaluated. Correlation between continuous TIL and RS was investigated. Logistic-regression analysis was performed to identify risk factors for high RS (≥26). The cut-off for high TIL was 50%. Recurrence-free survival (RFS) was investigated.

Results: A weak positive correlation between TIL level and RS was observed (correlation coefficient=0.283, p< 0.001) in all patients. Average TIL level of the high RS tumors was significantly higher. Two parameters were positively correlated in both two groups classified by age 50 years (correlation coefficient=0.281 in the age ≥50; correlation coefficient=0.288 in the age>50). Either continuous TILs or binary high TIL level was demonstrated to be an independent factor for high RS. When all patients were divided into 4 groups using TIL and RS (low-RS/low-TIL, low-RS/high-TIL, high-RS/low-TIL, and high-RS/high-TIL), the RFS was worst in the low-TIL/high-RS group (p< 0.001).

Conclusions: Our findings show that TIL level is correlated with RS in ER+ breast cancer regardless of age and suggest that high TIL level can be regarded as a risk factor for high RS. Multigene assay could be integrated in designing clinical trials evaluating immune-check point
blockades in luminal breast cancer.

Recurrence-free survival according to RS and TIL

<table>
<thead>
<tr>
<th></th>
<th>5-years RFS</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS-Low/TIL-Low</td>
<td>96.4±3</td>
<td>94.8-98.1±3</td>
</tr>
<tr>
<td>RS-Low/TIL-High</td>
<td>93.8±3</td>
<td>82.6-100.0±3</td>
</tr>
<tr>
<td>RS-High/TIL-Low</td>
<td>89.0±3</td>
<td>83.3-95.2±3</td>
</tr>
<tr>
<td>RS-High/TIL-High</td>
<td>94.4±3</td>
<td>84.4-100.0±3</td>
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</tbody>
</table>

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The Hierarchy of Biomarkers

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Background: Biomarkers with robust analytical and clinical validity can help optimize therapy decisions within clinical trials for patients with breast cancer, particularly if some data on clinical utility also exist. However, little is known about how physicians enrolling in clinical trials view them. Physician comfort with the integral use of conventional and investigational biomarkers for reducing chemotherapy intensity within clinical trials is explored in this study. Method: A convenience sample of academic and community oncologists from across the United States were invited to participate in qualitative interviews that explored their perspectives on the use of biomarkers for the de-escalation of chemotherapy in patients with breast cancer. Purposive sampling techniques were used to identify participants, ensuring even distribution of gender, work setting, and time practicing medical oncology. Interviews were audio-recorded and transcribed. Transcripts were analyzed by two independent coders to identify major themes and exemplary quotes in NVivo. A framework for understanding how providers conceptualize biomarkers was created. Results: There was a total of 39 physicians with a median age of 50; 51% of physicians were academic and 49% were community-based. 44% of oncologists have been in practice for less than 15 years, and 36% and 20% of oncologists were in practice for
15-30 years and over 30 years, respectively. The model on physician level of comfort for biomarker use consisted of 1) standard of care biomarkers, 2) standard biomarkers in newer contexts, and 3) experimental biomarkers with inclusion of additional related subthemes. There was a shared theme among physicians that historical experience with a biomarker made them more comfortable in de-escalation of chemotherapy. The greatest level of physician comfort with biomarker for de-escalation of chemotherapy came with biomarkers used in standard of care (e.g., MammaPrint, Oncotype DX). Themes related to these biomarkers included: strong level of evidence, agreement with NCCN guidelines, and widespread use in the community. For example, one physician stated, “for me to use a prognostic biomarker … typically it’s going to have to at least be within the NCCN guidelines or out there”. Secondly, physicians expressed reasonable confidence with some reluctance in the use of standard of care biomarkers in contexts that differ from where they were initially tested (i.e., use of biomarker in patients with different features or disease biology). These themes included the use of biomarkers in specific subtypes of cancer and when there is less supportive evidence. One physician commented, “It's just hard to analyze and really know whether [pathCR in ER+ setting] actually holds like it does for other tumor biology”. There was more hesitation and least comfort with experimental biomarkers (e.g., tumor-infiltrating lymphocytes, circulating tumor DNA). For experimental biomarkers, physicians were primarily concerned with the quality and quantity of evidence supporting their use. Prospective trials were favored over retrospective; however, physicians were accepting if the retrospective study included a large sample, other biomarkers were used in conjunction, or multiple studies confirmed the results. Other themes that emerged regarding experimental biomarkers were their testing in diverse populations and reproducibility. Physicians expressed contentment with experimental biomarkers that were proven in “multiple big enough studies”, were “reproducible and not subjective”, and “demonstrate utility in the patient population that's relevant”. Conclusion: Biomarkers can be divided into 3 successive levels: 1) standard of care biomarkers, 2) standard biomarkers in newer contexts, and 3) experimental biomarkers. Level of comfort concerning the use of biomarkers for de-escalation of chemotherapy is related to level of evidence for experimental biomarkers.

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Platelet-derived growth factor-CC expression in primary triple-negative breast cancer is associated with the basal-like molecular subtype and increased immune infiltrate

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Around 10-15% of all breast cancers are categorized clinically as triple-negative breast cancer (TNBC). TNBC is defined by lack of protein expression or over expression of treatment targets such as the Estrogen Receptor α (ER) and Human Epidermal Growth Factor Receptor-2 (HER2), and the prognostic factor PR (Progesterone Receptor). The negative definition of TNBC results in a heterogeneous mix of tumors with variable molecular characteristics and prognosis. Defining TNBC molecular subtypes in detail is of importance to improve prognostication and find new treatment options. Expression of Platelet-derived growth factor-CC (PDGF-CC) has previously been correlated with the TNBC subtype, and paracrine PDGF-CC signaling has been reported to be of importance for maintaining TNBC tumor cell phenotype. We aimed to characterize PDGF-CC expression within the TNBC patient population by combining studies of PDGF-CC in tissue microarrays (TMAs) with matching RNAseq data and clinical follow-up; all variables originating from the SCAN-B (Sweden Cancerome Analysis Network – Breast) clinical study (ClinicalTrials.gov: NCT02306096). TMAs constructed of primary TNBC patient samples were stained for PDGF-CC using the Dako PT Autostainer system. Tumor cell-specific expression of PDGF-CC intensity was scored as either absent (N=11), weak (N=86), intermediate (N=81) or strong (N=70), and the scores were used to
create corresponding TNBC PDGF-CC subgroups. We then explored associations of these subgroups with clinicopathological variables and time-to-event outcomes. Intermediate and strong PDGF-CC scores were associated with Nottingham Histological Grade 3 (p=0.001), increased proliferation (p< 0.001) and younger patient age at diagnosis (p=0.002). RNAseq data corresponding to tumors included in the TMAs was then retrieved, and differentially expressed genes were identified and used to perform Gene Set Enrichment Analysis (GSEA) comparing the TMA-derived PDGF-CC subgroups. Immune-related signatures were found to be enriched in the strong PDGF-CC subgroup vs. intermediate. Interestingly, strong PDGF-CC intensity was associated with a decreased risk of recurrence in the chemotherapy treated patient group (HR 0.28, 95% CI 0.10-0.80, p=0.017). Finally, patient samples were assigned a PAM50 subtype and a TNBC molecular subtype by the TNBCTYPE algorithm. Ninety-four percent of tumors in the strong PDGF-CC subgroup were classified as basal-like, whereas the corresponding number in the weak and intermediate PDGF-CC subgroups were 51% and 84%, respectively. The TNBC molecular subtype termed ‘ImmunoModulatory’ was more frequently represented in the strong PDGF-CC subgroup compared to weak and intermediate (33% vs. 13% and 16%, respectively). In conclusion, strong PDGF-CC protein expression identified basal-like TNBCs, with an increase in immune cell infiltrate shown by RNAseq analysis. Whether or not PDGF-CC has a direct effect on influx of immune cells into tumors remains to be investigated. Analyses are currently ongoing to better understand the improved outcome associated with strong PDGF-CC intensity and on the contrary, the worse outcome associated with weak and intermediate PDGF-CC intensity, and if paracrine PDGF-CC signaling may explain the discrepancy observed.

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Kristian Pietras, n/a: Baxter: Consulting Fees (e.g., advisory boards) (Terminated, April 30, 2022); Paracrine therapeutics: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing)
Multi-Parametric MRI-Based Radiomics Models from Tumor and Peritumoral Regions as Potential Predictors of Treatment Response to Neoadjuvant Systemic Therapy in Triple Negative Breast Cancer Patients

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PURPOSE Triple negative breast cancer (TNBC) is an aggressive and heterogeneous subtype of breast cancer. Pathologic complete response (pCR) to neoadjuvant systemic therapy (NAST) predicts better survival. Early prediction of the treatment response can potentially triage non-responding patients to alternative protocol treatments, spare them of the unneeded toxicity, and improve pCR. We evaluated the ability of radiomic textural analysis of intratumoral and peritumoral regions on the dynamic contrast enhanced (DCE) and diffusion-weighted imaging (DWI) MRI images obtained early during NAST to predict pCR. MATERIALS AND METHODS This IRB-approved prospective study (NCT02276443) included 182 patients with biopsy proven stage I-III TNBC who had multiparametric MRIs at baseline (BL), post 2 cycles (C2), and post 4 cycles (C4) of NAST before surgery. Tumors and peritumoral regions of 5 mm and 10 mm in thickness were segmented on the 2.5 minutes DCE subtraction images and on the b=800 DWI images. Ten histogram-based first order texture features including mean, minimum, maximum, standard deviation, kurtosis, skewness, 1st, 5th, 95th, and 99th percentile, and 300 radiomic Grey Level Co-occurrence matrix (GLCM) features along with their absolute and relative differences between the 3 imaging time points were extracted from the tumors and from the peritumoral regions with an in-house Matlab toolbox. Treatment response at surgery (pCR vs non-pCR) was documented. The samples were divided into training and testing datasets by a 2:1 ratio. Area under the receiver operating characteristics curve (AUC ROC) was calculated for univariate analysis in predicting pCR. Logistic regression with elastic net regularization was performed for texture feature selection. Parameter optimization was performed by using 5-fold cross-validation based on mean cross-validated AUC in the training set. RESULTS Of 182 TNBC patients, 88 (48%) had pCR and 94 (52%) did not achieve pCR. Eight multivariate models combining radiomic features from both DCE and DWI tumoral and peritumoral regions had AUC > 0.8 (0.807-0.831) with p-value < 0.001 in both training and testing sets. The highest AUC=0.831 was obtained from a model consisting of 15 radiomic features: tumor DWI (5 GLCM features) at C2, peritumoral region on DCE (skewness) at C2, tumor DCE (1st, 5th percentile) at C4, tumor DWI (3 GLCM features) at C4, peritumoral region DWI (1 GLCM feature) at C4, and the relative difference between C4/C2 on DCE (5th, 95th percentile and mean). CONCLUSION Multi-parametric MRI-based radiomics models from the tumor and the peritumoral regions showed high accuracy as potential early predictors of NAST response in TNBC patients.
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WITHDRAWN
Gene signatures provide independent prognostic information in elderly breast cancer patients

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Background: Elderly breast cancer patients (≥70 years old) are under-represented in clinical trials and remain an undertreated population. Gene expression signatures have been shown to add additional prognostic information beyond that of routine clinicopathological factors, however their utility in elderly breast cancer patients remains unclear. As such, the main aim of this study is to determine if gene signatures can provide prognostic information that may help to aid treatment decisions for elderly breast cancer patients.

Material and methods: Research versions of the genomic grade index (GGI), 70-gene, 21-gene recurrence score (RS), cell cycle score (CCS), PAM50 and PAM50 Risk of Relapse score - Proliferation (ROR-P) signatures were applied to 39 open access breast cancer datasets totalling 9583 patients. After filtering based on age ≥ 70 years old, the presence of Estrogen Receptor (ER) and survival information availability 871 patients remained. The prognostic capacity of signatures was tested in all (N=871), Estrogen Receptor positive/ Lymph node positive (ER+/LN+, N=335) and Estrogen Receptor positive/ Lymph node negative (ER+/LN-, N=374) patients using Kaplan-Meier and multi-variable Cox proportional hazard modeling. Models were adjusted for tumor size, grade, ER and lymph node status in all patients, and tumor size and grade in the ER+/ LN+ and ER+/ LN- subgroup analyses. Recurrence Free Survival (RFS) censored at 10 years was used as clinical endpoint and defined as the time from date of curative surgery to the time of recurrence or death. Both loco-regional recurrences and distant metastatic events were included in this endpoint.

Results: Tumours from patients ≥ 70 years of age showed high levels of ER (87%), were large (69% ≥ 20 mm) and were of intermediate or high grade (82%). All gene signatures were statistically significant in Kaplan-Meier analysis of all and ER+/LN+ patients (Logrank P < 0.001). This significance remained in multi-variable analysis (Cox proportional hazards, P ≤ 0.05) with the exception of PAM50 which showed a trend (P ≤ 0.1) in ER+/LN+ patients. In ER+/LN- patients the GGI, 70-gene, PAM50, ROR-P, and CCS signatures were significant in Kaplan-Meier analysis (Logrank P ≤ 0.05) but only the 70-gene, PAM50, ROR-P, and CCS signatures remained so in multi-variable analysis (Cox proportional hazards, P ≤ 0.05).
Conclusions: In general, we found that gene signatures provide statistically significant prognostic information in Kaplan-Meier and multi-variable analyses of all, ER+/LN+ and ER+/LN- breast patients over the age of 70.

Table 1: Multivariable proportional hazard (Cox) analyses for all gene signatures for patients above age of 70.

<table>
<thead>
<tr>
<th>Signature</th>
<th>N (%)</th>
<th>All patients a (N = 871)</th>
<th>Patients (ER+LN+) b (N = 335)</th>
<th>Patients (ER+LN-) b (N = 334)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H (%)</td>
<td>HR (95% CI)</td>
<td>P</td>
<td>H (%)</td>
</tr>
<tr>
<td>Luminal A (ref)</td>
<td>390/49</td>
<td>1.1 (1)</td>
<td>-</td>
<td>157/20</td>
</tr>
<tr>
<td>Luminal B</td>
<td>244/31</td>
<td>1.6 (1.1-2.2)</td>
<td>0.01</td>
<td>117/37</td>
</tr>
<tr>
<td>Herceptin</td>
<td>84/16</td>
<td>1.0 (1-1.4)</td>
<td>0.92</td>
<td>32/16</td>
</tr>
<tr>
<td>Basal</td>
<td>84/16</td>
<td>1.2 (0.7-2.4)</td>
<td>0.58</td>
<td>12/4</td>
</tr>
<tr>
<td>ROIMP</td>
<td>Low proliferation (ref)</td>
<td>177/20</td>
<td>1.1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate proliferation</td>
<td>415/56</td>
<td>1.6 (1-2.9)</td>
<td>0.04</td>
<td>252/35</td>
</tr>
<tr>
<td>High proliferation</td>
<td>209/24</td>
<td>2.6 (1.61-4.39)</td>
<td>&lt;0.001</td>
<td>100/9</td>
</tr>
<tr>
<td>GFG1 (ref)</td>
<td>403/32</td>
<td>1.1 (1)</td>
<td>-</td>
<td>198/30</td>
</tr>
<tr>
<td>GFG3</td>
<td>418/48</td>
<td>1.6 (1-2.2)</td>
<td>0.005</td>
<td>165/30</td>
</tr>
<tr>
<td>70-gene</td>
<td>Low risk (ref)</td>
<td>479/55</td>
<td>1.1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>High risk</td>
<td>392/45</td>
<td>1.7 (1.2-2.5)</td>
<td>&lt;0.001</td>
<td>143/40</td>
</tr>
<tr>
<td>Cell cycle score</td>
<td>Low (ref)</td>
<td>320/36</td>
<td>1.1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate</td>
<td>263/32</td>
<td>1.8 (1.2-2.6)</td>
<td>0.003</td>
<td>128/35</td>
</tr>
<tr>
<td>High</td>
<td>356/36</td>
<td>2.3 (1.6-3.3)</td>
<td>&lt;0.001</td>
<td>67/27</td>
</tr>
<tr>
<td>21-gene R5</td>
<td>Low risk (ref)</td>
<td>100/20</td>
<td>1.1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate</td>
<td>211/24</td>
<td>1.1 (0.9-1.1)</td>
<td>0.42</td>
<td>95/29</td>
</tr>
<tr>
<td>High risk</td>
<td>401/53</td>
<td>1.7 (1-2.5)</td>
<td>0.001</td>
<td>162/26</td>
</tr>
</tbody>
</table>

NOTE: Bold values indicate P < 0.05.
a Adjusted for tumor size, tumor grade, estrogen receptor status, and lymph node status.
b Adjusted for tumor size and tumor grade.
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Efficacy of platinum-based chemotherapy and germline mutational status in early-stage triple-negative breast cancer: a unicenter retrospective analysis with long-term follow-up

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BACKGROUND: In early-stage triple negative breast cancer (TNBC), the addition of carboplatin (CBDCA) to neoadjuvant chemotherapy (CT) increases pathologic complete response (pCR) and relapse-free survival. However, it is unclear whether CBDCA improves overall survival (OS). In addition, the prognostic and/or predictive role of pathogenic germline variants (PGV) in BRCA1/2 genes and other cancer risk in this setting is not fully understood. Here, we assessed the efficacy of (neo)adjuvant CBDCA and the prognostic and predictive role of a panel of 14 genes in patients (pts) with eTNBC.

METHODS: This is a retrospective study on 117 pts diagnosed with early-stage TNBC between 2000-2021 at Hospital Clinic of Barcelona. Eighty-one pts (69%) were candidates for PGV testing. Overall, 14 genes (PGV) (BRCA1, BRCA2, PALB2, BRIP1, CHEK2, TP53, ATM, RAD51C, RAD51D, BARD1, MLH1, MSH2, MSH6 and PMS2) were assessed using the TruSight hereditary cancer panel (Illumina MySeq platform) according to local guidelines. Univariable and multivariable logistic regression and Cox regression analyses were performed to identify clinical and molecular predictors of pCR and relapse-free survival (RFS), respectively. Chi-squared or Fisher’s exact tests were used to assess characteristics’ distribution as appropriate.

RESULTS: Of 117 pts, 83 (71%) received CT in the neoadjuvant setting and 28 (24%) in the adjuvant setting. CBDCA was added to standard CT in 68 pts (82%) in the neoadjuvant cohort and 7 pts (6%) in the adjuvant cohort. Among pts with germline testing, 32/81 (39%) harbored PGV. BRCA1 was the most frequently mutated gene (18/32, 56%), followed by BRCA2 (5/32, 16%), PALB2 (4/32, 13%), BRIP1 (2/32, 6%), CHEK2, TP53 and PMS2 (3/32, 6%). Percentages of pts receiving CBDCA were similar between patients with and without PGV (14/16, 87% and wild type (53/67, 79%)(p=0.120). In the neoadjuvant cohort (n=83), CBDCA was the only variable significantly associated with pCR at both univariate (pCR rates of 58.5% with CBCDA and 14.3% without CBCDA; odds ratio [OR]=8.2 [95% CIs 2.0-55.7], p=0.008) and remained statistically significant after adjusting for PGV, tumor size and nodal status (OR=6.9 [95% CIs 1.4-53.0], p=0.028). pCR rates according to PGV are reported in Table 1. In terms of RFS, addition of CBDCA to neoadjuvant therapy (hazard ratio [HR]=0.2 [0.1-0.45], p< 0.001), PGV (HR=0.2 [0.05-0.9], p=0.048), pCR (HR=0.2 [0.1-0.6], p=0.004) and nodal status (HR=5.1 [1.7-15.2], p< 0.003) were significantly associated with RFS in univariate analyses. In a multivariable model, CBDCA remained an independent predictor of improved RFS along with pCR. When the neoadjuvant and adjuvant cohort were pooled together (n=117), platinum-based CT remained significantly associated with better RFS (HR=0.2 [0.14-0.86], p=0.021) regardless of time of administration (i.e., neoadjuvant or adjuvant). With a median follow-up of 5 years, CBCDA use was not found associated with OS (HR=0.7 [0.3-1.8], p= 0.560).

CONCLUSIONS: The addition of CBDCA to standard CT was significantly associated with pCR and RFS but not OS, consistent with the phase III data. The benefit in terms of RFS was
independent of the presence and the type of pathogenic germline alterations.

Table 1. pCR rates according to PGV

<table>
<thead>
<tr>
<th>Pathogenic germline variants (PGV)</th>
<th>n_total</th>
<th>pCR rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>18</td>
<td>8/11 (73%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>PALB2</td>
<td>4</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>CHEK2/TP53/PMS2</td>
<td>3</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>Wild Type/ Unknown</td>
<td>86</td>
<td>28/67 (42%)</td>
</tr>
</tbody>
</table>

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WITHDRAWN
A UK prospective multicentre decision impact, decision conflict and economic evaluation of the use of Oncotype DX® to guide chemotherapy in 680 women with hormone receptor positive, HER2 negative breast cancer and 1 to 3 nodes involved.

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Introduction: For a test to be of value, it needs to demonstrate that it is changing clinical decisions, improving clinical confidence and of economic benefit.

This trial looked at the use of Oncotype DX Breast Recurrence Score ® (RS) assay against these criteria in 680 women with hormone receptor positive (HR+), HER2 negative early breast cancer with 1 to 3 lymph nodes positive (LN+) in the UK National Health Service (NHS) (5 teaching and 9 district general hospitals) between 2017 and 2022.

Methods: Patients with LN+ early breast cancer who were willing and fit to receive chemotherapy (CT) were consented to join the trial. At the initial oncologists’ appointment, physicians were asked to state their preference for or against CT and their level of confidence in their decision on a scale of 1 to 5. Following receipt of the RS result physicians were asked to make a final decision for or against CT and similarly record their level of confidence.

Descriptive analyses were used to characterize (1) patient and tumour characteristics, (2) change in treatment recommendations post-RS testing (by RS result and nodal status), and (3) change in physicians’ level of confidence post-RS testing (by RS result and nodal status). Average cost for chemotherapy and RS test price were used to estimate overall cost savings.

Results: A total of 680 patients were recruited. 16 patients were excluded (5 failed samples, 5 withdrew consent, 3 HER2 positives, 2 with advanced disease, and 1 specimen delayed in transit), leaving 664 assessable patients. The median age was 58 years and 77.1% of women were post-menopausal. Most patients had a RS of 0-17 (n=400, 60.2%); while 206 (31%) had a
RS of 18-30 and 58 (8.7%) had a RS of 31-100. Using post-RxPONDER cutoffs, 566 (85.2%) had an RS of 0-25; 98 (14.8%) had an RS of 26-100.

Decision impact results:

The decision impact results broken down by RS result and nodal status are detailed in Table 1. Of the 662 patients with complete decision impact data, in 359 (54.2%) the recommendation by the physician changed from CT+ hormone therapy (HT) to HT alone. In 286 (43.2%) cases the decision was unchanged and in 17 (2.6%) the recommendation changed from HT alone to CT+HT. Overall 342 (51.7%) cases were spared chemotherapy.

Decision conflict results:

The change in the physicians’ level of confidence by RS result and nodal status are detailed in Table 2. Of the 660 cases with complete decision conflict data, physicians reported an increase in confidence in their recommendations after receiving the RS in 363 (55.0%), confidence was unchanged in 219 (33.2%) and decreased confidence in 78 (11.8%) cases.

Economic analysis:

Using the estimates of Burdanov et al, the average costs of a course of chemotherapy in the UK is £6,000 to £7,000. An estimate of the overall cost saving of 342 courses is £2,064,000 to £2,408,000 and the overall cost of 664 RS assays at the list price of about £2580 (although an undisclosed discount applies to the NHS) is £1,713,120. This suggests that the use of RS assay represents a significant saving to the NHS.

Conclusion:

The use of Oncotype DX assay in node positive early breast cancer leads to about half of women being spared chemotherapy, a significant improvement in clinical confidence for oncologists and an economic saving to the health care system.

Table 1 Pre- vs Post-Oncotype DX Treatment Recommendation by Physician According to Recurrence Score and Nodal Status
### Table 1: Pre- vs Post-OncoType DX Treatment Recommendation by Physician According to Recurrence Score and Nodal Status

<table>
<thead>
<tr>
<th>Recurrence Score Categories, N (%)</th>
<th>0-17</th>
<th>18-30</th>
<th>31-100</th>
<th>0-17</th>
<th>18-30</th>
<th>31-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal Status Category</td>
<td>N1</td>
<td>N2</td>
<td>N3</td>
<td>N1</td>
<td>N2</td>
<td>N3</td>
</tr>
<tr>
<td>C+HT to HT</td>
<td>111</td>
<td>85</td>
<td>32</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HT to C+HT</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>1</td>
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<td>0</td>
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</tr>
</tbody>
</table>

HT = Hormone Therapy, CT = Chemotherapy, N1 = 1 node, N2 = 2 nodes, N3 = 3 nodes, RR = Micrometa

### Table 2: Change in Physicians’ Level of Confidence Post-OncoType DX Testing According to Recurrence Score and Nodal Status

<table>
<thead>
<tr>
<th>Nodal Status Category</th>
<th>0-17</th>
<th>18-30</th>
<th>31-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>N2</td>
<td>N3</td>
<td>N1</td>
</tr>
<tr>
<td>C+HT to HT</td>
<td>111</td>
<td>85</td>
<td>32</td>
</tr>
<tr>
<td>HT to C+HT</td>
<td>8</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>No change</td>
<td>75</td>
<td>95</td>
<td>1</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HT = Hormone Therapy, CT = Chemotherapy, N1 = 1 node, N2 = 2 nodes, N3 = 3 nodes, RR = Micrometa
<table>
<thead>
<tr>
<th>Disclosure(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Simon D. Holt, MBE MA MB BChir FRCS</strong>: Exact Sciences: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing)</td>
</tr>
<tr>
<td><strong>Priyadharshini Sai-Giridhar, PhD</strong>: No financial relationships to disclose</td>
</tr>
<tr>
<td><strong>Mark Verrill, MB BChir FRCP</strong>: AstraZeneca/Daiichi Sankyo: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Exact Sciences: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Gilead: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Lilly: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Novartis: Contracted Research (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Pfizer:</td>
</tr>
</tbody>
</table>

### Table 2 Change in Physicians’ Level of Confidence Post-OncoType DX Testing According to Recurrence Score and Nodal Status

<table>
<thead>
<tr>
<th>Recurrence Score Categories, N (%)</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>31</td>
<td>26</td>
<td>36</td>
<td>36</td>
<td>25</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>M2</td>
<td>27</td>
<td>25</td>
<td>20</td>
<td>19</td>
<td>16</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>M3</td>
<td>24</td>
<td>24</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td>27</td>
<td>26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence Score Categories, N (%)</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Confidence</td>
<td>46</td>
<td>45</td>
<td>44</td>
<td>38</td>
<td>28</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Decreased Confidence</td>
<td>30</td>
<td>27</td>
<td>32</td>
<td>25</td>
<td>15</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>No Change</td>
<td>24</td>
<td>22</td>
<td>22</td>
<td>28</td>
<td>17</td>
<td>18</td>
<td>23</td>
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<tr>
<td>Missing</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**N1** = Hormone Therapy, **CT** = Chemotherapy, **N1** = 1 node, **N2** = 2 nodes, **N3** = 3 nodes, **M1** = Microstats
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Predictive value of immune genomic signatures from breast cancer cohorts containing data for both response to neoadjuvant chemotherapy and prognosis after surgery

Presenting Author(s) and Co-Author(s):
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Abstract Background Previous studies of immune-related gene signatures (IGSs) in breast cancer have attempted to predict the response to chemotherapy or prognosis and were performed using different patient cohorts. The purpose of this study was to evaluate the predictive functions of various IGSs using the same patient cohort that included data for response to chemotherapy as well as the prognosis after surgery. Methods We applied five previously described IGS models in a public dataset of 508 breast cancer patients treated with neoadjuvant chemotherapy. The prognostic and predictive values of each model were evaluated, and their correlations were compared. Results We observed a high proportion of expression concordance among the IGS models (r: 0.56-1). Higher gene expression scores of IGSs were detected in aggressive breast cancer subtypes (basal and HER2-enriched) (P < 0.001). Four of the five IGSs could predict chemotherapy responses and two could predict 5-year relapse-free survival in cases with hormone receptor-positive (HR+) tumors. However, the models showed no significant differences in their predictive abilities for hormone receptor-negative (HR-) tumors. Conclusions IGSs are, to some extent, useful for predicting prognosis and chemotherapy response; moreover, they show substantial agreement for specific breast cancer subtypes. However, it is necessary to identify more compelling biomarkers for both prognosis and response to chemotherapy in HR- and HER2+ cases.

Disclosure(s):
Yidan Zhu, phd student: No financial relationships to disclose
Breast cancer (BC) is the most frequent malignancy in women worldwide. Breast cancer affects roughly 3,000,000 people worldwide, with triple negative breast cancer (TNBC) accounting for 10-15% of all cases. In comparison to other types of breast cancer, TNBC stands out for its heterogeneic disease, poor prognosis, and aggressive behavior. In the early stages of TNBC, neoadjuvant chemotherapy (NAC), which is given to the patient before surgery, has been considered a viable treatment strategy. Pathological complete response (pCR), which has been shown to increase estimates of disease-free (the amount of time following treatment during which there are no signs of malignancy), distant recurrence-free (the cancer has spread to far-off regions of the body) and overall survival, has been linked to NAC in 30% of patients. The objective of this study was to apply mass-spectrometry-based proteomics to serum samples from TNBC patients who have received NAC to identify i) biomarkers that might predict response to NAC, ii) biomarkers that might correlate with the extent of residual disease. These biomarkers will potentially inform treatment decisions such as the escalation/de-escalation of chemotherapy dosage for early TNBC patients. In this study, two proteomic approaches have been used to identify and measure protein candidate biomarkers: un-biased LC-MS/MS and targeted proteomics respectively. The discovery approach led to the identification of 17 unique proteins and 118 unique peptides that were differently expressed. The developing of a multiple reaction monitoring (MRM) assay for biomarker evaluation will be based on the prioritization of the potential signature proteins and other proteins obtained from public resources. Subject to successful evaluation and subsequent validation the candidate biomarkers may be beneficial for identifying TNBC patients who will achieve residual disease after NAC.

Disclosure(s):
Essraa metwali, phd: No financial relationships to disclose
Stephen Pennington, n/a: No financial relationships to disclose
Background: Locally advanced ER+/HER2- breast cancer (LABC) is an aggressive condition often requiring multidisciplinary management. While early and metastatic breast cancer are well characterized, LABC is largely underrepresented in clinical trials and genomic studies. Herein we present comprehensive molecular profiling of an ER+/HER2- LABC cohort and their oncology outcomes. Method: The clinical records of locally advanced ER+/HER2- LABC (EC IIIA or higher) patients diagnosed and treated with neoadjuvant chemotherapy at Hospital de
Base (Sao Jose do Rio Preto, Brazil) were reviewed. Comprehensive genomic profiling was performed on formalin-fixed paraffin-embedded (FFPE) tumor samples using capture-based hybrid next-generation sequencing (NGS) by targeting 425 cancer-related genes. The status of patients' homologous recombination deficiency (HRD) and tumor mutation burden (TMB) were also measured. Survival outcomes were estimated using the Kaplan-Meier method. Univariable and multivariable analyses were performed to assess the association between oncology outcomes with clinicopathological and molecular characteristics. A p-value of 0.05 was considered statistically significant. FDR was utilized for multiple comparisons adjustment.

Result: From May 2010 and December 2019, after inclusion and exclusion criteria, 90 patients were included. The median age of the cohort was 54 (24 – 88) years old. There were 21 (23%), 65 (72%), and 4 (5%) patients with stage IIIA, IIIB, and IIIC, respectively. A majority of the patients had tumors Grade 2 (72%, 65/90), with 10 (11%) Grade 1, 12 (13%) Grade 3, and the remaining 3 (4%) being undetermined. Most patients were postmenopause, 58% (52/90). All patients received chemotherapy-based neoadjuvant treatment, and 6 (7%) achieved pathological complete response (pCR). After a median follow-up of 63 months, the median recurrence-free survival (RFS) of the entire cohort was 80.4 months and the median overall survival (OS) was not reached yet. A lower tumor grade was strongly associated with better RFS (p = 0.00058) and OS (p = 0.00028), while the pCR subgroup did not show significantly better RFS or OS. In terms of genomic profiling, PICK3CA (32/90, 35.6%) and TP53 (27/90, 30.0%) were the most frequently mutated genes. The median TMB was 4.1 muts/Mb, ranging from 0 to 29.7 muts/Mb. Altered NOTCH pathway was a negative prognostic factor (HR: 2.6; 95%CI: 1.0 - 6.5, p = 0.042) while NRF2 pathway aberrations demonstrated poorer RFS compared to their wildtype counterparts (HR: 3.1; 95%CI: 1.1 - 8.9, p = 0.035). Of note, mutated CUL3, a key player of the NRF2 pathway, was associated with poor RFS (HR: 42.8; 95%CI: 7.0 - 262.5, adjusted p = 0.0004) and OS (HR: 48.4; 95%CI: 8.0 - 294.0, adjusted p = 0.0003) although the sample size was restricted. Furthermore, patients carrying NOTCH2 mutations (N = 2) showed significantly shorter RFS (HR: 14.9; 95%CI: 3.0 - 74.2, adjusted p = 0.004) and OS (HR: 28.8; 95%CI: 5.2 - 160.2, adjusted p = 0.0008). TMB was not a predictor of either pCR or survival. Eight patients carried BRCA1/2 pathogenic mutations (8.9%), and ten out of 44 HRD evaluable patients (22.7%) were HRD-high (HRD score ≥ 38). However, neither BRCA1/2 mutations nor HRD-positivity was associated with pCR, RFS, or OS. Conclusion: Comprehensive genomic profiling of ER+/HER2- LABC patients revealed that altered NOTCH and NRF2 pathway genes were associated with poor survival outcomes. An analysis involving residual cancer burden (RCB) is currently ongoing.

Disclosure(s):
Maira Abreu, MD: No financial relationships to disclose
Larissa Furlan, MD: No financial relationships to disclose
Yutong Ma, n/a: No financial relationships to disclose
Hanlin Chen, n/a: No financial relationships to disclose
Carla Ferreira, MD: No financial relationships to disclose
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Eduardo Constantino, MD: No financial relationships to disclose
Gustavo R. Nora, MD, MD: No financial relationships to disclose
Gabriela Lucio, MD: No financial relationships to disclose
Tatiana Colombo, PhD: No financial relationships to disclose
Rui Liu, n/a: No financial relationships to disclose
Xue Wu, PhD: No financial relationships to disclose
Qiuxiang Ou, n/a: No financial relationships to disclose
Daniel V. Araujo, MD: Ipsen: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Libbs: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, March 31, 2022); MSD: Consulting Fees (e.g., advisory boards) (Terminated, March 15, 2022)
Breast cancer patients with different hormone receptor subtypes receiving neoadjuvant chemotherapy (NAC) experience differential resistance overall survival according to their response to NAC.

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**Background:** Response to neoadjuvant chemotherapy (NAC) is an indicator of outcomes and can be quantified as achievement of pathologic complete response (pCR) (absence of residual invasive disease in breast and lymph nodes) and residual percent cellularity. However, the significance of residual tumor cellularity post-NAC is not well understood. We assessed the impact of NAC-induced reduction in tumor cellularity among hormone receptor subtypes and the effect of these reductions on overall survival (OS).

**Methods:** An IRB-approved retrospective review identified demographics, disease presentation, response to treatment, and outcomes. ER and PR status were categorized as low positive (1-9%), positive (≥ 10%) and negative. Treatment response was noted as percent residual cellularity (complete 0%, almost complete < 10%, good 10-30%, moderate >30-80% and poor >80%) in the surgical specimen and pathologic stage. We examined measures of response to NAC within breast tumor subtypes and the effect of these responses on associations with OS among hormone receptor subtypes.

**Results:** The clinical series comprised 384 patients who received curative intent NAC. This series was diverse in presentation, displayed considerable variability in response to NAC (Table 1). 88 (23.6%) patients did not experience tumor down staging, and of those presenting with clinical nodal Stage 1 or higher (n=197), 94 (47.7%) did not experience nodal down staging. Although
Triple Negative Breast Cancer (TNBC) status was not significantly associated with post-NAC residual tumor cellularity (p=0.74), ER, PR, and HER2 status were individually associated with this measure of response to NAC (p=0.04, 0.01, and 0.01, respectively). However, none of these associations explained more than 2.5% of the variability in this marker of treatment response. Median non-censored follow-up time was 4.26 years. Accounting for censoring, median survival was 13.65 years (lower 95% confidence limit was 11.79 years). Differential associations with OS were observed for three hormone receptor subtypes (ER: p< 0.001, HER2: p=0.04, and TNBC: p< 0.001) according to residual tumor cellularity, classified by percent residual cellularity categories of complete or almost complete response versus all others. Importantly, although ER negative patients with poor residual cellularity response had worse OS than ER positive patients with good response (Hazard Ratio [HR], 95% Confidence Interval [CI] = 4.74, 2.2-10.2), ER negative patients with good response did not have significantly worse OS than ER positive patients with good response (HR, 95% CI = 1.37, 0.57-3.26). Similar patterns were seen for patients with HER2 negative breast cancer or TNBC. Chemo resistant TNBC patients had higher risks for mortality than if they were not chemo resistant (HR, 95% CI: 2.41, 1.02-5.71).

Conclusions:
Our data suggest that OS associated with different hormone subtypes differs according to response to NAC. Differential OS according to response to NAC is greatest for patients classified according to ER status influences, with good response eliminating much of the differential mortality risk between ER negative and positive patients. There is a similar difference according to TNBC, although the difference appears to be less complete. Further studies should focus on understanding the chemo resistance of ER negative tumors, and perhaps TNBC, to identify mechanisms that may ultimately drive treatment response and survival.

Table 1. Demographic and other characteristics
Table 1. Demographic and other characteristics

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<tr>
<th>Characteristic</th>
<th>Mean</th>
<th>Standard Deviation</th>
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<tr>
<td>Age at Diagnosis</td>
<td>51.0</td>
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<tr>
<td>BMI</td>
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<td>6.3</td>
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<tr>
<td>Characteristic</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Race</td>
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<tr>
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<tr>
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<td>1</td>
<td>38</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td>ER</td>
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<tr>
<td>Negative</td>
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<td>Low-Positive</td>
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<tr>
<td>Partial PR</td>
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<td>8.9</td>
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Disclosure(s):

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Circulating Tumour DNA (ctDNA) Detection and Dynamics in Patients with Early Breast Cancer (EBC): Results of the Neoadjuvant TRACER cohort

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Background: ctDNA dynamics are associated with treatment response, and ctDNA detection following treatment is associated with disease recurrence in early breast cancer (EBC). Highly sensitive assays may permit effective risk stratification and guide interventional strategies. RaDaR, a bespoke assay using deep sequencing of tumour-specific variants, has been shown to detect recurrence in the postoperative setting. We quantified ctDNA using RaDaR in serial samples from a large prospective cohort of EBC patients who received standard neoadjuvant chemo- (+/- HER2-targeted) therapy.

Methods: Patients with EBC of all receptor subtypes receiving neoadjuvant therapy were enrolled in the TRACER cohort from 2015. Plasma samples (Streck) were collected at baseline, during treatment, perioperatively, and during follow-up. RaDaR was performed on all available timepoints for patients with tissue available for exome sequencing (assay requirement). Clinical and pathologic characteristics, treatment, and recurrence outcomes were collected.

Results: 145 patients were recruited as of April 2021, and over 700 plasma samples were collected through December 2021 (patient characteristics, Table 1). 115 (79%) tissue samples were retrieved for assay design. Data are presented for the initial 43 patients and 265 samples analyzed, including 82 post-surgical time points. Median time since diagnosis was 3.5 years (range, 1.5-5.0). Exome sequencing and assay generation were successful in all patients (n=43), yielding assays targeting a median of 48 (range 22-50) variants. 88% (38/43 patients) had ctDNA detected at baseline, with median variant allele frequency (eVAF) in positive patients of 0.15% (range, 0.0019-4.9%). ctDNA levels fell rapidly with treatment: 19/37 (51.3%; median eVAF in positive patients: 0.0098%, range 0.001-0.156%) had ctDNA detected prior to cycle 2, and 4/32 (12.5%) had ctDNA detected at cycle 4 or 5 (mid treatment; median eVAF in positive patients: 0.001%, range, 0.0007-0.011%). In the perioperative period, 17/18 (94%) of patients with available pre-operative specimens and 27/28 (96%) of patients with available post-operative samples had clearance of ctDNA. In adjuvant follow up, ctDNA was detected in 4 of the 43 analyzed patients, with ctDNA clearance observed following planned switch of endocrine therapy in one. Clinical follow-up continues, and analysis of the remaining samples (72 patients and over 425 samples) is underway.

Conclusion: RaDaR demonstrated high sensitivity for ctDNA prior to treatment in patients receiving neoadjuvant therapy for EBC, permitted dynamic monitoring of treatment effect, and identified patients with persistent ctDNA after curative-intent therapy, as well as ctDNA emergence prior to clinical recurrence. Full results for the TRACER cohort and analysis of clinical covariates will be presented at the meeting. ClinicalTrials.gov NCT03702309.

Table 1
Patient Baseline Characteristics

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**Aaron Dou, Medical Student**: No financial relationships to disclose

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<th>Results (n=43)</th>
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<td><strong>Age</strong> (Median [Range])</td>
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<tr>
<td>Pre-menopausal (%)</td>
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<tr>
<td><strong>HR+/HER2- (%)</strong></td>
<td>27.9</td>
</tr>
<tr>
<td><strong>HR+/HER2+ (%)</strong></td>
<td>20.9</td>
</tr>
<tr>
<td><strong>HR-/HER2+ (%)</strong></td>
<td>18.6</td>
</tr>
<tr>
<td><strong>TNBC (%)</strong></td>
<td>32.6</td>
</tr>
<tr>
<td>Taxane based (%)</td>
<td>9.3</td>
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<tr>
<td>Sequential Anthracycline + Taxane (%)</td>
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<td><strong>EC (%)</strong></td>
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<td>pCR = YES (%)</td>
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<tr>
<td>cT1/2 (%)</td>
<td>62.8</td>
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<tr>
<td>cT3/4 (%)</td>
<td>37.2</td>
</tr>
<tr>
<td>cNO (%)</td>
<td>46.5</td>
</tr>
<tr>
<td>cN+ (%)</td>
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A single-center prospective cohort study to evaluate circulating tumor cells as a monitoring tool in women with breast cancer treated with neoadjuvant chemotherapy

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Background
The presence of circulating tumor cells (CTCs) among women before and/or after completion of neoadjuvant chemotherapy (NAC) for breast cancer may be associated with an increased risk of recurrence, but limited data is available. Objectives To use the Epic Sciences platform to detect and enumerate CTCs in blood samples from women with a new diagnosis of non-metastatic breast cancer of any subtype both i) prior to commencing NAC, and ii) after completion of NAC and surgery. Methods Inclusion criteria included women of any age with non-metastatic breast cancer of any subtype who have not yet commenced NAC. Those diagnosed with prior invasive cancer at any site (apart from non-melanoma skin cancer diagnosed more than five years prior to enrollment) were excluded. Blood samples were obtained to measure CTCs prior to NAC and after NAC and surgery, respectively. CTC identification was based on immunofluorescence analysis using Epic Sciences platform as previously described (Ueno et al 2017). The presence of CTCs was correlated with clinical/pathological data and treatment response, which were abstracted from patients’ medical records. The association between the presence of CTCs and clinical/pathologic characteristics was tested using Fisher’s exact test for categorical variables and t-test or Wilcoxon rank sum tests for numerical variables. All analyses were performed using the R software package. An
ad-hoc preliminary analysis was conducted among the first 34 of 50 patients. Results 41 patients (out of an intended 50) have been recruited to-date. 34 participants have a pre- and/or post-treatment CTC measurement available, but 1 was excluded because it was identified to have metastatic disease shortly after enrollment. Among 33 evaluable patients without metastatic disease, 6 (19%) had triple negative breast cancer (TNBC), 13 (39%) had HER2+ and 13 (39%) had hormone receptor (HR)+/HER2- breast cancer. Most (94%) received anthracycline and taxane-based NAC. The median age of breast cancer diagnosis was 50 (29-75). A total of 53 samples were tested for CTC enumeration (5 mL per sample) including 33 pre-treatment and 20 post-treatment samples. CTCs were detected in 32 samples (n=32/53, 60%), including 24 pre-NAC (n=24/33, 73%) with a median of 0.9 CTCs per mL (0.2-19) and 8 post-NAC and surgery (n= 8/20, 40%) with a median of 0.6 CTCs per mL (0.3-3.3). Among the 24 patients (73%) who had detectable CTCs pre-NAC, 10 had HR+/HER2- (41.7%), 9 had HER2+ (37.5%) and 4 (16.7%) had triple negative disease. Among the 20 patients for whom matched pre- and post-treatment CTC results were available, 16 (80%) had detectable CTCs pre-treatment and 8 (40%) had detectable levels post-NAC and surgery. Among the 8 patients (40%) for whom CTCs were detectable post NAC and surgery, 4 (50%) had HR+/HER2-, 2 had HER2+ (25%) and 2 (25%) had triple negative disease. 3 of these patients had numerically higher CTC levels after completion of NAC and surgery compared to pre-NAC levels, 2 of whom had HR+/HER2- breast cancer and one of whom had TNBC. A total of 7 of 33 patients achieved a pathological complete response (PCR) to NAC, among whom 3 had matched pre-and post-treatment CTC results available; none of these 3 patients had detectable CTCs post-treatment. Conclusions Approximately 3 in 4 women with non-metastatic breast cancer who undergo NAC have detectable CTCs pre-treatment using the Epic Sciences Platform. Of 20 patients with matched pre-/post-treatment results, a high proportion (40%) have persistently detectable CTCs. Hence, CTCs may represent an additional measure of minimal residual disease for patients undergoing NAC for breast cancer.

Disclosure(s):
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Predicting response of triple negative breast cancer to neoadjuvant chemotherapy using a deep convolutional neural network-based artificial intelligence tool

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Background: Triple-negative breast cancer (TNBC) is commonly treated with neoadjuvant chemotherapy (NAC). Pathologic complete response (pCR) to NAC is associated with improved patient outcomes. The ability to predict which patients have high likelihood to achieve pCR has important clinical implications. We developed and validated a deep convolutional neural network (CNN)–based artificial intelligence (AI) model to extract morphometric features of TNBC to predict response to NAC. Methods: Whole-slide images (WSIs) of hematoxylin and eosin–stained core biopsies of 165 (pathologic complete response [pCR] in 60 and non-pCR in 105) and 78 (pCR in 31 and non-pCR in 47) TNBC patients, respectively, were used for training and validation of the model. The model extracted morphometric features from WSIs in an unsupervised way and transformed the image tiles from WSIs into high-dimensional vectors, generating clusters of morphologically similar patterns. Downstream ranking of clusters using neural networks provided regions of interest with high or low predictive value for NAC response. Morphometric scores combined with clinical TNM stage gave AI prediction scores; a low score close to 0 and high score close to 1, respectively, represented a high or low probability of pCR, respectively. Results: The predictive ability of the AI score for the entire cohort of 78 TNBC patients ascertained by receiver operating characteristic (ROC) analysis demonstrated area under the curve (AUC) of 75.5%. The AUC for stage I, II, and III disease was 88.1%, 73.7%, and 74.7% respectively. The performance of the AI scores was also analyzed based on their distribution into quartiles. Patients in the highest score quartile were predicted to not have pCR and those in the lowest score quartile were predicted to have pCR. Of the 20 patients in the lowest score quartile, 15 experienced pCR yielding a positive predictive value of the AI score for pCR of 75%. Of the 20 patients in the highest score quartile, 16 did not have pCR, yielding a negative predictive value of 80%. Conclusions: This is the first demonstration of using an AI tool to predict response to NAC in patients with TNBC. These results, if validated in subsequent studies, could inform individualized decisions regarding intensity of NAC, including options to de-escalate NAC in patients with TNBC who are likely to achieve pCR.

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Multiparametric MRI-based Longitudinal-radiomics Analysis for Early Prediction of Treatment Response of Breast Cancers to Neoadjuvant Chemotherapy: A Multicenter Study

Purpose: We evaluated the performance of the longitudinal-radiomics of multi-parametric magnetic resonance imaging (MRI), developed and validated based on a multicenter dataset adopting a radiomic strategy, for prediction of treatment response to neoadjuvant chemotherapy (NAC) in breast cancer.

Methods and materials: We analyzed clinical and pathological data of patients with breast cancer and compared machine-learning classification algorithms in predicting treatment response following NAC from four hospitals (primary cohort and external validation cohort 1-3) between July 2015 and December 2021. Patients were monitored with MRI before (pretreatment) and after (mid-treatment) three or four cycles of NAC. Longitudinal-radiomics analysis was performed at pre- and mid-treatment dynamic contrast-enhanced, T2-weighted imaging, and diffusion-weighted imaging mapping by using 3D Slicer software. Radiomics features were extracted from original and filtered images using PyRadiomics (V3.0.1) filtered images were generated using Laplacian of Gaussian and wavelet filters. The stacking strategy including LR, LDA and SVM (radial basis function) were used to combined the results of the base models, and gave a secondary prediction result.

Results: In total, 1048 cases were enrolled in the study. In identifying the residual cancer burden (RCB) 0 v.s. RCB 1-3, longitudinal-radiomic models achieved the highest area under the receiver operating characteristic curve (AUC) of 0.909 and 0.893 in the training and test sets. The accuracies of the stacking-SVM classifier were 84.3% (86/102), 75.6% (205/271) and
77.9% (265/340) in the external validation set. In identifying the RCB 3 v.s. RCB 0-2, longitudinal-radiomic models achieved the highest AUC of 0.981 and 0.923 in the training and test sets. In the external validation set, the performance was with accuracy=91.2%-92.2%. The cascade model also stratified 78.9%, 69.1% and 76.1% of the RCB 1-2 patients into RCB 1-2 prediction group to receive suitable NAC and feasible breast-conserving surgery. Our findings showed high predictive ability and reproducibility across multicenter dataset. By two-step prediction results of cascade models, the patient could be assigned to one of the three groups corresponding to three RCB status: RCB 0, RCB 1-2, or RCB 3. In this way, using the cascade models, some of RCB 3 patients may allow treatment to be tailored for optimal outcomes. RCB 0 and RCB 1-2 groups could receive suitable NAC and feasible breast-conserving surgery.

Conclusion: In conclusion, our study had good predictive ability for RCB assessment, which could help clinicians guide individualized treatment options for breast cancer patients in NAC. The application of stacking cascade model may have the potential to further reduce unnecessary NAC and economic costs associated with current breast cancer management.

Figure 1. The flowchart of the study. This was a multicenter study with patients retrospectively enrolled from four medical centers in different cities of China. Pretreatment and midtreatment multi-parametric MRI (DCE, T2WI, and DWI) and clinical information were proposed to predict treatment response to NAC in patients with primary invasive breast cancer. The data from Foshan was used as the primary cohort (PC), and the other three data sets were used as independent validation cohorts (VC). This study included radiomic feature engineering, model building, model comparison and clinical application.

Figure 2. ROC curves among different radiomic signatures and among different models in identifying the RCB 0 vs RCB 1-3. RCB, residual cancer burden; ROC, receiver operating characteristic; SVM, support vector machine; RF, random forest; MLP, multilayer perceptron; LR, logistic regression.
Figure 3. ROC curves among different radiomic signatures and among different models in identifying the RCB 3 vs RCB 0-2. RCB, residual cancer burden; ROC, receiver operating characteristic; SVM, support vector machine; RF, random forest; MLP, multilayer perceptron; LR, logistic regression.
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Luminal androgen receptor subtype and M2 macrophage signatures strongly associate with low pathological complete response rates and poor outcomes in patients with triple negative breast cancer receiving neoadjuvant chemotherapy

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Background: Triple negative breast cancers (TNBC) are a heterogeneous group of cancers and it is difficult to predict which patients will respond to neoadjuvant chemotherapies (NACT). Achieving pathologic complete response (pCR) to NACT is prognostically favorable, whereas lack of pCR is associated with high rates of recurrence and death from TNBC. Currently, there is no universally accepted biomarker to predict TNBC response to NACT. Methods: We analyzed 25 in-house TNBC biopsies that were treated with neoadjuvant adriamycin (A), cyclophosphamide (C) and paclitaxel (T) and 31 residual TNBC after NACT-ACT using RNA-seq data from macro-dissected tumor tissues from formalin fixed paraffin embedded (FFPE) blocks. Raw reads were mapped to the Human reference genome GRCH38 using the kallisto aligner v0.46.1. Immune infiltrate fractions were estimated using the Cibersort algorithm derived from the LM22 gene-signature matrix of 22 hematopoietic cell types. TNBCTYPE-4 classification of samples was determined calculating the enrichment of gene-sets for: Luminal Androgen Receptor (LAR), Basal-like 1 and 2 (BL1, BL2), Mesenchymal(M). Overall immune-infiltrate analysis and cancer-intrinsic subtyping were conducted independently on each transcriptional profile. Results were validated by running our novel analyzing protocol in independent cohorts including 182 TNBC cases treated with NACT-ACT from a published Vanderbilt cohort and 179 TNBC cases from the TCGA database. Results: Twenty one (68%) of the 31 residual TNBC after neoadjuvant ACT were luminal androgen receptor (LAR) subtype and significantly enriched in M2 macrophage signature. The LAR subtype and monocyte or M2 macrophage signatures strongly associated with lack of pCR in the 25 TNBC biopsy cases and 182
Vanderbilt TNBC cases treated with NACT-ACT. Survival analysis of 179 TNBC cases from the TCGA database showed a significant association of LAR subtype and M2 macrophage signature with worse survival. Conclusions: We developed a novel RNA-seq analyzing protocol that combines tumor subtype and immune profile. The LAR subtype and M2 macrophage signatures strongly associated with lack of pCR and worse survival in TNBC patients when treated with NACT-ACT. Both tumor subtype and immune profile should be considered in biomarker development and further studied in specimens from patients treated with modern chemoimmunotherapy regimens.

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Age, Ki-67, Nodal pCR and overall survival following Neoadjuvant Chemotherapy for Node Positive ER+/Her2- Breast Cancer

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Background
The role of chemotherapy in node positive (N+) luminal breast cancer (BC) is often debated, given low total pathologic complete response (pCR) rates following neoadjuvant chemotherapy (NAC) and discrepancy in adjuvant chemotherapy benefit. A prior single institution study of cN+ luminal BC showed that pts age < 50 and tumor Ki-67 ≥ 20% had high nodal pCR (> 35%). This study’s goals were 1) to validate Ki-67 and age in relation to nodal pCR and 2) evaluate the prognostic impact of nodal pCR on overall survival (OS).

Methods
We queried the National Cancer Database 2010-2019 for pts with cN+ ER+/HER2- BC treated with NAC and surgery. Breast pCR was defined as ypT0/ypTis and nodal pCR as ypN0/ypN0i+. Ki-67 was available in 2018 & 2019 only and was used to evaluate Ki-67 and nodal pCR. 2010-2018 data were used to evaluate nodal pCR and OS. OS was analyzed using multivariable Cox proportional hazards regression.

Results
In 2018-2019, 4,801 pts were identified and 2,473 (51.5%) had Ki-67 available. Nodal pCR was 23.7% and was higher in pts < 50 years old (28.1% vs 21.1%) and in those with Ki67 ≥ 20% (28.4% vs 12.7%), both p < 0.001. Pts < 50 with Ki67 ≥ 20% had the highest nodal pCR at 31.7%, followed by age ≥ 50 with Ki67 ≥ 20% at 26.3%. With Ki67 < 20%, nodal pCR was
15.4% (in age < 50) and 11.3% (in age ≥ 50).

From 2010-2018, we identified 20,084 cN+ ER+/HER2- BC pts treated with NAC. Total pCR was 7.4%, 14.3% had nodal pCR only, 3.8% had breast pCR only, and 74.5% had residual disease in breast and nodes. OS at 5 years was 79.1% and varied by NAC response: 90.8% with total pCR, 83.8% with nodal pCR only, 80.7% with breast pCR only, and 76.9% with residual disease in breast and nodes. Specifically nodal pCR (with or without breast pCR) was seen in 22.0% and was associated with 5-year OS rate of 86.4% compared to 77.1% without nodal pCR, p < 0.001. On multivariable analysis adjusted for other clinical and treatment factors, nodal pCR was associated with better OS (adjusted HR 0.56, 95% CI: 0.50-0.61, p < 0.001) in all ages combined and within both the age < 50 and age ≥ 50 subgroups (see Table).

In a subgroup of pts approximating RxPonder entry criteria (defined as cT1-3, N1, Grade I or II, ER+/PR+), results were consistent with the overall cohort: nodal pCR varied by both age (17.5% in age < 50 and 13.6% in age ≥ 50, p < 0.001) and by Ki67 ≥ 20% vs < 20% (16.8% vs 7.9%, p < 0.001) and nodal pCR remained prognostic for OS with adjusted HR 0.63 (95% CI: 0.50-0.81, p < 0.001).

Conclusion
In cN+ ER+/HER2- BC treated with NAC, nodal pCR is more common in pts< 50 and those with high Ki-67 and is highly prognostic for OS. These data strongly suggest that NAC chemotherapy benefit should not be evaluated using total pCR rates in isolation, but for N+ pts to also consider nodal response. Given that nodal pCR is highly prognostic for OS, future neoadjuvant strategies should consider nodal pCR as a potential intermediate biomarker for long term survival.

Multivariable analysis of factors associated with overall survival, including the adjusted effect of nodal pCR

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Overall Hazard Ratio (95% CI) p-value</th>
<th>Age &lt;50 Hazard Ratio (95% CI) p-value</th>
<th>Age ≥50 Hazard Ratio (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal pCR</td>
<td>0.56 (0.50, 0.61) &lt;0.001</td>
<td>0.56 (0.47, 0.64) &lt;0.001</td>
<td>0.55 (0.49, 0.63) &lt;0.001</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately vs well differentiated</td>
<td>1.49 (1.28, 1.71) &lt;0.001</td>
<td>1.76 (1.31, 2.31) &lt;0.001</td>
<td>1.39 (1.17, 1.65) &lt;0.001</td>
</tr>
<tr>
<td>Poorly vs well differentiated</td>
<td>2.40 (2.07, 2.78) &lt;0.001</td>
<td>2.34 (2.15, 4.19) &lt;0.001</td>
<td>2.09 (1.76, 2.49) &lt;0.001</td>
</tr>
<tr>
<td>PR Status, Positive vs Negative</td>
<td>0.55 (0.51, 0.59) &lt;0.001</td>
<td>0.52 (0.45, 0.59) &lt;0.001</td>
<td>0.57 (0.52, 0.62) &lt;0.001</td>
</tr>
<tr>
<td>Pathologic T Category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1 vs pT0/1a/pT2a</td>
<td>1.39 (1.21, 1.60) &lt;0.001</td>
<td>1.39 (1.21, 1.60) &lt;0.001</td>
<td>1.34 (1.06, 1.65) &lt;0.149</td>
</tr>
<tr>
<td>pT2 vs pT0/1a/pT2a</td>
<td>1.82 (1.58, 2.10) &lt;0.001</td>
<td>2.56 (2.00, 3.28) &lt;0.001</td>
<td>2.46 (2.13, 2.84) &lt;0.001</td>
</tr>
<tr>
<td>pT3 vs pT0/1a/pT2a</td>
<td>2.72 (2.34, 3.14) &lt;0.001</td>
<td>3.37 (3.07, 3.65) &lt;0.001</td>
<td>2.08 (1.73, 2.50) &lt;0.001</td>
</tr>
<tr>
<td>pT4 vs pT0/1a/pT2a</td>
<td>3.33 (2.81, 3.98) &lt;0.001</td>
<td>5.16 (3.81, 6.98) &lt;0.001</td>
<td>2.55 (2.10, 3.10) &lt;0.001</td>
</tr>
</tbody>
</table>

*Additionally adjusted for age, race, ethnicity, insurance, breast surgery, axillary surgery, adjuvant, radiation, and year of diagnosis. Unknown levels of some variables were included in the model but not reported in the table.

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Role of tumor infiltrating lymphocytes and PD-L1 expression in the response to eribulin and pembrolizumab in metastatic triple negative breast cancer (mTNBC) on the ENHANCE1 trial

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Background
Treatment with combination chemo-immunotherapy has become the front-line standard for eligible patients with PD-L1 positive mTNBC. PD-L1 is the only approved biomarker for pembrolizumab in metastatic breast cancer for response to combination chemo-immunotherapy, however given that it is not predictive of response in all cases additional biomarkers are needed. Tumor infiltrating lymphocytes (TILs) have been shown to be both predictive and prognostic in operable TNBC, but there are fewer data regarding the role of TILs in mTNBC. In this study we report the associations between TILs and outcomes in patients treated prospectively on the ENHANCE-1 study with eribulin and pembrolizumab. Methods ENHANCE-1 was a single arm phase Ib/II trial which evaluated the efficacy and safety of eribulin and pembrolizumab in 167 patients (pts) with mTNBC who had received 0-2 prior lines of therapy (66 pts in the first line setting [stratum 1] and 101 pts with 1-2 prior lines of therapy [stratum 2]). Objective response rate (ORR) was defined as percentage of pts with either
complete response (CR) or partial response (PR) by RECIST 1.1. The ORR was 25.8% in stratum 1 and 21.8% in stratum 2. Stromal TILs (sTIL) and intratumoral TILs were evaluated on whole slide H&E sections from biopsy specimens used for enrollment on ENHANCE-1 by breast pathology according to the International TILs Working Group guidelines. PD-L1 positivity was determined via immunohistochemistry using the Agilent 22C3 antibody. We also assessed TIL density digitally using machine learning classifiers to identify tumor/stromal tissue areas and individual lymphocytes. Results We found that there was statistically significant increase in sTIL counts in responders compared to non-responders in stratum 1 (p=0.002) but not in stratum 2 (p=0.99). We did not find any associations between intratumoral TILs and response. Quantitative PD-L1 scoring via combined proportion score (CPS) was also positively associated with response in stratum 1 (p=0.01) but not in stratum 2 (p=0.34). We also find that sTIL counts are most correlated to CPS scores (continuous) for non-responders within stratum 1 (R^2=+0.55, p< 0.01). Conclusion In this population of patients with mTNBC treated prospectively with eribulin and pembrolizumab, sTILs and PDL1 CPS were each individually associated with a positive response in patients treated with front-line combination chemotheraphy. Neither was predictive for patient response in stratum 2. One important caveat is the biopsies were not required immediately prior to enrollment, possibly confounding the tumor microenvironment (TME) at the time of analysis. Our data contribute to emerging data that sTILs can act as a biomarker for response to immune checkpoint inhibition when utilized in the front-line setting for mTNBC. Further characterization of the TME via quantitative immunofluorescence is ongoing. This study was funded by Eisai IIS-E7389

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Long-term outcome data using Endopredict® as risk stratification and chemotherapy decision biomarker in hormone receptor positive, HER2-negative early breast cancer

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Background: The Endopredict test is used for estimating risk of distant recurrence for women presenting with early-stage breast cancer with a positive estrogen receptor (ER) and negative human epidermal growth factor receptor 2 (HER2) status. The current ASCO Guideline Update on biomarkers confirms the value of the Endopredict test to guide decisions of adjuvant endocrine and chemotherapy. This study shows prospective long-term outcome data of early breast cancer patients whose chemotherapy decision was guided by the Endopredict test result (EPclin). Methods: ER-positive and HER2-negative early breast cancer patients with 0-3 positive lymph nodes treated between March 2012 and March 2015 were included in this single institution study. The Endopredict® test was carried out on all tumour samples. Demographic, clinical and pathological data were assessed for each patient at baseline. Treatment compliance, local recurrence, distant metastases and survival was evaluated. Risk estimates were obtained by the Kaplan-Meier method and cumulative risk functions in case of competing risks. Group comparisons were performed by Cox proportional hazards regression models and quantified through hazard ratios. Median Follow-Up was estimated by the inverse Kaplan-Meier
method. Exploratory hypothesis testing was conducted at two-sided 5% significance levels.

Results: In a cohort of 368 consecutive cases the median follow-up time was 8.2 years.

Endopredict allocated 238 pts (64%) in the EPclin low risk and 130 pts (34%) in the EPclin high risk group. The 5-year distant metastasis free survival (DMFS) in the EPclin low risk group was 96.6% (95% CI 0.943-0.989) and 85.5% (95% CI 0.796-0.920) in the EPclin high risk group. With a hazard ratio (HR) of 2.21 (95% CI: 1.27-3.88; p=0.005) the risk for distant metastasis in EPclin high risk patients was more than two-fold higher in comparison with EPclin low risk patients. 87 pts. (66.9%) of the EPclin high risk group underwent chemotherapy (compliant), whereas 43 pts (33.1 %) opposed the recommended chemotherapy (non-compliant). Kaplan-Meier plots in the EPclin high risk subgroups compliant vs non-compliant showed a significant disease-free survival (DFS) benefit towards the patients following the chemotherapy recommendation (HR 0.46; 95%CI 0.23-0.95; p=0.036). The 5-year DFS for the high risk compliant subgroup was 89.1% (95% CI: 0.827-0.961) vs. the high risk non-compliant subgroup with 68.9% (95% CI: 0.562-0.845). Regarding the subgroups pre- and postmenopausal, patients with a EPclin high risk test result were at significant higher risk of experiencing distant metastases than patients with a EPclin low risk test result in both subgroups (premenopausal: HR 3.55; 95%CI 1.17-12.32; p=0.025; postmenopausal: HR 1.19; 95%CI 0.99-3.7; p=0.054).

We analyzed the EPclin categorization in context of the ki67 subtypes luminal A (low; 0-10%) and luminal B (high; 25-100%). The EPclin-based risk stratification was significantly associated with improved DFS in both ki67 subtypes (ki67 low: HR 4; 95%CI 1.25-12.04; p=0.021 and ki67 high: HR 3.77; 95%CI 1.19-18.93; p=0.022). 33.3% (21 pts) of all tumor samples classified as luminal B (63 pts), were reclassified towards the low risk group via Endopredict, sparing chemotherapy recommendation. Contrary 19.2% (14 pts) of all luminal A (73 pts) were categorized to high risk EPclin. Conclusion: These first long term prospective outcome data confirm, that Endopredict can guide decisions on adjuvant chemotherapy in early ER positive, HER2 negative breast cancer. Pts categorized as EPclin high risk benefited from an adjuvant chemotherapy. Our results show that Endopredict risk stratification is also applicable in premenopausal women. Furthermore the Endopredict test showed a better classification accuracy in comparison to ki67 subtypes, resulting in a more precise estimation of prognosis.

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Evaluation of Multigene Assays as Predictors for Response to Neoadjuvant Chemotherapy in Early-Stage Breast Cancer Patients

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Background: Oncotype DX (ODX) and MammaPrint (MP) are gene-expression assays that have been established to predict distant cancer recurrence in the adjuvant chemotherapy setting. However, they have not been validated to predict pathologic complete response (pCR) to neoadjuvant chemotherapy (NACT). We sought to examine the ability of the ODX and MP assays to predict the likelihood of pCR to NACT in early-stage breast cancer patients.

Methods: Data from breast cancer patients diagnosed between 2010 and 2019 were obtained from the National Cancer Database. All patients who received NACT (at least 30 days of treatment) and had pathologic response data and ODX or MP results were included. Analysis of ODX was limited to patients with hormone receptor (HR)+/HER2- stage I-III disease, while analysis of MP included both HR+/HER2- and HR-/HER2- stage I-III patients. ODX scores were modeled both
as a continuous variable and a categorical variable classified as low (0-25) and high (≥26) per the TAILORx trial cutoff, whereas MP results were modeled as a dichotomous variable (i.e., low risk and high risk) because numeric values were unavailable. Multivariable logistic regression models were used to assess the relationship between pCR (defined as ypT0/Tis ypN0) and ODX or MP results, adjusting for age, race/ethnicity, clinical T and N stages, tumor grade, and progesterone receptor status. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated. Results: A total of 2,219 patients, treated at 630 institutions, who received NACT with an ODX recurrence score were included in the ODX cohort. Of 1,181 patients with a high ODX score, 11.2% achieved pCR, while only 1.6% of 867 patients with a low ODX score did. In the adjusted model, having a high ODX score was associated with greater odds of pCR (AOR = 4.48, 95% CI: 2.44-8.22). There was a significant monotonic increasing trend of pCR by continuous ODX score. The mean ODX score was 42.5 (SD = 15.5) in patients who achieved pCR, compared to 27.9 (SD = 13.7) in patients who did not; the discriminating capacity of ODX was moderate to strong (area under the ROC curve = 0.767). A total of 1,349 patients, treated at 337 institutions, who received NACT and had MP test results were included in the MP cohort. Of 1,141 patients with MP high risk disease, 11.8% achieved pCR, compared to < 4.8% of 208 patients with MP low risk disease. In the adjusted model, having MP high risk disease was associated with greater odds of pCR (AOR = 2.21, 95% CI: 1.02-4.77). A similar association between MP results and pCR was also found in the subset of patients who were HR+/HER2- (AOR = 2.25, 95% CI: 0.99-5.15). Conclusions: Both ODX and MP were independently associated with likelihood of pCR after NACT for early-stage, high-risk breast cancer. These findings suggest a potential role for ODX or MP testing as a predictive biomarker in the NACT setting, and can facilitate clinical decision making between physicians and patients.

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WITHDRAWN
Utilization of the Oncotype Dx Assay for Young Patients with Early Stage, Hormone-Receptor Positive, HER2-Negative Breast Cancer in an Integrated Health System

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Background: Oncotype Dx (ODX) is one of the most widely used prognostic multigene expression assays for early-stage, hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer. Previous studies demonstrated reduction in chemotherapy in patients with a low ODX Recurrence Score (RS). Over recent years, utilization of this tool has increased in young breast cancer (YBC) patients (age≤40 years), a population often underrepresented in randomized clinical trials. The purpose of this retrospective study was to assess the utilization of this assay over time in an integrated health system and whether ODX RS results altered
clinical practice. Methods: YBC patients with T1-T2N0 HR+HER2- breast cancer were retrospectively evaluated. Descriptive analysis examined the association between tumor characteristics, year of diagnosis, ODX testing, treatment, and recurrence outcomes. ODX risk categories were defined as: low risk 0-15; intermediate risk 16-25; high risk > 25. Recurrence was determined by the date of confirmation on pathology or imaging. Bivariate analysis compared characteristics between groups using Fisher exact tests for categorical variables and t-tests and nonparametric tests for continuous variables. Results: From 2008-2018, 1,436 Stage I-III YBC patients were diagnosed with invasive breast cancer, and 455 met eligibility criteria for ODX testing. Median follow-time (interquartile range, IQR) was 4.9 (2.8, 7.9) years for the 255 women who were tested and 5.7 (3.5, 8.7) years for the 200 women who were not tested (p< 0.05). Prior to 2018, 52.1% of patients were tested; after 2017, ODX testing rate increased to 88%. Overall, there were 255 patients who underwent ODX testing (55.9%). The median age (IQR) of patients who had an ODX test was 38.0 (35.0, 39.0). Of 225 tested patients, 42.0% (n=107) were White, 6.3% (n=16) Black, 33.7% (n=86) Asian/Pacific Islander, 15.7% (n=40) Hispanic, and 2.3% (n=6) identified as Other. There was no overall difference in testing based on ethnicity (p=0.42). More patients with grade 1 versus grade 3 disease were tested, 61.5% vs 45.2% (p=0.02 from overall Fisher exact test). Adjuvant chemotherapy was administered to 61.0% (122/200) patients who were not tested, whereas 38.4% (98/255) of those tested received chemotherapy (p< 0.001). In tested patients, 6% of low-risk (RS 0-15), 37% of intermediate risk (RS 16-25), and 92% of high risk (RS >25) patient received adjuvant chemotherapy. Among patients with T2 lesions, a higher proportion not tested (90.8% [59/65]) received adjuvant chemotherapy compared with those not tested (57.1% [40/70]). There were no differences in recurrence based on ODX testing, 11.0% (22/200) not tested vs. 9.4% (24/255) tested (p=0.26). Conclusions: Utilization of ODX testing increased after 2017. A significantly lower proportion of women who underwent ODX testing received chemotherapy, compared with women not tested for ODX. A higher percent of women with T2 cancer received chemotherapy if testing was not completed, which may reflect a greater fear of recurrence in younger patients. Further investigation is needed to better understand this potential risk of overtreatment in the YBC population.

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Tangling the clinicopathological significance of MRE11-RAD50-NBS1 complex in sporadic breast cancers

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The MRE11–RAD50–NBS1 (MRN) complex is critical for genomic stability. Although germline mutations in MRN may increase breast cancer susceptibility, such mutations are extremely rare. Here, we have conducted a comprehensive clinicopathological study of MRN in sporadic breast cancers. We have protein expression profiled for MRN and a panel of DNA repair factors involved in double-strand break repair (BRCA1, BRCA2, ATM, CHK2, ATR, Chk1, pChk1, RAD51, γH2AX, RPA1, RPA2, DNA-PKcs), RECQ DNA helicases (BLM, WRN, RECQ1, RECQL4, RECQ5), nucleotide excision repair (ERCC1) and base excision repair (SMUG1, APE1, FEN1, PARP1, XRCC1, Pol β) in 1650 clinical breast cancers. The prognostic significance of MRE11, RAD50 and NBS1 transcripts and their microRNA regulators (hsa-miR-494 and hsa-miR-99b) were evaluated in large clinical datasets. Expression of MRN components was analysed in The Cancer Genome Atlas breast cancer cohort. We show that low nuclear MRN is linked to aggressive histopathological phenotypes such as high tumour grade, high mitotic index, oestrogen receptor- and high-risk Nottingham Prognostic Index. In univariate analysis, low nuclear MRE11 and low nuclear RAD50 were associated with poor survival. In multivariate analysis, low nuclear RAD50 remained independently linked with adverse clinical outcomes. Low RAD50 transcripts were also linked with reduced survival. In contrast, overexpression of hsa-miR-494 and hsa-miR-99b microRNAs was associated with poor survival. We observed large-scale genome-wide alterations in MRN-deficient tumours contributing to aggressive behaviour. We conclude that MRN status may be a useful tool to stratify tumours for precision medicine strategies.

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Serial genomic analysis of circulating free DNA and change of immune-related gene signature in triple negative and HER2 positive advanced, metastatic breast cancer

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Background: Circulating tumor cells (CTCs) and circulating free DNA (cfDNA) have a promising role for detecting early response and progression in breast cancer. Furthermore, change of immune-related gene signature during systemic treatment influence the treatment response of breast cancer. Herein we report the outcome of serial genomic analysis of CTC, cfDNA and change of immune-related gene signature in advanced, metastatic triple negative breast cancer (TNBC) and HER2 positive breast cancer (BC).

Methods: Serial whole blood were prospectively collected in 18 early or advanced, and 10 metastatic BC patients periodically during systemic chemotherapy. CTC was isolated from whole blood through EpCAM positive bead selection, and ctDNA was isolated from plasma. For genomic profiling of CTC and ctDNA, Oncomine™ Comprehensive Assay Plus and Oncomine™ Pan-Cancer cfDNA assay (included BRCA1, BRCA2 and MYCN customized panel) was performed and analyzed, respectively. Total RNA was extracted using whole blood and analyzed using Nanostring Pancancer Immunology Panel.

Results: Total 61 serial samples were obtained from 28 patients during the study. At baseline, FGFR4 mutation was the most commonly detected (10 patients, 76.9%) with median variant of allele frequency (VAF) of 54.5% (range 20.87~99.8%) in advanced and metastatic TNBC based on CTC analysis. In case of cfDNA, 11 patients (84.6%) showed TP53 mutation with low VAF (median 1.8%, range 0.1~12.3%). In HER2 positive BC, FGFR4 was also the most common mutation (5 patients [62.5%]; median VAF 57.9%) in CTC analysis and TP53 was most frequently detected (5 patients, [62.5%]; median VAF 3.0%) in cfDNA analysis. In three pathogenic gBRCA1 mutated patients, BRCA1 was identically detected in 2 patients based on CTC analysis and in 3 patients based on cfDNA analysis with VAF of approximately 50%. There were no significant changes of VAF in target mutations of CTC and cfDNA during systemic treatment, irrespective of tumor response and subtype. However, in one patients who harbored 13 mutations detected based on baseline CTC analysis, showed disappearance of 12 mutations in final CTC analysis with partial response based on radiologic findings. In contrary,
there was another patient who gained multiple mutations during CTC analysis during neoadjuvant chemotherapy (NAC) with gain of tumor mutational burden (TMB). She did not achieve pathologic complete response and RCB score was 3 after completion of NAC. Most TNBC patients who received NAC and showed partial response, TMB showed gradual decrease during treatment. Baseline immune-related gene signatures were compared between HER2(+) BC and TNBC, and type 1 interferon signaling pathway was upregulated in HER2 (+) BC compared to TNBC. Conclusions: Our study suggest that serial follow up CTC and ctDNA, immune-related gene signature is feasible and reflect the general characteristics of baseline characteristics and dynamic molecular alteration of breast cancer. Further analysis with larger patient sample and correlation with tumor tissue is warranted in the future.

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PgR levels and Ki67 expression of Lobular Carcinomas of the Breast might indicate OncotypeDX testing to evaluate Chemotherapy benefit.

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AIM: The majority of invasive lobular carcinomas (ILC) of the breast are luminal A tumors of good prognosis, having a low or intermediate OncotypeDX Recurrence Score (RS). They are usually treated with hormonal therapy only and some have doubted the relevance of the RS for patients with ILC. However, in a number of ILC cases a high RS can be found, indicating chemotherapy benefit. The aim of the present analysis was to explore in our database of lobular carcinomas analyzed with OncotypeDX, the percentage of tumors with a RS >25 and test the hypothesis if Progesterone Receptor (PgR) and/or Ki-67 expression could be an indicator to have patients evaluated with OncotypeDX.

PATIENTS AND METHODS: Among 2,946 patients analyzed with Oncotype DX, we found 397 patients with pure lobular carcinomas (13.47%). Ki-67 expression was obtained from 315 patients and 13 of them (4%) had a high Ki-67 value of >30%. PgR expression was negative in 56 out of 397 patients (14%). We analyzed the possible relationship of RS values with PgR levels and Ki-67 expression. RESULTS: Overall, 94% of patients with ILC had a Recurrence Score ≤25 and only 6% (24/397) had a RS ≥26. There was a wide distribution of RS among patients with different values of PgR; however, there was a negative trend of Recurrence Score values and PgR expression levels. This trend was more obvious in the 56 patients with negative PgR expression. Although there were high RS values across all levels of Ki-67 expression, there was a trend towards high RS with higher Ki-67 expression; 5 out of 13 patients (38%) with ki-67 >30% had a RS ≥26. CONCLUSION: Our analysis shows that the majority of lobular carcinomas of the breast have a low OncotypeDX RS, suggesting that can be treated only with hormonal therapy. However, negative or low PgR levels and high Ki-67 expression might predict a high RS and thus chemotherapy benefit and those two parameters could be used as indicators for OncotypeDX evaluation of lobular carcinomas of the breast.

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WITHDRAWN
Evaluation of pathologic response and residual tumor cellularity following neo-adjuvant chemotherapy predict prognosis in breast cancer patients

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Introduction: Treatment of early-stage breast cancer (BC) has changed since recent evidence showed that neoadjuvant chemotherapy (NAC) can reduce residual tumor cellularity (RTC) and improve patient outcomes. Achieving a pathologic complete response (pCR) has been associated with significantly improved disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS). However, among patients treated with NAC, few experience pCR, while approximately 60-80% of them achieve a pathologic partial response (pPR). In previous studies, BC patients with different grades of pPR have been usually grouped and analyzed together, with inconsistent results and unclear prognostic significance. Objectives: The primary aims of this study were to describe the clinical and treatment characteristics of BC patients treated with NAC, to identify independent predictive factors of pCR, and to compare the oncologic outcomes between patients achieving pCR or pPR. The secondary aim of this study was to measure the RTC of BC patients with pPR and to compare the outcomes of
patients with different RTC in order to improve prognostic information. Methods: All the consecutive BC patients undergoing NAC at the Breast Unit of IRCCS Humanitas Research Hospital (Milan, Italy) between October 2006 and April 2020 and their corresponding post-operative pathology slides were reviewed. The following exclusion criteria were used: excisional biopsy or debulking surgery as first BC operation, patients with a previous BC diagnosis or other prior or synchronous malignancies, male patients, unknown NAC regimen, disease progression during NAC, and follow-up ≤12 months. Results: A total of 495 BC patients received NAC. Overall, 148 (29.9%) patients achieved pCR, while 347 (70.1%) had pPR, and median RTC was 40%. At multivariable analysis, 3 independent factors predicting pCR were identified. Tumor stage pre-NAC (cT1-2 84.5% versus cT3-4 15.5%, odds ratio (OR)=0.119, 95% confidence interval (95%CI)=0.048-0.189, p=0.001), BC sub-type (HER2-enriched 54.7% versus triple-negative 29.8% versus luminal-like 15.5%, OR=2.178, 95%CI=2.055-2.301, p=0.001), and vascular invasion (absence 98.0% versus presence 2.0%, OR=0.022, 95%CI=0.004-0.090, p=0.001). Patients with BC undergoing NAC and achieving pCR presented statistically significant longer DFS, DDFS, and OS (p = < 0.001). Patients with RTC < 40% presented statistically significant better DFS and DDFS (p = 0.033, p = 0.015, respectively). However, no statistically significant difference in terms of OS was observed between RTC < 40% and RTC ≥40% groups (p = 0.148). Conclusions: Tumor stage pre-NAC, BC sub-type, and vascular invasion are significantly and independently associated with pCR. Patients with pCR present a better prognosis compared to patients with pPR in terms of DFS, DDFS, and OS. Measurement of RTC in BC patients with pPR improves the prognostic information that can be obtained from the assessment of the pathologic response. Different patterns of residual disease play an important role in predicting the risk of subsequent loco-regional and distant recurrence, and patients with RTC < 40% present significantly better DFS and DDFS.

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Background: The apparent diffusion coefficient (ADC) presents a biomarker that is sensitive to tumor cellularity. ADC maps can be calculated from non-contrast diffusion-weighted magnetic
resonance imaging (DW-MRI) measurements. ACRIN 6698, a sub-study of clinical trial I-SPY 2, investigated mean ADC – averaged over the whole tumor – as a marker to predict pathologic complete response (pCR) \[1\]. This work compares a group of histogram-based ADC metrics in addition to mean ADC for early prediction of pCR in patients stratified by breast cancer subtype.

Methods: We performed a retrospective analysis of DW-MRI, dynamic-contrast enhanced (DCE) MRI, and clinical outcome (i.e., pCR at surgery) in a cohort of 79 female patients who were diagnosed with high-risk, stage II/III breast cancer. Patients underwent neoadjuvant chemotherapy (NAC) with paclitaxel (12 weeks), followed by doxorubicin plus cyclophosphamide (12 weeks). The included population represents a subset of the I-SPY 2 cohort and comprises 48 patients with hormone receptor [HR]+/HER2-, and 31 patients with HR-/HER2-. DW- and DCE-MRI acquisitions were performed according to the I-SPY 2 protocol at pretreatment (T0) and after three weeks (T1) and were analyzed to find early treatment percentage (%) change (T0 to T1) in any metric M; where %-change = 100 × (M(T1) – M(T0))/M(T0). Histogram analysis provided nine region-of-interest (ROI)-based ADC metrics (Table 1). ROIs were manually delineated by expert observers in three-dimensional ADC maps, focusing on diffusion-restricted regions \[2\]. DCE-MRI was analyzed for the integral I-SPY 2 imaging marker of %-change in functional tumor volume (FTV) between T0 and T1. Statistical analysis compared the predictive power of ADC metrics and FTV, including: the receiver-operating-characteristic (ROC) curve from a logistic regression model to predict pCR as ‘positive’, area-under-the-curve (AUC) assessment, and rank-sum Wilcoxon test (p< 0.05: statistically significant).

Results (Table 1): 16 out of 79 (20.3%) patients reached pCR at surgery, with 18.8% pCR among HR+/HER- and 22.6% among HR-/HER2- groups. For all nine computed ADC statistics (listed as median [Q1, Q3], across all patients), %-change was higher in patients who reached pCR than patients with non-pCR (highest value for metric ‘MIN’: 23.9% [-0.9%, 52.5] vs. 16.6% [0.4%, 27.6%], though without statistical significance: p=0.237). Likewise, %-change of FTV was also stronger in pCR patients than non-pCR patients (-58.8% [-80.6%, -22.5%] vs. -28.2% [54.2%, -2.7%], with statistical significance: p=0.036). For all patients combined (n=79), among the various reported ADC metrics, %change in ‘PCTL_95’ (95th percentile of histogram) yielded the highest AUC (0.7; 95% CI = [0.56, 0.83]; p=0.012). %change in FTV showed the second highest AUC (0.67; 95% CI = [0.52, 0.82]; p=0.036). By subtype, AUC was highest for %change of ‘PCTL_95’ (0.69; 95% CI = [0.5, 0.87]; p=0.072) in the HR+/HER2- subgroup; and highest for both %change of ‘MEAN’ (AUC = 0.73; 95% CI = [0.49, 0.94]; p=0.065) and ‘PCTL_75’ (AUC = 0.73; 95% CI = [0.49, 0.94]; p=0.073) triple negative (HR-/HER2-) subgroup. By comparison, %change of FTV yielded AUCs of 0.64 (95% CI = [0.41, 0.85]; p=0.191) and 0.71 (95% CI = [0.51, 0.9]; p=0.098) in the HR+/HER2- and triple-negative subgroups, respectively.

Conclusion: Various tumor ADC metrics from non-contrast DW-MRI demonstrate potential biomarkers for assessing responsiveness to NAC at an early treatment timepoint. ADC may have predictive performance that is comparable to FTV, depending on the breast cancer subtype. Observations for %change in ‘MEAN’ ADC at T1 differed from previous reports \[1\], which may be explained by the small sample size and single (paclitaxel) drug arm. Additional studies are warranted to include patients of experimental arms and of HER2+ subtypes.

\[2\] Nu et al., Tomography 8: 1208-20 (2022)
Results of statistical analysis of ADC-based and FTV markers for predicting treatment response at 3 weeks into NAC.

<table>
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<tr>
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<th>ADC statistics (mean ± SD)</th>
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<tr>
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<td>3-week T0</td>
<td>3-week T1</td>
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<td>T0</td>
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<td>MEAN ± SD</td>
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**Note:** Median values represent the median and interquartile range over the respective patient population regarding the %-change of the respective ADC (FTV) metric from T0 to T1.

- **T0:** pretreatment
- **T1:** 3-week timepoint
- **ADC:** apparent diffusion coefficient
- **MRI:** magnetic resonance imaging
- **DW:** diffusion-weighted
- **DCE:** dynamic-contrast enhanced
- **pCR:** pathologic complete response
- **AUC:** area under the ROC curve
- **95% CI:** confidence interval lower and upper limit
- **PCTL_x:** xth-percentile of tumor ADC histogram
- **MEAN:** mean of ADC within ROI
- **MIN:** minimum of ADC within ROI
- **MAX:** maximum of ADC within ROI
- **FTV:** functional tumor volume
- **:** statistically significant

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Longitudinal DCE-MRI Radiomic Models 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 prediction of neoadjuvant systemic therapy (NAST) response in triple negative breast cancer (TNBC) patients could potentially aid in the selection of alternative therapies and avoid unnecessary toxicity in patients unlikely to achieve pathologic complete response (pCR) with NAST. In this study, we investigated the radiomic features of the peritumoral and the tumoral regions from dynamic contrast enhanced (DCE) MRI acquired at different time points of NAST for early treatment response prediction in TNBC.

Methods and Materials: This study included 182 biopsy-confirmed stage I-III TNBC patients enrolled in an IRB approved prospective clinical trial (NCT02276433). All patients underwent DCE-MRI on a GE 3T MRI scanner at baseline (BL), after two (C2) and four (C4) cycles of doxorubicin/cyclophosphamide based chemotherapy and before surgery. The peritumoral and the tumoral regions were segmented manually by two fellowship-trained radiologists using early phase (2.5 min) DCE-MRI subtraction images. Ten first order radiomic features, 300 grey-level-co-occurrence matrix (GLCM) features along with their absolute and relative differences (C4/BL, C2/BL, C4/C2) between the 3 imaging time points were extracted from the peritumoral and the tumoral regions. Patients were randomly divided into training and testing sets in a 2:1 ratio. For univariate analysis, area under the receiver operating characteristics curve (AUC ROC) was measured to determine the features most predictive of pCR/non-pCR. Wilcoxon Rank Sum test was used to test the statistical significance of predictive performance. In multivariate analysis, radiomic models were established using logistic regression with elastic net regularization followed by 5-fold cross validation for performance assessment. Results: Eighty-eight (48%) patients had pCR (59 training, 29 testing) and 94 (52%) patients had non-pCR (63 training, 31 testing). Twenty-five radiomic features (4 from peritumoral C4, 5 from tumoral C4, 4 from peritumoral C4/BL, 6 from tumoral C4/BL, 2 from peritumoral C4/C2 and 4 from tumoral C4/C2) were statistically significant with AUC ≥ 0.75 in both the training and the testing sets at the univariate analysis. The significant features at C4 had AUCs of 0.75-0.79 for the training set and 0.76-0.81 for the testing set. Changes measured between C4 and BL or C2 showed AUC of 0.76-0.84 in the training and 0.75-0.81 in the testing datasets. Eleven multivariate regression models comprised of radiomic features at BL, C2, C4 and their changes (C4/BL, C4/C2 and C2/BL) showed an AUC of 0.80-0.84 for cross validation and an AUC of 0.80-0.82 for independent testing. Conclusions: Radiomic models using longitudinal DCE MRI parameters of peritumoral and tumoral regions during NAST have the potential to predict pCR in TNBC patients undergoing NAST.

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A Pre-operative Dynamic Contrast Enhanced MRI-Based Radiomics Models as Predictors of Treatment Response after Neoadjuvant Systemic Therapy in Triple Negative Breast Cancer Patients

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Background and Purpose Triple negative breast cancer (TNBC) is a biologically aggressive tumor and a refractory subtype of breast cancer due to the lack of therapeutic targets, such as estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2. In this study, we investigated the accuracy of radiomic models based on the dynamic contrast enhanced (DCE) MRI images obtained after the completion of NAST as discriminators of treatment response in TNBC patients. Materials and Methods This IRB-approved prospective study (ARTEMIS trial, NCT02276443) included 181 patients with biopsy proven stage I-III TNBC who had MRIs after completion of NAST and before surgery. Patients were classified as pathologic complete response (pCR) and non-pCR at the surgery. Tumors were segmented on the 2.5 minutes DCE subtraction images. Regions with necrosis or clip artifacts were excluded from the contour. If tumors were not visible, the tumor bed was contoured. Whole-tumor histogram-based first order texture features (p=10) including mean, minimum, maximum, Standard deviation, kurtosis, skewness, 1st, 5th, 95th, and 99th percentiles, and radiomic (p=300) Grey Level Co-occurrence matrix (GLCM) features were extracted with an in-house Matlab toolbox. The samples were split into training and testing data sets by a 2:1 ratio. For univariate analysis area under the receiver operating characteristics curve (AUC ROC) was performed for pCR status prediction. For texture feature selection logistic regression with elastic net regularization was performed. Parameter optimization was performed by using 5-fold cross-validation based on mean cross-validated AUC in the training set. A P-value less than 0.05 was considered statistically significant. Results Of the total 181 patients, 88 (49%) had pCR and 93 (51%) had non-pCR. Univariate analysis identified 7 statistically significant first order imaging features (Minimum, Maximum, Mean, 1st Percentile, 5th Percentile, 95th Percentile, and 99th Percentile) with AUC >= 0.7 (p< 0.001), in both training and testing data sets. Percentile 5 showed highest AUC = 0.78 (p< 0.001). Two multivariate models were statistically significant at
cross-validation with AUC>=0.7. The first model combined 2 first order data (Percentile 1 and Percentile 5) with AUC = 0.73 (p< 0.001). The second model combined 8 first order features (Percentile 1, 5, 95, 99, Mean, Minimum, Maximum, and Skewness) and 24 GLCM features with AUC = 0.7 (p=0.003). Conclusion DCE-MRI radiomic features from tumor and tumor bed regions in TNBC may be helpful imaging biomarkers for predicting treatment response after NAST.

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Validation of prognostic platform to further refine identification of High Risk Patients indicated for Chemotherapy Free Treatment in Early-Stage Breast Cancer

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Use of prognostic assays and clinical features to further risk stratify patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer has become standard of care. Stratification of patients into low/mid risk of disease recurrence enables physicians to decide which patients can safely forgo chemotherapy. Yet there exists a subpopulation of patients who tend to have recurrences following endocrine therapy alone. Complicating the issue, recent data has shown these proliferation-based markers assessed from a single site tissue biopsy may not be reliable for minority populations, potentially owing to spatial heterogeneity of tumors. To address this, we used a novel 2-paramenter pharmacokinetic modeling framework that allows biosignatures to be extracted from dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) studies that contain 3-6 timepoints spaced 60-90 seconds apart. These parameters, referred to as P1 and P2, represent leakiness from vessels into the extravascular space and vice versa. This approach was previously developed in a study of 111 breast cancer patients where the 21-gene
recurrence score and DCE-MRIs were available. Low P1 showed better outcomes in low- and mid- patients (n=88, p≤0.028; log-rank test). Patients with a high P1 had a 20.2% chance recurrence at six years. The same trend was observed in mid-recurrence score patients only (n=23, p≤0.058). No recurrences were observed in patients with low P1 in either the RS-low or RS-mid categories. There were no recurrences in the high P1, RS-low/-mid category that received chemotherapy, suggesting that chemotherapy could be beneficial in this category of patients, although the trend was not statistically significant (n=10, p=0.46). Here we present an independent, single site validation of these prognostic markers in patients who received only neoadjuvant endocrine therapy and had corresponding pre-treatment MRIs. Two hundred ninety-eight patients with early-stage breast cancer and pre-treatment MRIs were identified via chart review. Of the patients assessed, 33 patients were treated with neoadjuvant endocrine therapy and qualified for the analysis. Consistent with the previous analysis, the 5-year event-free survival rate in low P1 population was 100% while that in the high P1 population was 45.8% (p=0.053). Overall, we find strong support that these markers could help physicians further fine tune their decision-making when determining who to forgo chemotherapy.

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Tumor microenvironment subtype influence the response of neoadjuvant chemotherapy in breast cancer

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Introduction Recent transcriptome analysis developed a holistic tumor microenvironment (TME) classification platform based on immune and fibrotic markers. This TME classification had four categories, immune enriched, fibrotic (IE/F); immune enriched, non-fibrotic (IE); Fibrotic (F); and Immune Desert (D). And these four TME subtypes are a predictive biomarker to immunotherapy in multiple cancer and four subtypes have been changed during treatment. Previously our study suggested baseline immune features and dynamic immune response on-treatment were predictive of treatment outcome in BC with neoadjuvant chemotherapy (NAC). In this study, we evaluated the impact of TME classification and dynamic change of TME classification on treatment outcome in BC with NAC. Methods Early and locally advanced BCs which would be planned to receive standard NAC (four cycles of anthracycline plus cyclophosphamide and four cycles of docetaxel or docetaxel plus trastuzumab for human epidermal growth factor receptor 2[HER2+] disease or six cycles of docetaxel, carboplatin, trastuzumab and pertuzumab for HER2+ disease) followed by curative surgery. We prospectively collected tumor tissue and matched blood three times for each patients: at BC diagnosis (T1), three weeks after the first cycle of NAC (T2), and curative surgery (T3). RNASeq was performed to classify TME subtype. In terms of clinical variables, clinical stage and IHC subtype at diagnosis, pathologic complete response (pCR), distant recurrence free survival (DRFS) and overall survival (OS) were used. Generalized logistic regression was used
for predicting RCB class and pCR with clinical and genomic characteristics at T1. Kaplan-Meier analysis were performed to analysis DRFS and OS. Results In total, 210 patients who were treated with scheduled NAC were enrolled. Finally, RNASeq in 240 BC tissues (T1:119, T2:91 and T3:30) were conducted from 142 patients. In 119 BCs which was performed RNASeq at T1, hormone receptor(HR)+, HER2- BC was 32 (26.9%), 29 of HR+HER2+ BC (24.4%), 18 of HR-HER2+ BC (15.1%) and 44 of triple negative BC (TNBC) (37.0%). In TME classification, immune desert (D) was most frequently observed (45.3%), followed by IE (35.3%), F (10.1%) and IE/F (9.2%). The association between BC subtype and TME subtype suggested that HR+HER2- BC was frequently categorized into D (22 of 32, 68.8%) whereas TNBC was into IE (24 of 44, 54.5%) (p< 0.001). TME subtype has been dynamically changed during NAC. At T2, IE subtype was most frequently observed (27.5%) followed by D (25.3%), IE/F (24.2%) and F (23.1%). The inclination of TME change were different according to NAC response. In BC achieved pCR, IE/F subtype had increased (4 at T1 and 10 at T2) and decrease of D subtype (15 at T1 and 3 at T2). In BC with non-pCR, IE/F subtype had slightly increased at T2 (7 at T1 and 12 at T2) but there was no IE/F subtype at T3 point. Contrarily, D subtype had decreased at T2 but increased at T3 (39 at T1, 20 at T2 and 24 at T3). The impact of TME subtype was different according to pCR status. In BC with pCR, F subtype had poor prognosis in DRFS and OS compared to other subtype ([5year DRFS rate for F vs. others: 66.7% vs. 93.2%, p=0.028], [5year OS rate for F vs. others: 70.7% vs. 100%, p< 0.001]). In BC without pCR, there was no different DRFS and OS according to TME subtypes. Conclusion Our data suggested that TME subtype has been changed during NAC and the subtype switching was affected by the NAC response. Moreover, TME subtype may have prognostic role in DRFS and OS according to pCR status.

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Predictive efficacy biomarker for chemotherapy agents against triple-negative breast cancer bioprinted organoid tumors (BOTs) using solid tumor biopsy-on-a-chip

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Background: Despite $90 billion in preclinical research and clinical trials every year, 90% of cancer clinical trials are unsuccessful. Thus, there is considerable interest in predicting clinical efficacy of preclinical formulations early in discovery using patient derived ex vivo platforms. However, extracting adequate tissue for such models can be difficult depending on tumor type and site. Dominant mechanisms for expanding patient tissue include xenografts and organoids. However, the former imposes a large time window to establish while the latter is constrained in space by sizescales. Here, we present a novel approach for expanding TNBC tissue, specifically for use in ex vivo models, that addresses these constrains with 3D bioprinted organoid tumors (BOTs). Objective: The aim of this study is to generate TNBC BOTs that mimic core biopsy tissue for use in ex vivo precision and personalized predictive biomarkers for chemotherapies. Methods: BOTs were generated using alginate-based bioink prepared with MDA-MB-231 TNBC cells. Briefly, specially prepared fresh TNBC bioink was deposited layer-by-layer using a Cellink BIO X6 bioprinter in geometrical configurations to mimic 14- to 18-gauge tumor biopsies. These were chemically cross-linked and cured in stages to allow cells and matrix to self-assemble with limited degrees of freedom. Fully cured BOTs were loaded in our ex vivo solid tumor biopsy-on-a-chip and treated with chemotherapy agents to evaluate sensitivity and resistance, with outcomes determined using immunofluorescent live and dead cell staining methods. Results: A 3-minute crosslinking time with calcium chloride provided a stable and functional sodium alginate medium for treating cellular BOTs. Two layers of TNBC bioink was determined to be the optimal size and shape for compatibility with our ex vivo...
biopsy-on-a-chip predictive efficacy biomarker platform. TNBC cells were verified to be evenly distributed within the cured sodium alginate matrix using live cell nuclear stains. Successful diffusion of multiple agents to spatially distinct regions of the bioprinted tissue was verified with fluorescently labeled small molecules and nucleic acid stains up to 200 µM deep. Impact: Patient derived BOT core mimics and other configurations could be used in ex vivo breast cancer chemotherapy screening models to obtain sensitivity and resistance profiles as predictive functional biomarkers both on the bedside for personalized treatment strategy development and on the bench to uncover new therapeutic targets. Due to their potential to replicate biophysical and biochemical characteristics of a tumor and its microenvironment, BOT based precision and personalized medicine platforms can provide more accurate drug efficacy readout compared to in vitro cancer models.

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The impact of the 21-gene Recurrence Score® assay upon physician treatment recommendations in the neoadjuvant setting in lymph node-negative breast cancer patients in a multicenter prospective study in Quebec

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Background: Although the role of the 21-gene Breast Recurrence Score® assay is well established to predict response to adjuvant chemotherapy in the setting of node-negative hormone receptor (HR)-positive, HER2-negative breast cancers (BC), fewer studies have evaluated the assay in the neoadjuvant setting. Due to the correlation between a high Recurrence Score® (RS) result and pathological complete response (pCR), the Breast Recurrence Score assay has been used to aid in selecting between chemotherapy (CT) or endocrine therapy. We wanted to further understand the impact of the assay upon physician treatment recommendations and the use of chemotherapy in this patient cohort. Methods: We conducted a multicenter, prospective, observational study in patients with clinically node-negative HR-positive, HER2-negative BC with T2-T3 disease being considered for neoadjuvant therapy. Physicians were required to complete two questionnaires indicating treatment choice, including CT, endocrine therapy, or surgery, prior to and post availability of RS result. Patients were followed up for 6 months after commencement of neoadjuvant therapy. The primary objective was to evaluate the change in the physician’s recommendation for neoadjuvant CT prior to and post assay results. As a secondary objective, we also evaluated the impact of the RS result on physician’s expressed level of confidence. Results: A total of 70 patients were enrolled between April 2018 and November 2021 at five hospital centers, as part of the McPeak Sirois Group of Quebec. The median age of the cohort was 60 years (range, 30 to 79 years). 24.3% (n=17) of the cohort consisted of patients aged < 50 years, and 75.7% (n=53) were ≥ to 50 years. 29.0% (n=20) of the patients had a RS < 16, 39.1% (n=27) had a RS between 16-25, and 31.9% (n=22) had a RS > 25. For the entire cohort, the RS result led to a net reduction in
chemotherapy recommendation by 33.3% (OR (odds of having CT post-RS recommendation versus pre-RS recommendation) = 0.23 [95% CI: 0.12-0.44]; P< 0.0001), and 39.2% net reduction in the use of chemotherapy at 6-month follow-up (OR = 0.18 [95% CI: 0.09-0.35]; P< 0.0001). Furthermore, the RS result led to a 35.3% net reduction in physician recommendation of CT for patients < 50 years (OR = 0.19 [95% CI: 0.04-0.83]; P=0.027) and a 32.7% net reduction for patients ≥ 50 years (OR = 0.24 [95% CI: 0.11-0.50]; P=0.0001). For patients with a RS < 16, there was a reduction in CT recommendation by 75.0%, and by 44.4% for patients with a RS between 16 - 25 (OR = 0.15 [95% CI: 0.06-0.38]; P< 0.0001). Moreover, RS results led to an increase in confidence in physician treatment decisions for 59.4% of patients (OR = 12.53 [95% CI: 5.46-28.78]; P< 0.0001). Conclusion: We determined that the 21-gene Breast Recurrence Score assay altered neoadjuvant treatment decisions, leading to a reduction in the use of chemotherapy by about one-third, regardless of age. Additionally, the assay increased physician confidence in their treatment recommendation for about 60% of patients. This demonstrates the potential clinical utility of the assay to decrease the use of CT in the neoadjuvant setting amongst HR-positive, node-negative BC patients in Quebec.

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Integrative transcriptomic analysis and cohort validation identify key genes in chemotherapy treatment response in Latino breast cancer patients.

Purpose: Breast cancer (BC) is one of the most frequent invasive cancers and one of the main causes of cancer mortality in women. Effective treatment interventions for BC are urgently required to improve survival rate and quality of life. Chemotherapy has been widely applied in BC treatment; however, therapeutic resistance remains an unresolved issue. Currently, only a minority of patients benefit from chemotherapy, emphasizing the need to identify more effective hub genes associated with therapy response. The overarching goal of this study is to assess hub genes correlated with BC chemotherapy treatment response via multiple databases and validate the workflow in an independent cohort of Hispanic/Latino (Colombian) women diagnosed with invasive Luminal B BC candidates for neoadjuvant chemotherapy. Design: Screening and multistep filtering of common genes correlated with chemotherapeutic response was performed by integrating differentially expressed genes between responders and non-responders in publicly available datasets. For each database, the differentially expressed genes (DEGs) between non-responders and responders were identified using GEO2R and LIMMA. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted for the identified common genes using Metascape and
DAVID. Functional enrichment analysis and protein-protein interaction (PPI) network for DEGs were constructed using (STRING) database. Hub genes were identified from PPI network by Cytoscape software analysis. The mRNA expression of hub genes in BC and normal tissues was subsequently explored by UALCAN. Evaluation of the effect of hub genes on survival was performed using Kaplan-Meier plotter. Hub genes were imported into the DGIdb to obtain the potential for BC chemotherapy-associated treatment drugs. The previous workflow was then applied/validated to an Illumina high-throughput RNA sequencing of 50 Luminal B cases (HER2+ and HER2-) of Hispanic/Latino patients. Results: 490 DEGs were obtained from the intersection of five public databases. Pathway enrichment analysis revealed DEGs were associated with cell cycle, estrogen response, adaptive immune response, and regulation of kinase activity, among others. Thirty-two hub genes were identified from PPI network analysis with high degree nodes and betweennesscentrality. Significant differential expression of hub genes between BC tissue and normal tissues was observed in UALCAN. These genes were significantly associated with survival probability. Fifteen potential targeted therapeutic drugs were identified through DGIdb database. Validation workflow in independent Luminal B cohort showed 238 DEGs, 90 hub genes with high degree and enrichment in the regulation of hormone levels, cellular response to EGFR, signaling by ERBB2 and MAPK. GATA3 was the hub gene found in both databases and the validation set. Both databases and validation set show hub genes, enriched pathways, and drugs that indicate their close association with tumorigenesis and would contribute to acting an important role in therapy response prediction. Conclusions: This workflow was created using public databases and applied to a patient’s cohort of different ancestries. This methodology can successfully provide potential biomarkers that correlate with therapy response. Genes were selected from PPI network. Most of them were independent biomarkers of BC treatment response, including that in underrepresented patients. Moreover, these genes may exert critical function in non-response and progression.

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Influence of HER2 expression status in the distribution of recurrence score from the OncotypeDx assay among women with early-stage estrogen-receptor-positive/HER2-negative breast cancer

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BACKGROUND: The OncotypeDX assay analyzes the expression of 21 genes, including HER2 and Grb7, to assess the predictive effect of chemotherapy in breast cancer recurrence among women with early-stage estrogen-receptor (ER) positive/HER2-negative breast cancer. In this study, we evaluate the distribution of recurrence score from the OncotypeDX assay based on the HER2 expression status by immunohistochemistry (IHC). METHODOLOGY: Utilizing the National Cancer Database, we identified adult women with a diagnosis of stage I – III ER+/HER2- invasive ductal carcinoma of the breast between the years 2010 and 2018. Recurrence scores were classified into low (< 11), intermediate (11-26), and high risk (>26); and the distribution of these recurrence scores cross-tabulated with different IHC scores of HER2 expression (0, 1+, and 2+) by IHC. Women with an IHC score of 2+ had to be negative for HER2 gene amplification by FISH. Multivariate logistic regression model adjusting for age, race, origin, progesterone receptor status, grade, and cancer stage was used to assess the odds of receiving a high OncotypeDx Score (≥26). RESULT: Among 198,931 women with ER+/HER2 negative breast cancer, 59,632 (30.0%) had HER2 IHC score of 0, 102,170 (51.4%) had IHC score of 1+, and 37,129 (18.6%) women were with IHC score of 2+. The median age at diagnosis of breast cancer among all three categories of HER2 expression was 59 years. The median recurrence score for women with IHC scores of 0, 1+, and 2+ was 15, 15, and 16 respectively (p < 0.001). A higher proportion of women with HER2 IHC score of 2+ had a high recurrence score compared to women with an IHC score of 0 (15.2% vs. 13%, p < 0.001). In multivariate analysis, compared to women with HER2 IHC score of 0, women with HER2 IHC score of 2+/FISH negative were observed to have higher Odds (OR: 1.16; 95% CI: 1.11 – 1.20, p < 0.001) of receiving high recurrence score. There was no significant difference in the odds of receiving a high recurrence score between women with IHC 0+ and 1+(OR: 0.99; 95% CI: 0.96 – 1.03, p 0.82). CONCLUSION: Women with a HER2 IHC score of 2+ were observed to have a higher odds of receiving high-risk recurrence scores as compared to women with IHC score of 0. This needs to be further correlated with the response to chemotherapy and the risk of recurrence.

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BASELINE 18FDG-PET METABOLIC TUMOUR VOLUME (MTV) AS A POTENTIAL PREDICTIVE FACTOR OF RESPONSE TO METRONOMIC CHEMOTHERAPY (mCHT) IN HR+/HER2- METASTATIC BREAST CANCER (MBC) PATIENTS (pts). PRELIMINARY RESULTS OF THE METRO-PET STUDY

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Background:
MBC is an incurable disease and chemotherapy (CHT) represents one option of treatment upfront, in TNBC pts, or at failure of an endocrine therapy + targeted agents in HR+ ones. mCHT was extensively studied in different types of ABC pts and is largely used in clinical practice. 18FDG-PET is often used as a tool for disease staging at baseline and for disease restaging during treatment. Different quantitative and semi-quantitative 18FDG-PET parameters have been investigated as predictive and prognostic biomarkers in NSCLC and other tumours. Aim of the present study is to evaluate the role of baseline SUVmax, global SUVmean, SUVpeak, Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG) as predictive factors of response to mCHT.

Patients and Methods
We identified 36 MBC pts treated with mCHT between 2014 and 2021, with at least two separate 18FDG-PET evaluations. Patients and biological tumour characteristics, previous treatments, site of relapse as well as quantitative pre-treatment 18FDG-PET parameters have been collected. Tumour response was assessed using PERCIST Criteria. Median and mean ± SD 18FDG-PET parameters have been reported according to the type of response. Complete and Partial responses have been grouped together with Stable Disease.

Results
Median age was 69 (33-82). Luminal pts were 25 (67.6%), TNBC pts were 16.2%); most were heavily pre-treated for their metastatic disease (≥ 3 lines: 14, 37.8%) and presented ≥ 3 metastatic sites (14, 37.8%). All pts received mCHT, 26 (70.3%) as combination therapy (VRL+CAPE or VRL+CAPE+CTX), or single agent (VRL, 11). Bone was the commonest metastatic site (62.2%). ORR was 43.2%; 7 pts had SD (18.9%), the remaining developed PD (37.8%). Similar values have been observed between the 2 groups in terms of SUVmax, global SUVmean and SUVpeak. Mean MTV was higher in responder (n=22) vs non responder (n=14) pts, as TLG. Details are reported in Table 1.

Conclusions
High mean baseline MTV and TLG seem to be related to response to mCHT in MBC pts. Our
observation is in contrast to what is described for other cancer types, especially NSCLC, and for standard neoadjuvant treatment of BC. Considering the peculiar mechanisms of action of mCHT, our preliminary findings warrant further exploration in a larger series of BC pts.

Table 1 - Baseline 18FDG-PET uptake values in responder and non responder patients

<table>
<thead>
<tr>
<th></th>
<th>SUNmax</th>
<th>global SUNmax</th>
<th>SUN%max</th>
<th>MTV</th>
<th>TLG</th>
</tr>
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<tr>
<td>RESONER</td>
<td>Mean</td>
<td>12.42</td>
<td>4.97</td>
<td>9.31</td>
<td>129.83</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>9.28</td>
<td>3.75</td>
<td>7.50</td>
<td>38.17</td>
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<tr>
<td></td>
<td>SD</td>
<td>7.58</td>
<td>2.82</td>
<td>6.94</td>
<td>211.28</td>
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<tr>
<td>NON RESPONDER</td>
<td>Mean</td>
<td>10.20</td>
<td>4.09</td>
<td>6.81</td>
<td>38.92</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.17</td>
<td>3.54</td>
<td>6.89</td>
<td>22.31</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.55</td>
<td>1.63</td>
<td>2.44</td>
<td>37.49</td>
</tr>
</tbody>
</table>

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Predictors of Response to Neoadjuvant Chemotherapy in Breast Cancer: OncotypeDX versus MammaPrint versus Liquid Biopsy

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Background: OncotypeDX (ODX) is a 21-gene recurrence score (RS) assay that is predictive of the benefit of adjuvant chemotherapy in early-stage hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer. MammaPrint (MP) is a 70-gene signature validated to prognosticate distant metastasis and survival. We have previously presented data suggesting that the presence of circulating tumor cells (CTCs) evaluated via liquid biopsy may also have prognostic and predictive utility in HR+/HER2- breast cancer. In this study, we compare the value of ODX, MP and liquid biopsy evaluating CTCs and disseminated tumor cells (DTCs) in predicting pathologic complete response (pCR) following neoadjuvant chemotherapy (NAC).

Methods: This retrospective analysis used the National Cancer Database (NCDB) 2004-2017 breast cancer dataset to identify a cohort of patients with HR+/HER2-, AJCC clinical stage I-III breast cancer who received NAC. A series of multiple logistic regression models were used to assess the value of a. ODX (RS < 26 versus ≥26), b. MP, c. the presence of CTCs, and d. the presence of DTCs in predicting pCR to NAC. Each model controlled for age, race, Charlson/Deyo comorbidity scoring, disease histology, grade, and nodal status. Results: A total of n=52,463 patients with stages I-III HR+/HER2- breast cancer received NAC. The patient characteristics of this cohort were as follows: the majority were White (n=42,826, 81.6%), between 50-70 years of age (n=27,683, 52.8%), and with invasive ductal carcinomas of the breast (n=40,197, 76.6%). N=6,111 (11.6%) had Grade I or well-differentiated disease, n=23,546 (44.9%) Grade II or moderately-differentiated disease, and n=2,605 (43.5%) had Grade III or poorly-differentiated disease. N=3,823 have documented recurrence scores based on ODX: with n=2,653 having RS < 26 (69.4%) and n=1,170 (30.6%) having RS ≥26. After controlling for age, race, comorbidity scoring, disease histology, grade and nodal status, RS ≥26 was found to be significantly associated with pCR to NAC (OR 1.85, 95% CI 1.46-2.35, p<0.001). High-risk scoring per MP was also correlated with pCR but this relationship was not
statistically-significant (OR 1.68, 95% CI 0.93-3.03, p=0.084), possibly due to the smaller size of this sample (n=828 patients underwent MP testing). Liquid biopsy data was also limited, with n=250 patients having documented CTC status and n=211 having documented DTC status. Neither the presence of CTCs (OR 0.96, 95% CI 0.44-2.09, p=0.908) nor DTCs (OR 0.61, 95% CI 0.25-1.50, p=0.279) was significantly associated with pCR to NAC. Conclusions: ODX is found to be predictive of pCR to NAC in early-stage, HR+/HER2- breast cancer. Utility of MP and liquid biopsy data in this context appears less robust, however, data is limited. More research is needed to validate existing data in a prospective trial setting, and explore for novel biomarkers across breast cancer subtypes.

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Alteration of DNA methylation landscape in breast patients treated with adjuvant chemotherapy

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Background Exposure to cytotoxic chemotherapy treatment may alter DNA methylation (DNAm) in treated patients. Methods We performed DNAm analysis in 1,244 and 897 breast cancer patients treated and not treated by adjuvant chemotherapy using the Illumina MethylationEPIC array (1,804 blood, 337 saliva). DNAm changes of 620,095 individual CpGs and 41,581 promoters were evaluated using linear regression models, adjusting for age at diagnosis, ethnicity, years between sample collection and diagnosis and cell-type heterogeneity. Results from datasets normalized separately were combined by meta-analysis (random effects model). Gene set enrichment analyses were conducted to identify key processes or pathways associated with chemotherapy treatment. Results A total of 425 differentially methylated CpGs and 20 promoters were significantly associated with chemotherapy treatment (p< 5e-8). Enriched gene sets among 3,495 chemotherapy-associated promoters (unadjusted p< 0.05, preranked by Z scores) included three suppressed Gene Ontology (GO) terms that survived Bonferroni correction (GO:0002376, immune system process; GO:0009605, response to external stimulus; and GO:1903034: regulation of response to wounding). Using meta-analysis regression coefficients for all promoters as a ranking metric, olfactory transduction (KEGG, hsa04740) was found to be significantly suppressed (unadjusted p=6.38e-06, adjusted...
p=0.002). Taste transduction (hsa04742, unadjusted p=1.73e-03, adjusted p=0.565) was the next most significantly suppressed pathway. Conclusion The enrichment of imprinted genes within biological processes and pathways suggests a biological mechanism by which chemotherapy treatment could affect immune response, wound healing and changes in the perceptions of smell and taste.

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Introduction: Neoadjuvant chemotherapy, one of systemic treatment of breast cancer, is employed for downstaging of inoperable tumor. Pathological complete response (pCR) after neoadjuvant chemotherapy is associated with good prognosis for breast cancer. The critical role of anti-tumor immune responses in conventional chemotherapy and targeted therapy has been reported. However, the pCR-associated immune genes are still ambiguous. Materials and Methods: Thirty-seven primary breast cancer patients receiving neoadjuvant chemotherapy as the first-line treatment for breast cancer were recruited in this VGH-TAYLOR study (NCT04626440). Total RNA of fresh tumor tissues was isolated and then reverse transcribed into cDNA. The Oncomine Immune Response Research Assay was employed for examination of immune-related gene expressions. In silico analyses were performed using the public databases, including Gene Expression Omnibus, Kaplan-Meier plotter, ROC Plotter, Cancer Therapeutics Response Portal, and The Cancer Genome Atlas. Results: Patients achieved a
pCR were associated with lower tumor stage and HER2 expression. The next-generation sequencing-based analysis showed that the expression of eight genes were higher in tissues of patients with pCR than non-pCR, including KLRK1, IGJ, CD69, CD40LG, MS4A1, CD1C, KLRB1, and CA4. The 8-gene score was associated with better recurrence-free survival in patients receiving chemotherapy. Data from an ROC Plotter database showed that higher expressions of IGJ, CD69, and MS4A1 in patients respond to neoadjuvant chemotherapy compared to non-responders. In silico analysis revealed that the negative correlation between pCR-associated gene expressions and IC50 values suggesting the gene high expression was sensitive to the drugs. Moreover, the levels of pCR-associated gene were downregulated in breast tumor tissues and positively correlated with immune cell infiltrations. Conclusion: We identified eight immune genes which were associated with better prognosis and drug responses. The 8-gene score may serve as a prognostic marker for breast cancer patients who receiving neoadjuvant chemotherapy.

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Frequency of pathogenic germline mutations beyond Germline BRCA gene mutations among Saudi patients with breast cancer

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Background: Breast cancer is the...
commonest cancer diagnosed in the kingdom of Saudi Arabia. Although the majority of breast cancer cases are sporadic, around 25-30% are related to hereditary and familial components. Germline BRCA gene mutations are most common mutations associated with hereditary breast cancer predisposition syndromes. In Saudi Arabia, the reported frequency of germline BRCA mutations is 11%. There is no data about the prevalence non BRCA pathogenic germline mutations in Saudi population. We aimed to study the prevalence of these mutations in Saudi patients with breast cancer. Methods: We analyzed all the confirmed breast cancer cases who were referred to the cancer genetic clinic at King Abdulaziz medical city in Riyadh, Kingdom of Saudi Arabia by using our cancer genetics database. Since November 2018, a comprehensive hereditary cancer gene panel is offered to all referred breast cancer cases who meet the NCCN testing guidelines after obtaining a genetic counselling assessment and an informed consent. All testing was internally funded by the institution. The comprehensive panel tested genes are; ABRAXAS1, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, DIS3L2, EPCAM, FANCC, FH, FLCN, GALNT12, HNF1B, HOXB13, KIT, MC1R, MEN1, MET, MITF, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MUYTH, NBN, NF1, NTHL1, PALB2, PMS1, PMS2, POLD1, POLE, POT1, PRSS1, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RECQL, RET, RNF43, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, WT1, XRCC2, XRCC3. Result: Between November 2018 and May 2022, a total of 332 patients with breast cancer have been tested. The median age was 45 and 54 years for females and males, respectively. The majority of patients were females (n=322, 97%). Most of the patients had stage III disease (n=183, 55%) followed by stage II(n=91, 27%). Pathogenic variant(PVs) was reported in 16% (n= 52), variant of uncertain significance (VUSs) was reported in 10% (n=32) while no mutation reported in the rest of the patients. TNBC was the most common phenotype among carriers of pathogenic mutation (50%). The PVs reported were BRCA1 (n=19), BRCA2 (n=21), PALB2(n=2), PTEN (n=2), ATM(n=1), BARD1(n=1), BLM(n=1), BRIP1(n=1), CDKN2A(n=1), CHEK2(n=1), MSH2(n=1) and RECQL(n=1). Conclusion: This study shows that extended panel testing beyond BRCA gene increases the rate of detection of pathogenic germline mutations that has preventative and possibly therapeutic implications. In addition, to the best of our knowledge this is the first study that gives insight about the frequency of non germline BRCA mutations which represent unmet needs for breast cancer patients in Saudi Arabia. 1. J Glob Oncol. 2018 Aug;4:1-9. 2. Breast Cancer Res Treat. 2018 Apr;168(3):695-702

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Challenges and Dilemmas Following a Traceback Approach for Genetic Counseling and Genetic Testing for Pathogenic Germline Mutations among High-Risk Patients Previously Diagnosed with Breast Cancer

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Background: Accounting for almost 20% of all cancer cases, breast cancer continues to be the most common cancer and the leading cause of cancer-related deaths among females. In our region, almost 50% of breast cancer patients are diagnosed at age 50 or younger. Around 5-15% of breast cancers are hereditary and mostly related to BRCA1 or BRCA2 gene mutations. Risk-reducing interventions, like bilateral mastectomies and oophorectomies, are highly recommended for carriers of pathogenic variants. More recently, data had shown that specific breast cancer treatment may be informed by BRCA1 or BRCA2 mutation status. Until very recently, genetic testing and genetic counseling services were prohibitively expensive and were not available or routinely offered. Given the recently identified high prevalence of pathogenic
variants among our patients, and the wider availability and the lower cost of genetic testing, an opportunity exists to look back and offer such patients the chance to do genetic testing. Patients with positive tests can then be counseled, along with their close family members, for appropriate risk-reducing programs. Methods: Using our hospital-based cancer registry, we identified patients with breast cancer who fulfilled at least one of 3 approved indications for genetic testing but never had it. Eligible patients were those diagnosed at age 45 or younger, patients with triple-negative (TN) disease diagnosed at age 65 years or younger, and those with close blood relatives with breast or ovarian cancers. Patients were initially contacted over the phone and then seen by one of the investigators in our genetic counseling clinics. Testing was performed using next-generation sequencing (NGS)-based multi-gene panel (MGP) on a peripheral blood sample at a referral lab. Results: A total of 377 eligible patients were identified. The median age (range) was 48 (31-75) years. Genetic testing was performed on 198 (52.5%) and results were reported on 192. Age ≤45 years (n= 157, 79.3%) and TN-disease (n= 59, 29.8%) were the most common indications for testing. In total, 20 (10.4%) patients were found to have pathogenic/likely pathogenic variants; mostly in BRCA2 (n=9) and BRCA1 (n=7). An additional 4 patients had TP53, PALB2, and ATM. Variants of uncertain significance (VUS) were identified in 53 (27.6%) patients. Following the visit to the genetic counseling clinic, an additional 41 (22.9%) patients agreed to test. The remaining 136 (36.1%) failed to be tested because of lack of updated contact information (n=54, 39.7%), living outside the country (n=19, 14.0% ) or lack of insurance coverage (n=36, 26.5% ). Fear of social stigma, lack of interest, or emotional stress were the reason for refusal among 24 (17.6%) patients. Conclusions: The Traceback approach may provide an opportunity to diagnose pathogenic/likely pathogenic variants among previously diagnosed patients with breast cancer. The high percentage of patients couldn’t be tested for manageable reasons while fear of social stigma and emotional stress continued to be important barriers, especially in societies like ours. Given the important implications of genetic testing and its availability and affordability, reaching out to untested high-risk patients raises an ethical and professional dilemma that needs to be addressed from the physician, patients, and insurance perspectives.

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Breast Health Assessment: A family health history tool using the electronic health record and clinical decision support to facilitate guidelines-driven hereditary breast cancer genetic testing at the time of screening mammogram

Title: Breast Health Assessment: A family health history tool using the electronic health record and clinical decision support to facilitate guidelines-driven hereditary breast cancer genetic testing at the time of screening mammogram

Background: Genetic testing (GT) is recommended for women who have a personal or family history of breast cancer and are at increased risk of carrying an inherited breast cancer risk gene pathogenic variant (PV) as defined by the National Comprehensive Cancer Network (NCCN) guidelines. Data shows that traditional GT workflows do not reach a large proportion of women eligible for GT. NorthShore University HealthSystem previously implemented the Genetic Wellness Assessment, a family health history (FHH) screening tool utilizing the electronic health record (EHR) and clinical decision support, to identify individual and familial risks to health conditions and personalize screening and prevention practices in primary care. To increase access to hereditary breast cancer GT, we implemented a similar FHH screening tool called the Breast Health Assessment (BHA) for patients completing routine screening mammogram. We describe uptake and results from implementation of the BHA in conjunction with routine screening mammogram.

Methods: Patients scheduled for screening mammogram were assigned the BHA prior to their mammogram via the EHR portal. BHA questions addressed personal and family history of breast cancer and other cancer types associated with hereditary breast cancer syndromes. Upon completion of the BHA, patients who screened positive, i.e. identified as having a high-risk personal or family cancer history based on NCCN guidelines, were offered a comprehensive hereditary cancer panel (HCP). HCP included 38 genes associated with common cancer types, including all high and moderate risk breast cancer genes for which there are NCCN management guidelines. Individuals who were not identified as high-risk were offered a genetic health screen, which consisted of 148 genes associated with common cancer types, genetic forms of heart disease, medication response, and other health conditions. Saliva sample collection for GT occurred at the time of the patient’s screening mammogram appointment.

Results: From August 2021 through May 2022, 32,438 patients were assigned the
BHA prior to screening mammogram. Of these patients, 14,128/32,438 (44%) completed the BHA questionnaire. Based on BHA response, 3,490/14,128 (25%) screened positive and met NCCN criteria for GT for hereditary breast cancer risk genes and 529/3,490 (15%) completed GT. Additionally, 713/10,638 (7%) patients who screened negative on the BHA completed testing. In total, 1,242/14,128 patients (9%) completed GT and 78/1,242 (6%) were found to carry an inherited PV in a cancer risk gene, 35 of which were in an NCCN guidelines breast cancer risk gene. Of the 78 patients with a positive GT result, 57/78 (73%) had not been previously recommended for a genetics evaluation and/or received a genetics referral.

Conclusion: The BHA is a novel FHH tool which increases access to hereditary breast cancer GT at the time of screening mammogram. Nearly half of women who completed screening mammogram completed the BHA and learned valuable information about their breast cancer risk and were invited to complete GT. Genetic testing completed through the BHA identified 78 patients with an actionable inherited PV in a cancer risk gene. This invaluable information will lead to potentially lifesaving personalized cancer screening and risk reduction and help identify additional at risk family members. Notably, 73% of patients who carried an inherited PV had not been previously recommended by their medical teams for genetic counseling and/or testing. The BHA has the potential to help close the care gap in GT for women at increased risk of breast cancer.

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Use of breast surveillance between women with pathogenic variants and variants of uncertain significance in breast cancer susceptibility genes

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Background: Surveillance is a fundamental tool in the early detection and secondary prevention of many cancers. For women at increased genetic risk of breast cancer, mammography and breast magnetic resonance imaging (MRI) serve as the standard screening modalities. Use of surveillance mammography and MRI has been understudied among women with variant of uncertain significance (VUS) compared to pathogenic and likely pathogenic variants (P/LP). To address this gap, we examined the use of breast cancer surveillance and breast surgery in women who underwent multiple gene sequencing in a multicenter cohort of patients. We also expanded the surveillance literature by assessing correlates of breast MRI and mammography among women with VUS and investigating how rates of imaging changed over time after genetic testing. Methods: Using data from two cancer settings, we calculated use of risk reducing mastectomy (RRM) and surveillance for all women at genetically elevated risk of breast cancer, regardless of their personal history of breast cancer, with VUS or P/LP variants in a breast cancer susceptibility gene of high penetrance (BRCA1, BRCA2, PALB2, PTEN, TP53) and moderate penetrance (ATM, CDH1, CHEK2, NBN, NF1, STK11). The primary outcome was longitudinal use of surveillance mammography and breast MRI for women during the 13-month span after genetic testing, and each subsequent 13-month period up to 6 years
afterwards. Results: Of 889 women, those with and without personal history of breast cancer were similar with regards to race/ethnicity, marital status, and high- or average-risk status. However, women with a personal history of breast cancer were on average older (54.1 vs 48.2 years), had longer follow-up time since genetic testing (3.4 vs 3.0 years), and were more likely to have VUS (62.5% vs 37.7%) compared to those without personal history of breast cancer. VUS carriers were less likely to undergo RRM compared to those with P/LP (HR=0.17, p=< 0.001) and high-risk women were more likely to undergo RRM than average-risk women (HR=3.91, p=0.005). Longitudinally, surveillance use among unaffected women decreased from 49.8% in the first year to 31.2% in the sixth year after genetic testing. In comparison, a greater proportion of women with a personal history of breast cancer underwent surveillance, which increased from 59.3% in the first year to 63.6% in the sixth year after genetic testing. Mammography rates did not differ between women with P/LP and VUS within the first 13 months after genetic testing and up to 4 years afterwards. Over the first four years after genetic testing, women with VUS were less likely to undergo annual MRIs compared to P/LP. This observation was true for women without a personal history of breast cancer (OR=0.34, p=0.003; OR=0.37, p=0.03; OR=0.19, p=0.004 for years 1, 2, and 3 respectively) as well as for women with a personal history of breast cancer (OR=0.31, p<=0.001; OR=0.33, p=0.002; OR=0.37, p=0.012; OR=0.3, p=0.14 for years 1, 2, 3, and 4 respectively). Conclusion: In this study of surveillance mammography and breast MRI use among women at elevated risk of breast cancer, we found that women with P/LP variants in breast cancer susceptibility genes are more likely to undergo annual breast MRI compared to those with VUS, whereas there was no difference between the groups in their use of annual surveillance mammography. This study is one of the first to examine maintenance of breast surveillance in a sample of women at elevated risk of breast cancer with non-negative genetic test results in BRCA1/2 as well as non-BRCA1/2 genes, while adjusting for personal and family history of cancer. In addition, we found that VUS, whether in high or moderate penetrance breast cancer susceptibility genes, was associated with lower use of annual breast MRI compared to P/LP variants, and equivalent use of annual mammography. These results add important evidence to dispel the myth of VUS-associated mismanagement of care.

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Prevalence of non-BRCA germline pathogenic variants in Mexican women with breast cancer referred for genetic cancer risk assessment

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Background: The prevalence of germline pathogenic variants in Mexican women with breast cancer who met the reference criteria for genetic cancer risk assessment (GCRA) has been previously reported as close to 20%. However, information regarding the spectrum of gPVs in genes other than BRCA in this population is limited. Methods: This prospective study included
Mexican women who were diagnosed with BC and met international criteria for GCRA. Participants were enrolled in the Clinical Cancer Genomics Community Research Network (CCGCRN) registry and at two referral breast cancer centers in Mexico, the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City and at the Hospital Zambrano Hellion TecSalud, Monterrey. Participants underwent multigene panel testing (MGPT) for 37 cancer susceptibility genes. For this analysis, only the results of pathogenic and likely pathogenic variants in the index cases were reported. The demographic and molecular characteristics of the variants are described here. Results: From August 2017 to September 2021, 1020 Mexican women with BC underwent MGPT, with a median age at diagnosis of 41 y (range 20-86), of whom 206 (20.2%) were carriers. 208 gPVs were identified with BRCA1/2 representing 70% (145/208) of the gPVs (BRCA1 n=89, BRCA2 n=56). 63 (30%) of gPVs were identified in genes other than BRCA (CHEK2 n=21, PALB2 n=13, TP53 n=7, RAD51C n=5, ATM n=4, NFI n=3, PTEN n=2, MUTYH homozygous n=2, RAD50 n=1, BRIP1 n=1, CDH1 n=1, NBN n=1, MSH2 n=1 and MSH6 n=1). The recurrent variants previously proposed as founders in the Hispanic population were frequent among those identified in their respective genes: CHEK2 c.707T>C 81% (17/21), PALB2 c.2167_2168delAT 46% (6/13) and BRCA1 del(exons 9-12) 18% (16/89). As a group, the 4 most frequent genes where gPVs were identified (BRCA1, BRCA2, CHEK2 and PALB2) represented 86% (179/208) of the positive results. Conclusion: Among the variants identified in this population of Mexican women with BC, the proportion of gPVs in genes other than BRCA was significant (about 1 out of 3 pts), which justifies the use of MGPT in the assessment of our population. However, a tailored panel (sequencing of BRCA1/BRCA2/CHEK2/PALB2 and MLPA for BRCA1) could be proposed in areas of Mexico with limited medical resources, including the analysis of other genes in selected patients according to clinical suspicion and family history of cancer.

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Implementation and outcomes of population-based hereditary cancer testing across a diverse multi-location breast imaging center

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Introduction: Up to 10% of all breast cancers (BC) are attributed to inherited pathogenic variants (PV) in BC susceptibility genes, and genetic testing at the time of breast imaging may identify more patients who could benefit from enhanced surveillance and/or risk reduction interventions. Data are limited on the yield of PVs in the setting of a breast imaging center. Hypothesis: Hereditary cancer gene screening at the time of breast imaging may identify patients and families who could benefit from cancer risk management. Methods: This retrospective cohort study included de-identified clinical data and commercial multi-cancer panel (40 genes) test results from sequential patients undergoing breast imaging at 3 centers in Texas over a 17 month period. Patients of providers who elected not to participate were excluded from this cohort. PV prevalence was quantified and stratified based on level of risk for BC and other cancers: high-risk (relative risk >4) for BC, moderate-risk (relative risk 2-4) for BC, high-risk for other cancers, moderate-risk or undefined risk for other cancers. Results: A total of 1,943 patients undergoing breast imaging chose to have genetic testing during the study period. Median age was 66 yrs (range 18-89 yrs). Self-reported race/ethnicity: White (34.5%), Hispanic (27.7%), African American (17.9%), Asian (4.5%), Ashkenazi Jewish (0.6%), Other (3.5%) and unreported (13.0%). A personal history of breast or ovarian-related cancers was reported in 4% (n=78) and a family history of these cancers was reported in 38.9% (n=835) of
Among those tested, 44/1,943 (2.3%) had one or more PV in an autosomal dominant clinically actionable gene, further categorized as: high-risk BC gene (36.3%) moderate-risk BC gene (34.1%), high-risk gene for other cancers (13.6%), moderate-risk gene for other cancers (6.8%), or uncertain level of increased risk for other cancers (9.1%). A heterozygous PV in an autosomal recessive gene was present in 31/1943 (1.6%) patients. Overall, 354/1943 (18.2%) patients met current NCCN guidelines for hereditary breast and ovarian cancer (HBOC) gene testing. Only 15/44 (34.1%) patients with an autosomal dominant clinically actionable PV met current NCCN guidelines for HBOC testing. Genetic education was provided to 20/44 (45.5%) patients by lab-based genetic counselors and/or the patient’s healthcare provider. Conclusions: Offering genetic testing in a diverse breast imaging center population was associated with a significant yield (4%) of both dominant and recessive clinically actionable PVs. Of note, almost 2/3 of PVs in hereditary cancer genes were among women who did not meet NCCN testing guidelines. Identification of a PV enables risk stratification, cascade testing of family members and an opportunity to access enhanced surveillance and risk reduction interventions.

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Uptake of Breast Cancer MRI Screening in Patients After Multiplex Gene Panel Testing

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Purpose: Multiplex gene panel testing (MGPT) is used to identify individuals with an inherited susceptibility to cancer. However, little is known about the uptake of screening and surveillance among patients after MGPT and genetic counseling. The purpose of this study was to measure the uptake of guideline-concordant breast cancer screening after genetic testing and counseling.

Patients and Methods: 2,000 patients who met NCCN testing guidelines or had ≥2.5% probability of a pathogenic/likely pathogenic variant (PV) were recruited at three cancer genetics clinics (University of Southern California (USC) Norris Comprehensive Cancer Center, Los Angeles County + USC Medical Center, Stanford Cancer Institute) from July 2014 through November 2016. All patients had 25- or 28-gene MGPT and results were disclosed by a genetic counselor, who provided screening recommendations to patients based on their risk. Post-test surveys were administered at three months, six months, one year, two years, and three years. Results: 1,614/2,000 (80.7%) patients were female and 1,147/1,614 (71.7%) completed at least one survey regarding MRI screening for breast cancer over the three years of longitudinal follow-up. Of these, 94/1,147 (8.2%) patients tested positive for at least one PV in a breast cancer risk gene; 58/94 (61.7%) tested positive for PVs in a high-risk breast cancer gene (BRCA1/2 (n=53), CDH1, PALB2, TP53 (n=5)), and 34/94 (36.2%) of patients tested positive for a PV in a gene characterized as moderate-risk at the time of disclosure (CHEK2, ATM, NBN). MRIs were recommended to 43/58 (74.1%) patients with a high-risk breast cancer gene PV, 20/34 (58.8%) patients with a moderate-risk gene PV, and 171/1,053 (16.2%) patients without a breast cancer risk gene PV. Multivariate logistic regression models revealed that patients with a high-risk gene PV were more likely to undergo MRI screening within 3 months of receiving genetic test results (OR=6.54 95% CI [3.09 - 14.43], p< 0.001), within one year (OR=1.34 95% CI [1.18 - 1.52], p< 0.001), two years (OR=1.43 95% CI [1.24 – 1.65], p< 0.001), and three years (OR=1.44 95% CI [1.25 – 1.66], p< 0.001) when compared to patients without a PV. Patients with a moderate-risk PV were also more likely to have undergone MRI within 3 months of receiving genetic test results (OR=2.89 95% CI [1.05 - 7.81], p=0.036), within one year (OR=1.33 95% CI [1.10 - 1.62], p=0.004), two years (OR=1.31 95% CI [1.09 - 1.59],
p=0.004), and three years (OR=1.44 95% CI [1.18 - 1.76], p< 0.001), compared to those without a PV (Table 1).

Conclusions: After three years of longitudinal follow up of 2000 patients in this multicenter prospective cohort study, patients with a PV in a breast cancer susceptibility gene were more likely to undergo guideline concordant breast MRI compared to patients without a PV. Carriers of high-risk breast cancer gene PVs were over six times as likely to have undergone MRI compared to patients without PVs within the first three months after genetic results disclosure and counseling. These results demonstrate the effectiveness of MGPT and genetic counseling in guiding patients with PVs in breast cancer susceptibility genes to the appropriate adoption of guideline-concordant screening.

Odds ratios of MRI screening in patients carrying PV in breast cancer risk genes. Odds in relation to patients who do not carry a PV

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk gene PV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>6.54</td>
<td>3.09 - 14.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 year</td>
<td>1.34</td>
<td>1.18 - 1.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 years</td>
<td>1.43</td>
<td>1.24 - 1.65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 years</td>
<td>1.44</td>
<td>1.25 - 1.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Moderate-risk gene PV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>2.89</td>
<td>1.05 - 7.81</td>
<td>0.036</td>
</tr>
<tr>
<td>1 year</td>
<td>1.33</td>
<td>1.10 - 1.62</td>
<td>0.004</td>
</tr>
<tr>
<td>2 years</td>
<td>1.31</td>
<td>1.09 - 1.59</td>
<td>0.004</td>
</tr>
<tr>
<td>3 years</td>
<td>1.44</td>
<td>1.18 - 1.76</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

High risk gene PV: BRCA1/2, CDH1, PALB2, TP53; Moderate Risk PV: CHEK2, ATM, NBN.

Percent of patients having undergone an MRI at the specified time points

<table>
<thead>
<tr>
<th></th>
<th>3 Month</th>
<th>12 Months</th>
<th>2 Year</th>
<th>3 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk gene PV</strong></td>
<td>59.6%</td>
<td>67.2%</td>
<td>81.3%</td>
<td>81.6%</td>
</tr>
<tr>
<td><strong>Moderate risk gene PV</strong></td>
<td>44.0%</td>
<td>57.7%</td>
<td>67.7%</td>
<td>81.5%</td>
</tr>
<tr>
<td><strong>No PV</strong></td>
<td>28.7%</td>
<td>39.1%</td>
<td>49.0%</td>
<td>50.9%</td>
</tr>
</tbody>
</table>

High risk gene PV: BRCA1/2, CDH1, PALB2, TP53; Moderate Risk PV: CHEK2, ATM, NBN.

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Identifying preferences that may motivate choice of ovarian cancer risk prevention strategies using a discrete choice experiment.

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Background: Women with a familial or hereditary risk for ovarian cancer are at a much greater risk of developing ovarian cancer compared with women in the general population. This high risk demands prevention strategies to reduce ovarian cancer incidence and mortality. Currently, there is little information about how women with a hereditary risk for ovarian cancer make trade-offs when choosing among prevention strategies and their associated risks. In anticipation of the likelihood that when given more personalized risk estimates, patients may have different preferences based on their mutation specific cancer risk as well as demographic and clinical factors, it is critical that we have the necessary information to develop counseling models that are tailored to individual patients' preferences for cancer risk reduction and tolerance of associated risks. Methods: We performed a discrete choice experiment to investigate how women at higher risk of ovarian cancer weigh benefits (e.g., reduced risk of ovarian) versus costs (e.g., increased risk of heart disease) in choosing a treatment strategy. N=396 pre-menopausal women with a personal history of breast cancer or familial history suggestive of increased breast and/or ovarian cancer risk were surveyed from August, 2019, to January,
2022. Participants were asked to choose between two sets of attributes that specified type of surgery (risk-reducing salpingo-oophorectomy [RRSO], risk reducing salpingectomy [RRS] vs. non-surgical surveillance), age of menopause (natural versus immediate), quality of menopausal symptoms (mild, moderate, severe), and risk of ovarian cancer, heart disease, or osteoporosis. Risks of disease varied in discrete intervals. We fit a Bradley-Terry logistic regression to estimate preferences. The binary response was the randomly generated choice set selected versus the set not selected. Results: Women were more likely to choose sets with either surveillance (odds ratio [OR]= 1.28, 95% confidence interval [CI] 0.98, 1.67) or RRSO (OR= 1.39, 95% CI 1.07, 1.81) over RSS. In weighing trade-offs in the choice sets that included type of surgery, women had a stronger independent preference for reducing the risk of ovarian cancer (OR= 0.66 of choosing set per 10% increase in risk, 95% CI 0.62, 0.71) than in reducing the risk of osteoporosis (OR= 0.82 per 10% increase, 95% CI 0.75, 0.90) or heart disease (OR = 0.82 per 10% increase, 95% CI 0.76,0.88). Women also had a strong preference for delaying the expected age of ovarian cancer (OR= 1.34 per 10-year increase in age, 95% CI 1.19, 1.51). Women had strong preferences for having a natural age of menopause (OR= 1.58 compared to immediate menopause post-treatment, 95% CI 1.27, 1.95), and better less severe symptoms (OR= 0.65 for each ordinal increase in the severity of symptoms, 95% CI 0.60, 0.70).

Conclusions: Our results suggest that women may prefer either surveillance or the most extensive type of surgery (RRSO) over more limited surgery (RRS). In weighing trade-offs, reducing the risk of ovarian cancer seemed to be more important than reducing the risk of osteoporosis or heart disease. Still, having a natural age of menopause and reducing the severity of symptoms could motivate the choice of treatment. Our work will allow us to estimate thresholds of measured factors that may motivate women to choose a specific treatment strategy.

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Racial/Ethnic Groups Have Different Rates of Pathogenic Variants in Common Cancer Genes

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Background:
Racial/ethnic disparities have been well-documented in access to cancer screening and treatment, as well as treatment outcomes. Less is known regarding the yield of genetic pathogenic variants (PVs) in non-white populations.

Methods:
Patient data was obtained from the Informed Genetics Annotated Patient Registry (iGAP), an IRB-approved multi-center longitudinal, observational study, in which 2148 patients self-declared race/ethnicity and underwent germline genetic testing at any lab. Analyses were limited to 24 cancer susceptibility genes (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, TP53, APC, BMPR1A, CDK4, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, RAD51C, RAD51D, SMAD4), 21 of which have clinical management guidelines from the NCCN (excluding NBN, BARD1, CDK4).1 Descriptive statistics were used to assess and compare data from these populations and germline genetic testing results.

Results:
The Registry included 2148 patients, 1662 (77.37%) with a personal history and 1536 (71.51%) with a family history of cancer. The patients were 74.39% White, 6.33% Hispanic, 5.59% African/Black, 5.03% Asian, 1.63% Other, 1.35% Ashkenazi, and 5.68% Unknown. The overall germline PV rate in the cohort was 0.1089 PVs/patient tested, with 234 PVs detected in 227 patients.

The PV rate among racial/ethnic groups were as follows: White 170/1598 (0.1064), Asian 8/108 (0.0741), Hispanic 27/136 (0.1985), African/Black 11/120 (0.0917), Ashkenazi 6/29 (0.2069). In patients self-reporting as Hispanic, the PV rate was similar to PV rate in those self-reporting as Ashkenazi, and significantly higher (p=0.00027) than PV rate in those of other self-reported race/ethnicity. Gene level PV rates are shown in Table 1.

Conclusions:
Those who reported being Hispanic had an increased overall PV rate. This could be due to the greater representation of Hispanics from New Mexico who may have Ashkenazi ethnicity. Further studies are needed to understand whether these differences are a result of disparate access to testing, true population differences, lack of data in non-White populations skewing variant classification or other factors.

Gene PV Rates by Racial/Ethnic Category
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Background. Carcinoma in situ (CIS) of the breast is a non-obligatory pre-malignant breast lesion and a highly suspected precursor of invasive cancer. Although the selection criteria for referral to genetic testing are well established for patients diagnosed with invasive breast cancer, these are not clear for patients diagnosed with CIS. Our goal is to assess the prevalence of predisposing pathogenic variants in key genes, as well as to describe factors in patients with CIS that might be associated with genetic predisposition. Methods. A total of 267 patients solely diagnosed with CIS (mean age 43.65 years, range 18-74) through years 2010-2022, were referred for genetic testing and were analyzed, following their informed consent,
implementing a 42-gene panel. Of these, 81.5%, 12.4% and 5.8% were ductal, lobular and mixed CIS, respectively. Patients having a synchronous invasive breast cancer diagnosis were not included in the study. Of patients with known grade, 52.28%, 28.9% and 18.8% were grade 3, 2 and 1, respectively. Strong family history for breast cancer (>2 close family relatives) was positive in 28% (75/267) of patients, while 67.8% of CIS were hormone receptor positive.

Results. A total of 12.7% (34/267) of patients carried pathogenic variants in seven clinically actionable genes, i.e. CHEK2 (10), BRCA2 (9), BRCA1 (5), ATM (5), PALB2 (2), MSH6 (2) and TP53 (1). Mean age at diagnosis of carriers was 42.1 years (range 29-61 years, p=0.26), 60% of patients had a grade 3 CIS diagnosis (OR 1.1, 95% 0.589-2.1, p=0.73), 96% had a hormone positive diagnosis (OR 1.4, 95% 0.78-2.50, p=0.24), while 73.5% (25/34) reported as having at least two close family relatives with breast cancer (OR 2.9, 95% 1.6-5.1, p=0.0001). The vast majority of carriers had a ductal CIS (DCIS) diagnosis, i.e. 91.2% (31/34) although this did not reach statistical significance (OR 1.087, 95% 0.64-1.82, p=0.72), probably due to small numbers. Notably, carriers were more likely to have a diagnosis with comedo characteristics, although this parameter has not been monitored closely for the whole cohort. Conclusion. Herein, an important fraction of patients with breast CIS carried pathogenic variants in clinically actionable genes, with the most frequent being CHEK2, BRCA2, BRCA1 and ATM. Notably, the prevalence is comparable to that of patients with invasive breast cancer. Strong family history for breast cancer was strongly associated with the identification of predisposing variants. Other factors, such as high grade, hormone positivity, age at diagnosis and others might also be associated with predisposition to CIS, but larger, prospective, studies are needed to confirm these. This is one of the few studies evaluating the inherited predisposition associated with both high and moderate penetrant breast cancer genes, highlighting that individuals with CIS diagnosis and strong family history for breast cancer should be offered the option to genetic testing via multigene panel.

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Implementation of multigene panel testing in triple-negative breast cancer. The PERSONA-breast trial

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Kahler Ribeiro Fontana S1, Bonetti E2, Bernard L3, Calvello M4, Bonanni B4, Bonizzi G 5, Veronesi P1,6, Mazzarella L 2, Galimberti V1 Introduction Triple-negative breast cancer (TNBC) is frequently associated with germline genetic variants associated with cancer predisposition. Approximately 20% of TNBC carry a germline BRCA1 or BRCA2 mutation. Germline mutations in other genes involved in DNA repair, specifically Homologous Recombination (HRR), including ATM, BARD1, BRIP1, CHEK2, PALB2, RAD50, RAD51C, RAD51D may be associated with TNBC however remain imprecise in several populations as in
Italy. In recent years, there has been an increase in multigenic panel testing thanks to better technology and the fact that genetic testing is no longer done just for prevention but they have become relevant in the clinical setting and this is especially true for triple negative disease. At the European Institute of Oncology, we conducted a prospective clinical trial, the PERSONA Breast trial, aimed at providing a more comprehensive picture of the mutational landscape and cancer risk in patients with TNBC by multigene germline genetic testing. Methods PERSONA is a prospective observational trial conducted between June 2018 and January 2022 on 313 patients with a diagnosis of TNBC ≤ 60 years and able to undergo surgery (primary or post-neoadjuvant). Peripheral blood DNA was sequenced with the Illumina TruSight Cancer panel (94 cancer predisposition genes). Genes were classified as germline actionable (n. 15) or non-actionable (n. 79) according to their associated relative risk of cancer. Genetic variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines and the databases of genetic variants (ClinVar, LOVD, BRCA-Exchange,). All enrolled patients were followed up six-monthly for 10 years from informed consent or to death or withdrawal of consent. Results We present preliminary germline results from a 94-gene panel testing performed on a cohort of 313 TNBC patients. The clinical data of these patients was considered for a descriptive analysis of the cohort. Data on outcome such as overall survival and disease-free survival were not yet available. Germline multigene testing detected 62 unique (i.e., n. 49 in actionable, n. 13 in non-actionable genes) pathogenic (C5) and likely pathogenic (C4) variants in 25.2% of TNBC patients (79/313). As expected, 53.2% (42/79) of TNBC patients were carriers of a C5/C4 in BRCA1. C4/C5 were identified also in other actionable genes: 13.9% (11/79) in BRCA2, 8.9% (7/79) in MUTYH, 3.8% (3/79) in PALB2, 2.5% (2/79) in MSH2, 1.3% (1/79) in PMS2, and 1.3% (1/79) in TP53. In addition, 12 TNBC patients had C4/C5 variants in non-actionable genes, and 4 were carriers of both C4/C5 variants in actionable and non-actionable genes. Multigene testing resulted in the identification of 655 (i.e., n.82 in actionable, n. 573 in non-actionable genes) variants of uncertain significance (C3 or VUS) in 89.8% (281/313) of patients. Of the 281 C3 carriers, 60 had other variants (C4 and/or C5), of an uncertain result (in whom C3 was the highest class of variant) only in 70.6% (221/313) of TNBC patients. In 13 patients (13/313; 4.1%) only benign (C1) or likely benign (C2) variants were identified. Regarding family history, 67% of BRCA1 carriers versus 30% of BRCA2 carriers were familial. Conclusion Germline multigene testing in TNBC can identify C4/C5 in actionable genes providing information for a more tailored management of TNBC. Our study showed that the rate of VUS remains high using multigene testing. Of note, VUS were mainly identified in non-actionable genes supporting the rationale of the use in the clinical setting of phenotype-specific multigene panels, including a minor, but more appropriate, number of genes.
Introduction

10% of Breast Cancer (BC) cases are thought to carry a germline pathogenic variant (PV) in a susceptibility gene. Most clinicians utilize the National Comprehensive Cancer Network (NCCN) guidelines criteria to both identify these patients and, in those who test positive, to provide adequate follow-up and/or surgery recommendations. In Chile, BC Guidelines, established in 2004, defined treatment strategies for invasive BC (iBC) which significantly reduced mortality. However, these guidelines do not define strategies for germline genetic testing nor contemplate coverage for those who needs them. Thus, we face many obstacles to genetic testing implementation such as out-of-pocket cost and lack of genetic counsellors. The aim of the study is to determine how many BC Chilean patients are at risk according to international guidelines, how many are being tested and what are their clinical characteristics. Methods

Retrospective analysis of a prospective database of iBC patients treated in a public hospital (PH) and in an Academic Private Centre (AC) in Santiago, Chile from January 2012 to March 2022. All patients who had enough information (age, family history (FH), BC subtype) for NCCN Version 2.2022 categorization were included. Patients whose only indication for germline testing was the potential use of PARP-inhibitors were excluded. Clinical characteristics were extracted from clinical charts. Results

4,365 iBC patients met criteria. 51.1% were treated in PH and 49.9% in a AC. 2,260 patients (51.8%) fulfilled NCCN criteria for germline testing, distributed unevenly between PH (46.0%) vs. AC (56.9%, p=0.0001). Compared to PH, patients in AC were diagnosed at younger age (54 vs 56 years, p=0.0001) and were more likely to report FH (69.4% vs. 53.7%, p=0.0001). No difference between BC
subtypes was reported. Considering only those fulfilling criteria, germline genetic testing was performed in 326 patients (14.4%) with a significant difference according to UH vs AC (18.7% vs. 9.1%, p=0.0001). 58% of these tests were performed in the last 3 years. Multivariate logistic regression showed that being diagnosed before 46 (HR=5.3, p=0.0001); FH (HR=2.2, p=0.0001); localized vs. metastatic disease (HR=3.7, p=0.001); triple negative (TN) BC (HR=1.8, p=0.0001) and being treated in AC (HR=1.9, p=0.0001) were independently associated with germline genetic testing being performed in patients fulfilling NCCN criteria. 82 PV were documented, being the most frequent BRCA1/2 (18.1%) followed by PALB2 (1.8%) and ATM (1.2%). Being diagnosed with TNBC (HR=3.8, p=0.0001) and having a first-degree relative with cancer (HR=4.4, p=0.0001) were the only factors associated with carrying a pathogenic BRCA1/2 mutation. Conclusion In Chile, less than 20% of iBC patients who meet NCCN criteria for germline testing are being tested. In this sample of our Public Health System, where over 80% of the Chilean population is treated, fewer than 1 in 10 individuals fulfilling criteria have undergone testing. New evidence suggests that probably a wider span than suggested by NCCN of patients should be counselled and tested, deepening even further the underutilization of germline testing in Chile. Lack of knowledge and training in oncology providers and out-of-pocket costs might influence these results. National guidelines are urgently needed.

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Expanding the reach of germline genetic testing: Use of web-based risk assessment to inform medical management amongst patients at breast and imaging centers

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Background: Developing an effective approach to the identification of individuals at increased cancer risk is key to preventing and/or providing early diagnosis of cancer. However, outside of targeted genetics clinics, under identification of individuals with hereditary cancer risk is well recognized, due in part to ever evolving complexity of germline genetic testing criteria and lack of systematic framework to perform robust risk assessment on all patients. In contrast, breast and imaging centers are ideally positioned to maximize the impact of positive genetic test results due to immediate availability of surveillance and diagnostic tools. Here we present data from breast and imaging centers using a patient-facing digital platform offered universally to all patients before their scheduled appointment designed to collect personal and family health information and assess cancer risk and genetic testing eligibility based on current guidelines.

Methods: We conducted a retrospective observational study of patients in breast and imaging centers who used a web-based risk stratification tool before standard ambulatory appointments to assess their lifetime risk for breast cancer based on the Tyrer-Cuzick (version 8.0) risk algorithm and eligibility for National Comprehensive Cancer Network (NCCN®) genetic testing criteria at the time of assessment. Testing criteria included hereditary breast, ovarian, pancreatic, and prostate cancers, Lynch syndrome, and familial adenomatous polyposis (FAP). Data was pulled for patients seen from June 2020 through May 2022 at participating breast and imaging centers throughout the United States. Outcome measures included percentage of individuals who completed the risk-assessment, met testing criteria, pursued germline genetic testing, received a positive germline result, and/or had a Tyrer-Cuzick breast cancer risk ≥20%.
Results A total of 251,492 individuals completed assessments; 250,011 (99%) were females aged 18 years or older. Overall, at the time of assessment 80,814/251,492 (32.1%) met genetic testing criteria and 24.4% (19,694) of those meeting criteria opted to proceed with germline genetic testing. An additional 1,561 individuals who did not meet criteria pursued genetic testing. Of the 18,532 completed genetic tests, 1,507 (8.1%) had positive genetic test results. The majority of positive individuals (93%) met testing criteria. 40.7% (613/1,507) of positive results had an impact on breast cancer risk management options. In addition to individuals identified as high-risk through germline genetic testing evaluations, 13.1% (28,108/214,269) of individuals assessed using the Tyrer-Cuzick algorithm had ≥20% lifetime risk of breast cancer and met the threshold for modified medical management. Conclusion In this study, the web-based assessment tool provided a standardized workflow that enabled individuals interested in receiving cancer risk assessment and germline testing an opportunity to do so. When offered to all patients, this digital platform can offer a scalable opportunity for breast and imaging centers to identify individuals eligible for modified medical management for breast cancer risk and other inherited cancer syndromes, which may ultimately improve the prevention and early treatment of individuals with cancer predisposition.

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Contralateral breast cancer risk in patients with or without BRCA mutation

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Background: Patients who carry mutated BRCA1 or BRCA2 genes have a significantly increased risk of breast cancer and developing contralateral breast cancer (CBC). In this study, we aimed to investigate the acceptance rate of BRCA1/2 testing in Korean breast cancer patients and to determine the risk of CBC in Korean patients with BRCA 1/2 germline mutations. Methods: This study included 13,109 patients with first primary breast cancer who were treated at Seoul National University Hospital from January 2005 to December 2018. These patients were divided into high-risk for BRCA1/2 mutation group and low-risk group. High risk patients were defined as those who were eligible for BRCA testing per Korean National Health Insurance Service. The high-risk group was further classified into three groups; BRCA1/2 mutation carrier, BRCA 1/2 non carrier and BRCA/12 untested. Results: Among the 4,446 high-risk patients, 962 (21.7%) patients underwent BRCA1/2 testing. The testing rate varied among different indications (47.8% of patients with a family history, 23.3% of patients under 40 years of age, and 13.0% of patients with triple negative breast cancer). The risk of the CBC in BRCA mutation group was higher than other groups (p value < 0.001). The 10-year cumulative risk of CBC was 11.0% BRCA1 mutation carrier and 7.4% for BRCA2 mutation.
carrier. In the BRCA1/2 non-carriers, the cumulative risk of CBC was 5.7%. Interestingly, the CBC risk for BRCA1/2 non-carriers significantly higher than BRCA1/2 untested group and the low-risk group (p < 0.001). When compared to the BRCA1/2 untested group, the relative risk for CBC was 6.7-fold increase for the BRCA1/2 mutation carrier group (95% CI = 3.65-12.22, p < 0.001), and 2.3-fold increase for the BRCA1/2 non-carriers group (95% CI = 1.44-3.83, p < 0.001). The relative risk for CBC in high-risk group also depended on subtype of breast cancer and family history. Hormone receptor negative breast cancer patients had a 1.5-fold (95% CI = 1.02-2.31, p = 0.04) increased risk of CBC and patients with one or more 1st degree relative with breast cancer had 2.4-fold increased risk (95% CI = 1.55-3.67, p < 0.001). Conclusion: About one out of five Korean breast cancer patients, who are eligible for the BRCA1/2 testing, undergo testing for BRCA1/2 germline mutations. We observed increased CBC risk not only for the BRCA1/2 mutation carriers but also for the BRCA1/2 non-carriers. At present, we are conducting multi-gene panel testing for the BRCA1/2 non-carriers to understand the mechanisms of the increased CBC risk.

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Don’t get lost in translation: Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) recommendations for reporting germline cancer susceptibility gene variants in 19 languages – breast cancer as a model

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Genetic testing for cancer susceptibility is a cornerstone of precision cancer prevention and care. Major communication hurdles remain for the differently specialized professionals involved in the identification, counselling, and clinical management of at-risk individuals. This may be ascribed to gaps in the genetic/genomic literacy of health care providers and to an ambiguous lexicon used for variant description. The Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) international consortium endorses controlled terminology and a framework for interpretation and reporting of germline variants in cancer susceptibility genes (PMID: 30962250). However, for most ENIGMA affiliates a language other than English is used for written and verbal communication of genetic test results, potentially confounding local application of the published framework. The ENIGMA Clinical Working Group thus launched a Vocabulary Translation Project (VTP) to translate the ENIGMA recommendations into the various languages spoken by the membership. The VTP involved 65 ENIGMA members from 22 countries organized into 19 language-specific teams, covering Catalan, Chinese, Czech, Danish, Dutch, Finnish, French, Galician, German, Greek, Italian, Japanese, Malay, Norwegian, Polish, Portuguese, Spanish (Castilian), Swedish, and Tagalog. Excerpts from the original publication were selected for translation based on a majority consensus and
included a glossary of terms and recommendations for interpreting and reporting germline sequence variants in (breast) cancer susceptibility genes. Using a two-step process, each team conducted the relevant translation followed by independent back-translation to English. The VTP proved useful to reappraise the reference text. It disclosed transnational issues, which prompted revision of the original source to emphasize that risk estimates and actionability were based on breast cancer as an exemplar. It also highlighted country-specific differences with regards to breast cancer risk assessment (e.g. different absolute/relative breast cancer risk cut points) and management. As a secondary outcome, via electronic survey of the participating teams we documented the perceived high value of the translation effort and its expected positive impact on more consistent clinical management of carrier individuals. The identified target audience encompasses medical geneticists, physicians of other specialties participating in multidisciplinary teams, genetic counselors, primary care physicians, as well as non-health care professionals, e.g. journalists and science communicators. The outreach program includes dissemination of the translations via local, regional, and especially national networks and their use for education and training purposes. Because French, Portuguese, and Spanish are widely used as official, co-official, or secondary languages, the reach of the VTP potentially extends to a greater number of countries and territories, mostly in Central and South America, Caribbean, and Africa. By moving a step forward towards terminological coherence across disciplines and borders, we will facilitate more precise delivery and clinical application of genetic test results for breast cancer predisposition. Our translated recommendations will improve interdisciplinary cross-talk and carriers’ awareness of the risks and implications associated with their status, contributing to more informed decision-making. We used breast cancer as a blueprint.

Application of the model to other cancer types will require calibration on the cancer-specific absolute and relative risks.

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Breast cancer prognosis of germline BRCA1/BRCA2 mutation carriers of young women: a retrospective hospital-based cohort

Background
Studies evaluating prognostic impact of germline BRCA1/2 mutations (gBRCAm) on breast cancer patients reported controversial results. The primary aim of this study was to investigate outcomes of young gBRCAm patients with very early onset of breast cancer (< 30 years) compared with noncarriers. Methods In this retrospective study, 149 patients 30 years aged or younger at early breast cancer diagnosis between 2005 and 2019 were included in Oscar Lambret Center. Outcomes were overall survival (OS) and disease-free survival (DFS), defined as time from first diagnosis to first recurrence, second cancer or death from any cause, at 2 years, 5 years, and 10 years. Key patient data, kaplan-meier plots and outcomes were described by BRCA mutation status. Hazard ratios (HR) were calculated using Cox proportional-hazards models. Results Twenty-eight (18.8%) patients were gBRCAm carriers. The median follow-up was 6.5 years (IQR 0.25-16.5). Twenty-three deaths, 41 recurrences and 2 second cancers were reported. OS was 89.3% [70.4–96.4] in gBRCAm patients vs 99.1% [95% CI 93.9–99.9] in non-carriers patients at 2 years; 85.0% [64.7–94.1] vs 92.3% [85.1–96.1] at 5 years and 75.3% [52.5–88.3] vs 80.2% [66.6–88.7] at 10 years. There was no difference in OS between groups in multivariable analysis (HR=1.63 [0.55–4.77], p=0.37). Similar results were noted when comparing disease-free survival (HR=1.42 [0.64–3.11], p=0.38). Conclusions In this cohort of 149 patients with very early onset breast cancer, outcomes of gBRCAm mutation carriers did not differ from non-carriers when adjusted for others prognostic factors.

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A Real-World Study of BRCA1 and BRCA2 Germline Mutations among High Hereditary Risk Subjects and Patients with Breast and Ovarian Cancer in Lebanon

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Background: The prevalence of pathogenic BRCA mutations in high hereditary risk breast cancer patients (pts) in ethnic Lebanese Arab women was 5.6% in a study published in 2015 (El Saghir, et al. The Oncologist). In this study, we look at real world practice prevalence of BRCA mutations among pts with breast and/or ovarian cancer referred for testing because of positive family history (FH) and/or young age at the American University of Beirut Medical Center (AUBMC).

Methods: The study was approved by the Institutional Review Board at AUBMC. We retrospectively collected clinical, radiological, pathological and genetic information on breast and ovarian cancer pts at a high hereditary risk for whom Sanger sequencing of all coding exons and immediately flanking intronic regions of BRCA1 and BRCA2 was performed between January 1, 2010 and Jan 1, 2019 at AUBMC. Between Jan 2019 and Aug 2020, Next Generation Sequencing (NGS) of 70 cancer-associated genes was referred to and done in Centogene labs (Germany). 346 subjects were included in the study; 235 pts with breast and/or ovarian cancer, and 101 subjects of young age or with a positive family history.

Results: 210 pts had breast cancer (209 females, 1 male); 81 were diagnosed at age ≤40, 81 aged 41-50, and 48 aged >50. 185 pts had BRCA sequencing and 25 had NGS panel testing. 31 pts had ovarian cancer; 28 had BRCA testing and 3 had NGS. 3 pts had ovarian and breast cancer; all had Sanger sequencing, 1 male pt with both breast and prostate cancers had BRCA testing. The 101 subjects who were tested in the setting of positive FH of cancers or a known deleterious mutation in first degree family members were either target tested for the known
familial mutation or had BRCA screening. The incidence of BRCA1 and BRCA2 mutations in women with breast cancer was 8.5% (18/210 patients) and 19.3% (6/31 patients) in women with ovarian cancer. Of the 3 pts who had both breast and ovarian cancer, 1 had a BRCA1 mutation. Almost all patients with hereditary breast cancer had a positive FH and the majority were < 40 years of age. 8 out of 13 BRCA1 pts had Triple Negative disease (61%). Of the 101 subjects with no history of cancer, 9 out of 30 with relatives who had BRCA1 mutation carried the same mutation, and 3 out of 15 with BRCA2 carried the mutation. The remaining 56 pts were tested because of positive FH; 3 out of 56 had a pathogenic mutation (1 BRCA1, 1 BRCA2 and 1 RAD51D). Of the 28 pts who had NGS panel sequencing, 1 patient had RAD51D, 1 had a PALB2 mutation, 1 had BARD1 and 1 had APC risk variant.

Conclusions: In this real-world practice study of patients and subjects referred for germline mutation testing, BRCA mutation rate in pts with breast cancer was 8.5% (18/210) and 19% in ovarian cancer (6/31). Young age (< 40 years) and a positive FH are the most useful criteria to select pts with breast cancer for mutation testing, especially in the setting of limited resources. This is the first study to report a 20% rate of BRCA pathogenic variants in patients with ovarian cancer in Lebanon and Arab countries; we highlight the need to refer all ovarian cancer pts for counseling and genetic testing. NGS is important to detect mutations other than BRCA1 and BRCA2 in our population where 50% of cases are below age 50.

Table 1. Incidence of BRCA1/2 mutations, age, and family history in pts with breast and ovarian cancer

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Gene</th>
<th>Deleterious Mutation (%)</th>
<th>Age at diagnosis</th>
<th>Positive FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>BRCA1</td>
<td>13/210 (6.2%)</td>
<td>&lt;40: 11/13</td>
<td>12/13</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>BRCA1</td>
<td>5/210 (2.4%)</td>
<td>&lt;40: 3/5</td>
<td>5/5</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>4/11 (12.9%)</td>
<td>&lt;50: 2 &amp; &gt;50: 2</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>2/31 (6.4%)</td>
<td>&lt;40: 1 &amp; &gt;50: 1</td>
<td>2/2</td>
</tr>
<tr>
<td>Breast and Ovarian Cancer</td>
<td>BRCA1</td>
<td>1 out of 3</td>
<td>45</td>
<td>1/1</td>
</tr>
</tbody>
</table>

Table 1. Incidence of BRCA1/2 mutations, age, and family history in pts with breast and ovarian cancer

Disclosure(s):
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Background: The MERIT cohort (Mammography, Early Detection, Risk Assessment, and Imaging Technologies, 2017-present) has enrolled women receiving annual screening mammograms (MG) at MD Anderson with a primary goal to integrate clinical data and imaging data with blood biomarker profiles to determine risk of developing breast and other cancers. Here we report interim results for breast cancers among post-menopausal women in the cohort categorized based on breast density and BMI and differences between participants who underwent MRI/MG screening vs standard annual MG screening.

Methods: The study annually collects comprehensive health measurements, questionnaire information, imaging data, and blood specimens. Plasma is processed and frozen within 4 hours of collection (draw-to-freeze, >500,000 aliquots to date) for biomarker research. Part of the cohort also has MRI screening every 6 months alternating with standard mammography (MRI/MG). BI-RADS breast density was determined by radiologist scoring using the baseline mammogram. Self-reported post-menopausal status (12 months without a menstrual period) was used to classify participants. When not available, those participants older than 50 years were classified as post-menopausal.

Results: 4,392 of the 6,222 eligible subjects from MERIT were post-menopausal and included in the analyses. The average follow up was 2.4 mammograms per participant. MRI/MG screening was used for 385 (8.8%) participants who were more likely to be younger (59.6 vs 62.1 years, P< 0.01), have lower BMI (27.9 vs 28.6, P = 0.02) and dense breasts (64% vs 50%, P< 0.01). The rates of breast cancer were overall higher for those screened by MRI/MG vs standard MG (13.9 vs 6.9 cases per 1,000 mammograms). A total of 79 breast cancers (7.6 cases per 1,000 mammograms) were diagnosed with the highest rate of breast cancers in high BMI participants with dense breasts (see table). A blood-based biomarker profile for risk of breast cancer with high BMI was developed using matched pre-diagnostic plasma by mass spectrometry metabolomic analyses.

Conclusions: The MERIT cohort has a higher-than-average rate of breast cancers, in part explained by a high-risk MRI/MG screening group. High BMI and dense breasts were generally associated with higher rates of breast cancer. The differences in the rates of breast cancer
incidence for the high BMI group between non dense and dense breasts is likely understated for the standard mammogram group because of the lower sensitivity of mammography in dense breasts. Interestingly, the rates of breast cancers in the low BMI/non dense breast group were almost equally high as the low BMI/dense breast group, likely a result of reduced sensitivity of mammography for dense breasts. For future work, we will integrate the blood biomarker profiles with the breast density and BMI information to develop a more personalized risk model.

### MERIT Cohort Breast Cancers

<table>
<thead>
<tr>
<th>Breast Density</th>
<th>Annual MG Screening</th>
<th>MRI/MG Screening</th>
<th>All Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25.0 BMI</td>
<td>≥25.0 BMI</td>
<td>All BMI</td>
</tr>
<tr>
<td>Non dense (a,b)</td>
<td>10.8</td>
<td>4.8†</td>
<td>6</td>
</tr>
<tr>
<td>DCIS</td>
<td>3.2</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Invasive BC</td>
<td>7.5</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Dense (c,d)</td>
<td>3.9*</td>
<td>11.7†‡</td>
<td>7.8</td>
</tr>
<tr>
<td>DCIS</td>
<td>2.1</td>
<td>3.8</td>
<td>3</td>
</tr>
<tr>
<td>Invasive BC</td>
<td>1.7</td>
<td>7.9</td>
<td>4.9</td>
</tr>
<tr>
<td>All</td>
<td>5.8</td>
<td>7.5</td>
<td>6.9†‡</td>
</tr>
</tbody>
</table>

Rates of diagnosed breast cancers per 1,000 mammograms for post-menopausal women (N = 79 breast cancers)‡P<0.01, †P<0.05, Fisher’s exact test

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Recent studies have found that both food deserts (FD) and lower socio-economic status (SES) are individually associated with increased breast cancer mortality in the US. However, further work is needed to investigate their combined contribution to breast cancer mortality. Furthermore, valid inference for area-level disease mapping requires careful consideration of spatial clustering. In our study, we utilize data from the USDA Food Access Research Atlas and the American Community Survey. Breast cancer mortality data come from the National Center of Health Statistics 2014 report. We consider a latent class mixture model to determine deprivation categories which incorporate six SES proportion variables (no car, poverty, no HS graduation, crowded housing, unemployment, crowded housing), two FD (Low income and > 1 mile from supermarket and receiving snap benefits and > 1 mile from supermarket) variables. Our latent class model has three levels: Low, Moderate, and High, making up 36.6%, 45.6%, and 17.8% of US counties, respectively. We then incorporated these levels as a fixed effect in a Bayesian hierarchical spatial negative binomial model using R-INLA. In this model, we account for both spatially structured and unstructured effects. Counties classified as “High” on our deprivation categories were associated with a 50% increase in breast cancer mortality rates (95% CrI: [1.12, 2.02]). Also, the county proportion of women >65 was significantly associated with 1.42 times higher breast cancer mortality (95% CrI [1.37, 1.42]). Policies that allow for access in the face of deprivation may contribute to lower overall breast cancer mortality.

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Persistence and compliance of the French metastatic breast cancer population

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Keywords Metastatic breast cancer, Endocrine therapy, Targeted therapy, Oral chemotherapy, French population Context Oral anti-cancer treatments have been shown to be effective when followed carefully. Tamoxifen, for example, reduces the risk of relapse by half within 10 years of the diagnosis [1]. However, these treatments are frequently poorly adhered to. To determine the categories of patients at risk and the appropriate moment to contact them, we developed predictive models trained on anonymised reimbursement data extracted from the French Health Insurance database. Objective The primary objective is to model a metastatic breast cancer patient's persistence and compliance to the treatment. We aim at detecting unwanted episodes (non persistence and non compliance) six months before they happen. The oncologist may then follow the patient more closely. Methods Patients data is extracted from the SNDS database, one of the largest structured databases of health data in the world. It contains reimbursement data of the French Health System, covering 98% of the French population (66 million persons). Useful data are, for example, hospitalisations, drug purchases or the patient's age and city of residence. From this database, patients were selected on the basis of a diagnosis of metastatic breast cancer (if hospital stay) or on the basis of specific treatments for metastatic breast cancer. Men and patients under 18 are excluded from the study. We consider that a patient has a non persistent event if she has no treatment stock for 2 months (during a phase of targeted therapy or oral chemotherapy) or 3 months (during a phase of endocrine therapy) and if no change in treatment, palliative care entry or death is observed. The
compliance is labelled through the MPR (Medical Possession Ratio): a patient is considered non-compliant if the MPR of her 3 nexts purchases is below 80%. The proposed models are trained to detect non-persistence and non-compliance events in the next 180 days. We created several groups of features describing the patient and her healthcare pathway. Results 250 000 patients were spotted with a breast cancer in the SNDS database. Amongst these, around 40 000 were spotted for a metastatic breast cancer between 2013 and 2018. 14% of the patients had at least one non-persistence episode and 46% had at least one non-compliance episode.

For the persistence study, we used a logistic regression with a feature selection. This model has a Gini coefficient of 0.35. For the compliance study, we used a deep learning model based on a GRU model. This model has a Gini coefficient of 0.37. A multivariate analysis shows that the following features had a significative impact on both predicted risks (persistence and compliance): age, previous compliance, type of oral treatment(s) currently followed (endocrine therapy, targeted therapy, or oral chemoterapy), number of different oral treatments followed in the past year. In both models, if the patient’s age is between 50 and 70 years it does not correlate with an increased risk. On the other hand, the more they deviate from this interval, the more likely they are to be non-compliant. Conclusion Both studies have models with quite the same interpretation. Patients younger than 50 or older than 70 are more likely to be non-persistent and non-prevalent. The past compliance is highly correlated to the future events. The consumption of oral chemotherapy in comparison to oral endocrine and targeted therapy is linked to an increased risk in both studies. Bibliographie [1]: E. Ekinci, S. Nathoo, T. Korattyil et al. (2018) Interventions to improve endocrine therapy adherence in breast cancer survivors: what is the evidence? J Cancer Surviv 12:348-356

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Ipsilateral infusions are not associated with increased risk of breast cancer-related lymphedema in patients enrolled in a prospective screening program.

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BACKGROUND: Patients treated for breast cancer (BC) who are at risk of breast cancer-related lymphedema (BCRL) have been instructed for decades to avoid venipuncture, injections and infusions in the extremity ipsilateral to BC treatment. These instructions are given in theory to prevent BCRL development, despite lack of supporting data. Given fear of BCRL is high amongst the population at risk, it has been found that patients heed this advice regardless of level of BCRL risk. It has been previously found that there is no association between blood draws or injections in the ipsilateral arm and increases in arm volume in patients treated for BC and screened for BCRL. Despite these findings, risk of BCRL associated with the most invasive of BC treatments, infusions in the ipsilateral arm, has not been examined. As patients with BC
require ongoing invasive medical procedures, data would inform patient care and drive clinical practice guidelines during and after BC treatment. PURPOSE: The purpose of this study was to determine whether patients treated for breast cancer who receive one or more infusions in the arm ipsilateral to BC treatment are at higher risk of BCRL than those who do not receive ipsilateral infusions. METHODS: From 2005 to 2021, 2049 patients treated for BC were enrolled in a prospective BCRL screening trial and screened from preoperative baseline through last follow-up. Screening included objective arm volume measurements via perometry; relative volume change (RVC) increase ≥10% from preoperative baseline >3 months postoperatively was used to define BCRL. Infusions data were collected directly from the electronic medical record and all postoperative infusions were included in data analysis. Patients were censored at cancer recurrence. Infusions data included route, laterality, date and substance infused. Demographic and clinical information were obtained through medical record review. Marginal structural models were used to estimate the hazard of BCRL attributable to any (vs. no) ipsilateral infusion. Time-varying inverse-probability weights were used to account for time-varying confounding by RVC and earlier adjuvant infusions, and adjusted for baseline confounding by baseline BMI, axillary lymph node dissection (ALND), regional lymph node radiation (RLNR), neoadjuvant chemotherapy, and number of neoadjuvant ipsilateral infusions. RESULTS: The eligible cohort included 2018 patients. 240 patients received at least one ipsilateral infusion; 651 did not receive ipsilateral infusions; 1,127 did not receive infusions. Patients who received ipsilateral infusions received a median of 2 (interquartile range (IQR) 1, 3) ipsilateral and 8 (IQR 4, 15) total infusions. 681 (34%) patients received adjuvant chemotherapy infusions; the most frequent adjuvant regimens received included ACT (314 patients, 16%); TC (162 patients; 8.0%); and ACTH (±P) (47 patients, 2.3%). Of those who received any ipsilateral infusions, 77% had chemotherapy drugs infused, compared to 84% of participants who did not have ipsilateral infusions. Fluids, antacids, and antihistamines were the most common non-chemotherapy infusions. Patients underwent BCRL screening over a median of 5 visits (IQR 3,8) with a median follow-up of 56 months (IQR 31, 90 months). There was no significant difference in BCRL risk between patients who received at least one ipsilateral infusion and those who did not receive ipsilateral infusions (HR, 0.85; p=0.60). CONCLUSIONS: Infusions in the at-risk arm were not associated with increased risk of BCRL in this cohort of 2018 patients at risk of and prospectively screened for BCRL.

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Clinico-pathological co-variates define a predictive model of breast cancer related lymphoedema (BCRL) in patients undergoing axillary surgery for breast cancer

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Clinico-pathological co-variates define a predictive model of breast cancer related lymphoedema (BCRL) in patients undergoing axillary surgery for breast cancer CC Tang1*, J Timbres2*, KWD Ramsey1, A Mera2, S Irshad2, E Sawyer2, AA Khan1 1 Department of Plastic Surgery, The Royal Marsden Hospital, London, UK 2 School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences and Medicine, Guy’s Cancer Centre, King's College London, London, UK. *These authors contributed equally

Introduction
Breast cancer-related lymphoedema (BCRL) negatively impacts body image, limb function and quality-of-life during cancer survivorship and affects 20% of women undergoing axillary clearance (ALND).1

Stratifying women undergoing axillary intervention into high- and low-risk groups for BCRL is important to identify those most likely to benefit from surgical interventions for lymphoedema prevention (eg LYMPHA) and mitigate BCRL risk in this subset of patients. In this study, we aimed to identify prognostic factors for lymphoedema incidence to develop a more accurate model of BCRL risk. Methods We performed a retrospective cohort study of breast cancer patients undergoing axillary surgery with (Ly+) and without (Ly-) subsequent lymphoedema. Controls were identified from the Breast Cancer Clinical Database, Guy’s and St Thomas’ Hospital NHS Foundation Trust (GSTT)) and diagnosed between 2000-2016, while cases were
identified from the Lymphoedema Clinic at GSTT, diagnosed between 2000-2020. A multivariate logistic regression model was derived from univariate analyses using a stepwise, iterative process, confirmed with lasso regression, and evaluated within training and validation datasets to define a predictive risk score using methods described by Pavlou et al.2 Results 2040 patients (Ly+=541, Ly-=1499) who underwent axillary surgery (ALND = 1171, SLNB = 755) (were included in our analysis with a median follow up of 7.2 years (Ly+) and 9.8 years (Ly-). The final predictive model of BCRL risk contained variables for: mastectomy, grade, T-stage, N-stage, ER status, chemotherapy and radiotherapy. Here, specifically radiotherapy including a supraclavicular fossa field was associated with developing lymphoedema. The Hosmer–Lemeshow goodness-of-fit test showed the model to be well calibrated, and evaluation of the risk score using ROC curves showed good discrimination (AUC: 0.795). Lymphoedema was not found to negatively affect overall (unadjusted HR: 1.19 (95% CI: 0.92-1.53); p=0.178 and adjusted HR: 0.53 (95% CI: 0.38-0.73); p< 0.001) or disease free (unadjusted HR: 2.03 (95% CI: 1.59-2.61); p< 0.001 and adjusted HR: 0.92 (95% CI: 0.68-1.23); p=0.57) survival. Conclusion Our study identified clinico-pathological factors such as mastectomy, grade, T-stage, N-stage, ER status, chemo- and radiotherapy (specifically radiotherapy including a supraclavicular fossa field) to be predictive of developing BCRL following axillary surgery. Our model requires further validation but may have utility in stratifying patients for whom surgical strategies for lymphoedema prevention could be deployed to mitigate BCRL risk. References 1. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol. 2013 May;14(6):500-15. doi: 10.1016/S1470-2045(13)70076-7. Epub 2013 Mar 27. PMID: 23540561. 2. Pavlou M, Ambler G, Seaman S R, Guttmann O, Elliott P, King M et al. How to develop a more accurate risk prediction model when there are few events BMJ 2015; 351 :h3868 doi:10.1136/bmj.h3868

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Background Triple-negative breast cancer (TNBC) is more frequently diagnosed in young patients, with an incidence of 26% of this population compared to 12% overall, and is characterized by high malignancy and poor prognosis. Limited data are available that contribute to a comprehensive summarization of the prognostic factors and the determination of surgical strategy that are associated with young patients with TNBC. We aimed to determine the optimal surgical approach (breast-conserving versus mastectomy) for patients aged < 40 years with TNBC and establish a prognostic model. Methods We performed a cohort study with a median follow-up of 31 months using the Surveillance, Epidemiology, and End Results (SEER) data of young patients < 40 years diagnosed with stage I–III TNBC between 2010 and 2016. A Cox proportional hazards model was used to investigate the effects of baseline characteristics on breast cancer-specific survival (BCSS) and overall survival (OS). To ensure that differences in outcomes were not based on baseline differences in demographic and clinical characteristics, we performed Kaplan–Meier analysis before and after propensity score matching (1:1). Subgroup analyses stratified by TNM stage as well as further propensity score matching analyses were performed. A nomogram was constructed from the multivariate logistic regression to incorporate all the prognostic factors to predict the BCSS rates of patients at 3 years and 5 years. Young patients < 40 years diagnosed with stage I–III TNBC between 2006 and 2016 in Shenzhen Second People's Hospital (SSPH) were enrolled as external validation. Results A total of 2,854 patients from SEER dataset and 250 from SSPH were included in this study. On multivariable analysis, unmarried status, lack of health insurance, advanced T stage, advanced N stage, invasive lobular carcinoma or mixed histologic type, were all significantly associated with poor BCSS and OS. Young patients with TNBC were more likely to undergo mastectomy than breast-conserving surgery. Notably, patients with T1N0M0 or T2-4N+M0 tumors who underwent breast-conserving surgery achieved longer BCSS and OS than those who underwent mastectomy; however, the type of surgery did not influence survival rates among patients with T1N+M0 or T2-4N0M0 tumors. The nomogram was constructed by the five variables and passed the calibration and validation steps (C-index: 0.774 for training cohort and 0.768 for validation cohort). The area under the receiver operating characteristic curves (AUCs) predicting the 3-year and 5-year BCSS rates were calculated (0.783 and 0.774 in training cohort; 0.786 and 0.772 in validating cohort). Conclusions A localized surgical approach may be a superior option for young patients with TNBC, especially those with T1N0M0 and T2-
4N+M0 tumors. Marital status, health insurance status, T stage, N stage, and histological type were independent prognostic factors, and a nomogram established based on these variables successfully predicted the 3- and 5-year survival probabilities among these patients.

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Development of an at-home breast health assessment test, to increase compliance with screening mammography using proteins from tears.

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Background: There is a growing body of evidence to support tears as a non-traditional biological fluid in clinical laboratory testing. In addition to the simplicity of tear fluid processing, the ability to access key cancer biomarkers in high concentrations quickly and inexpensively make them an attractive biofluid source. Here we report our biomarker discovery study on tears to identify and validate candidate biomarkers for breast cancer and develop a model that is significantly associated with a positive breast cancer diagnosis.

Methods: Participants were recruited from individuals having a yearly screening mammogram, biopsy, and/or recently diagnosed with breast cancer. Imaging results were obtained from clinical sites and samples were then classified as: control (normal imaging no biopsy) or diagnosed breast cancer pre-treatment (diagnosed by biopsy). Biomarker discovery was conducted using 102 individual tear samples collected using the Schirmer strip collection method. Liquid chromatography/tandem mass spectrometry (LC-MS/MS) was performed to identify protein biomarker candidates with altered expression levels in breast cancer patients. ELISA assay to confirm LC-MS/MS trends for biomarkers of interest was conducted using 171 tear samples. An additional round of validation utilizing 848 samples was performed which included protein concentrations determined by ELISA and collection of demographic and clinical covariates. The resulting concentration data, combined with the demographic and clinical covariates, was analyzed using logistic regression analysis to build a model for classification of samples as positive or negative. Results: A total of 301 proteins were identified by LC-MS/MS and narrowed to a list of 14 proteins (p-value < 0.05) with potential significance in breast cancer patients. Three biomarkers, S100A8 (p-value = 0.0069), S100A9 (p-value = 0.0048), and Galectin-3 binding protein (p-value = 0.01) with an increased expression in breast cancer patients were selected for validation using ELISA. Logistic regression analysis produced three models, which were then evaluated on breast cancer cases and controls at two diagnostic thresholds and resulted in sensitivity ranging from 52% - 90% and specificity from 31% - 79%.
Conclusions: Our results demonstrate clinical feasibility for tear proteins to detect breast cancer and includes the most extensive published data set of individually analyzed tear samples. This analysis suggests that models developed using tear fluid have clinical validity and could be used in further development of a biological assay. We envision positioning this assay as a tool for activation around breast health screening for low to average risk patients who may be screening avoidant or adverse to encourage participation in screening mammography.

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Ki67 Assessment Protocol: Companion Diagnostic Biomarker for LUMINA Prospective Cohort Study

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Introduction: Luminal A breast cancer is associated with low proliferation, indolent disease biology and limited benefit from chemotherapy. The LUMINA prospective study recently demonstrated a very low 5 year local recurrence rate (2.3%) in women ≥55 years with grade I-II, T1N0 luminal A breast cancer (defined as ER ≥ 1%, PR>20%, HER2 negative and Ki67 index ≤ 13.25%) treated with breast conservation surgery and endocrine therapy without radiation, supporting the safe omission of radiation in this molecularly defined low risk group. Here, we report the protocol for multicentre Ki67 scoring, the embedded integral companion diagnostic employed in LUMINA. Methodology: Ki67 immunohistochemistry was performed on full-face sections at one of the 3 labs and scored by pathologists using an adaptation of the International Ki67 Working Group (IKWG) method. Prior to the start of the study, quality assurance and quality control programs were set up to standardize staining and scoring protocols. All pathologists completed the IKWG training and calibration exercise using a tissue microarray-based series of 18 breast cancers. Inter-laboratory variability was assessed annually during the study period on a set of 9 breast cancer cases with a range of Ki67 scores that purposely over-represented the 13.25% threshold. Stained slides were scanned and images annotated to demarcate invasive carcinoma. Next, 5 random, non-overlapping, 1 mm virtual cores were generated via software and 100 nuclei assessed per core using a keyboard-based counting aid. Ki67 index was derived as the percentage of all counted tumor nuclei that...
are positively stained. For cases with high Ki67 heterogeneity, additional virtual cores were generated and scored and a 95% confidence interval (CI) of Ki67 index was estimated. The goal was to confidently assign a case as luminal A (≤13.25%) or B (> 13.5%). If the 95% CI crossed 13.25% a recount was performed by an additional pathologist. Results: Quality Assurance Programs: Mean Ki67 index across all cases, labs and years was 13% with high concordance across specimens and score ranges. Observed intra-class correlation coefficients (ICC) were ≥ 0.9, showing near perfect agreement in quantitative Ki67 evaluation. About the 13.25% cutpoint, the observed Kappa statistics were ≥ 0.7 indicating excellent agreement for assignment of luminal A vs. B status. A sub-study was conducted to compare the method of randomly selected virtual fields with the IKWG ‘global weighted score’ method for visual assessment of full-face sections. For this purpose, the 9 quality control cases were reassessed by the same pathologist using the updated IKWG method. Results showed an ICC of 0.96 (0.95% CI: 0.91-0.98) indicating that the Ki67 score generated by the methodology employed in LUMINA trial is highly concordant with the IKWG scoring methodology validated for use on full face sections. Ki67 index summary statistics across LUMINA: Of the 724 eligible cases, 69% (n=500) were assigned as luminal A (median Ki67=7.5%; IQR 5.2-9.8%) and 31% (n=224) as luminal B (median Ki67=19%; IQR 17-23%). Median pathologist scoring time was 4 minutes / case; 45% of cases required scoring of > 5 virtual cores. Per protocol, 39% cases where the initial CI crossed 13.25% were rescored by additional pathologist for final luminal A consensus assignment. Conclusions: Ki67 is a practical biomarker for identifying molecularly defined low-risk luminal A cancers. Our structured quality assurance approach for the trial led to excellent reproducibility and concordance among decentralized labs, supporting applicability of a distributed, inexpensive methodology beyond clinical trial settings and in resource restricted environments.

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Computational pathology based HER2 expression quantification in HER2-low breast cancer

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Background HER2 directed therapies for breast cancer (BC) rely on accurate estimation of HER2 expression by pathologist scoring of immunohistochemically (IHC) stained tissue according to ASCO/CAP guidelines. Emerging HER2-targeted antibody drug conjugates (ADCs) like trastuzumab deruxtecan (T-DXd), have demonstrated efficacy in the HER2-low (IHC 1+ or IHC 2+/ISH-) population (Modi, NEJM 2022). A deeper understanding of the spectrum of HER2 expression and its spatial distribution could provide insights about the mode of action of ADCs, including potential bystander activity. Computational pathology-based methods like Quantitative Continuous Scoring (QCS) can help here by objectively quantifying HER2 expression levels on a per cell basis from digitized HER2 IHC slides (Gustavson, SABCS 2020). We applied QCS to a cohort of HER2-negative (HER2-neg) patients (pts) from a retrospective study (NCT04807595) to quantify the prevalence of HER2 expression in this population and investigate the relationship with manual scoring.

Methods To analyze the prevalence of HER2 expression in the HER2-neg population, we used available digital images (N=207 pts) from retrospectively rescored HER2 slides from tumors categorized as HER2-low or IHC 0 (IHC 0 or >0< 1+). QCS algorithm was applied to perform an instance segmentation of each tumor cell into the membrane, cytoplasmic and nuclear sub-compartments. HER2 expression levels on the membrane were estimated from a Hue-Saturation-Density model (Van der Laak, JQCS 2000) in terms of optical density (OD). Descriptive statistics and spatial modelling were used to aggregate cell-level information to a slide level score using the membrane OD values and tumor cell locations. A novel Spatial Proximity Score (SPS) was used to mathematically model the proportion of tumor cells that could potentially be targeted either directly or via bystander activity of ADCs. The analysis is ongoing, complete results with additional patient data to be presented. Analytical validation of the QCS algorithm demonstrated high correlation between OD values as measured on the automatically detected membranes from QCS and those measured on consolidated manual membrane annotations (N=2157 cells) from three pathologists (R = 0.993). This is very similar to the correlation observed between individual pathologists (R = 0.995). Results In the analyzed cohort (N=207), median OD of HER2-low tumors was significantly higher compared to IHC 0 tumors (one-sided Wilcoxon p-value < 0.001). A significant increase of OD values was observed for increasing IHC categories from 0 through >0 < 1+ and 1+ to 2+/ISH- (one-sided Jonckheere-Terpstra p-value < 0.001). OD values within each IHC category showed considerable variability, particularly in IHC 1+ and IHC 2+. In 49% of pts (N=101), greater than 88% of tumor cells expressed HER2 at any intensity (OD≥10). Among the remaining 106 pts, the number of potentially ADC-susceptible cells (within 25μm radius of HER2 expressing cells) as estimated by SPS was at least double the amount estimated by single cell-based scores alone in 45 cases (42%) and increased by at least 50% in another 12 cases (11%). Conclusions Computational approaches such as QCS can help us to objectively characterize the spectrum and spatial distribution of HER2 expression. These mathematical models contribute to our understanding of potential mechanisms of action of ADCs. While this study confirmed a general association of QCS-based scores with manual IHC categories, we also saw considerable variation, as some IHC 1+ or 2+ samples had low OD. Building on these and other promising initial results (Gustavson et al, SABCS 2020), we will further explore clinical relevance of QCS-based scoring. Eventually, digital scoring may be able to define data-driven signatures to select HER2-low pts that might benefit from HER2 targeted therapies.
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Background: Immune checkpoint inhibitors such as PD-L1 are promising therapy targets in triple negative breast cancer (TNBC). In the present study, we examined the clinical relevance of PD-L1 and CD8 expression in TNBC patients treated with adjuvant chemotherapy. Methods: FFPE tumor material from 118 patients with early TNBC treated between 1999 and 2012 was included in our analysis. Immunohistochemical (IHC) expression of PD-L1 was determined by immune score using the diagnostic antibody SP142 (Ventana). CD8 IHC was performed using the SP57 antibody (Ventana). Follow-up data were available for all 118 patients with a median follow up time of 19.4 years. Biomarkers were examined as continuous or categorical variable (predefined cutoffs). Invasive disease-free survival (IDFS) and overall survival (OS) were analyzed using Cox regression models. Results: The median PD-L1 immune score was 1% and PD-L1 expression was classified as positive in 79/116 (68.1%, cutoff ≥1%) cases. Median CD8 expression was 10% and was scored as positive in 51/115 (44.3%, cutoff >10%) samples. Significant associations were observed between PD-L1 expression and tumor grade, Ki67, and CD8 expression. PD-L1-positive tumors were more frequently in the G3 group (p=0.006) and had higher Ki67 (p<0.001) and higher CD8 expression (p<0.001). PD-L1 but not CD8 expression was associated with IDFS or OS. Univariate Cox regression analyses showed that PD-L1-negative patients had a shorter IDFS (HR 0.52, 95%CI 0.30-0.89, p=0.02) and showed a trend towards shorter OS (HR 0.56, 95%CI 0.30-1.03, p=0.06). CD8 expression was neither associated with IDFS (HR 0.74, 95%CI 0.43-1.27, p=0.27) nor with OS (HR 0.87, 95%CI 0.48-
In multivariate analyses, PD-L1 expression was an independent prognostic factor for IDFS (HR 0.51, 95%CI 0.29-0.88, p=0.016) but not for OS (HR 0.53, 95%CI 0.28-1.01, p=0.052). Conclusions: Our results suggest that PD-L1 but not CD8 expression assessed by IHC predicted outcome in TNBC. Further analysis of larger, suitable patient cohorts is warranted to further assess the prognostic and predictive value of PD-L1 expression.

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A fully automatic artificial intelligence system for accurate and reproducible HER2 IHC scoring in breast cancer

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Objective: Tumor HER2 expression is a key prognostic and treatment influencing factor in breast cancer. As with all immunohistochemistry (IHC) staining, visual interpretation of HER2 expression is subjective, which leads to intra- and inter-pathologist variability. Recent findings on the efficacy of HER2-targeted therapy on HER2-low patients raise the need for accurate and reproducible scoring. We developed a fully automated, artificial intelligence (AI) -based algorithm for HER2 scoring. The algorithm was based on ASCO/CAP 2018 guidelines and validated against rigorous ground truth (GT) established by multiple blinded expert pathologists.

Methods: Algorithm development: We developed a solution that employs two steps: The first step consists of an ensemble of Deep Learning networks that process tissue regions and classify them as various tissue classes: Invasive cancer, Ductal Carcinoma In Situ (DCIS) and other morphologies. These networks were trained on slides that were automatically labeled by a separate AI system that analyzed the corresponding H&E slides and projected its findings to the HER2 IHC slides using a registration algorithm. To further enrich the training set, especially with rare and difficult cases, a team of 8 expert pathologists manually marked tissue areas and assigned them to one of the tissue classes. In total, the training set consisted of 6,400 manual annotations and 1,300 automatically-annotated slides, both collected from 9 laboratories and
scanned using 3 different scanners. The second step is an ensemble of Object Detection networks that process only the regions classified as invasive cancer, detect the tumor cells within them, and classify their staining pattern (e.g., Not stained, Moderate incomplete, etc.). Finally, the detected cells are counted, and the ASCO/CAP guidelines are applied to derive the slide-level HER2 score. Validation: The validation set was comprised of 453 HER2 slides stained using the VENTANA anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody as per manufacturer’s instructions. HER2 slides included biopsies and excisions with different breast cancer diagnoses (e.g., Infiltrating Ductal Carcinoma (IDC), Infiltrating Lobular Carcinoma (ILC), rare invasive subtypes, with and without DCIS) from 3 different laboratories. Ground truth was established by the consensus scores of a panel of 3 pathologists, who scored HER2 according to the guidelines without additional clinical considerations, such as scoring borderline 1+/2+ cases as 2+ to have additional tests performed. Results: The algorithm showed very high performance for detecting invasive cancer in HER2 tissue sections, with AUC of 0.967 (measured on 4-fold Cross-Validation classifying invasive vs. other regional classes). The algorithm demonstrated an overall accuracy of 80.3% for the HER2 scores when compared to the GT. When using different cutoffs for binary classification the resulting performance was: for 0 vs 1+/2+/3+ Kappa was 0.800; 0/1+ vs 2+/3+ Kappa was 0.728; for 0/1+/2+ vs 3+ Kappa was 0.954. The Quadratic Kappa between the AI score and the GT was 0.898, which is considered almost perfect. The performance of the AI was similar across the different laboratories and diagnoses (e.g. IDC, ILC). Conclusion: This study reports the successful development and independent validation of a fully automatic AI-based solution for accurate HER2 scoring in breast cancer. AI solutions, such as the one reported here, could be used as decision-support tools for pathologists in routine clinical practice, enhancing the reproducibility and consistency of HER2 scoring, thus enabling optimal treatment pathways and better patient outcomes. Accurate and automatic IHC scoring solutions can also contribute to the development of new prognostic, predictive and companion diagnostic tools.

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Objective This study aimed to clinically validate the use of an AI-based solution by pathologists for the primary diagnosis of breast core needle biopsies as compared with the gold standard practice (review on the microscope). Methods A two-arm prospective reader study comparing the performance of pathologists using an AI-based solution with pathologists using a microscope was performed at two sites (different staining and digital scanners). Both arms were compared to ground truth (GT) established by the consensus of two breast pathologists. Rates of major discrepancies between each arm and GT, as determined by an adjudicating pathologist, were compared. Results Eight pathologists participated in the study and reported on 385 cases (442 HES and 330 H&E slides), each case being reported twice, once in each study arm. Pathologists first reviewed only H&E/HES slides, if requested and available, they were provided with IHCs, while the AI results were on H&E/HES only. The major discrepancy rates of the microscope arm and of the AI arm against GT were 4.42% and 3.12%, respectively, demonstrating a 29.4% reduction in major discrepancies. Pathologists with AI demonstrated very high accuracy for the detection of invasive carcinoma with sensitivity and specificity of 100% for both, as well as for DCIS/ADH with sensitivity of 92.4% and specificity of 97.8%. Conclusions This multi-site reader study reports diagnostic accuracy improvements by pathologists performing diagnosis and reporting with the support of a first read AI solution for
breast biopsies. The AI solution performed accurately and generalized well for different staining platforms and different scanners. Thus, AI solutions could be used as significant aiding tools for pathologists in clinical decision-making in routine pathology practice, enhancing the quality and reproducibility of diagnosis.

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Machine learning-based characterization of the breast cancer tumor microenvironment for assessment of neoadjuvant-treatment response

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Background:
Neoadjuvant treatment of breast cancer has been shown to potentially reduce the extent and morbidity of subsequent surgery. Response to neoadjuvant therapy may also be prognostic; complete pathologic response (pCR) following neoadjuvant treatment is associated with improved long-term outcomes. pCR, defined as the absence of residual invasive cancer, is determined by evaluation of H&E-stained breast resections and regional lymph nodes following neoadjuvant treatment; however, pathologist assessment is subject to intra- and inter-reader variability. Here we report machine learning (ML)-based models to identify tissue regions and cell types in the tumor microenvironment (TME) of H&E-stained breast cancer specimens. Model predictions were used to derive tumor bed area, a key component of the residual cancer burden score (RCB) used to assess neoadjuvant-treatment pathological response.

Methods:
Convolutional neural network (CNN) models were trained using digitized H&E-stained whole slide images (WSIs) of 2700 neoadjuvant-treated breast cancer specimens (resections and biopsies) from 4 sources, and an additional 1100 breast cancer primary resections from TCGA. 229,901 pathologist annotations were used to train CNN models to segment tissue regions (cancer epithelium, stroma, diffuse inflammatory infiltrate, ductal carcinoma in situ, lymph nodes and necrosis) and cell types (cancer epithelial cells, fibroblasts, lymphocytes, macrophages, foamy macrophages and plasma cells) at single-pixel resolution. These tissue region segmentations were then used to derive tumor bed area using a convex hull algorithm. Each model was evaluated by board certified pathologists for performance. Model predictions of tumor bed area were evaluated in comparison to mean measurements from 3 pathologists for each of 22 held-out test slides. To further assess cell model performance, 5 pathologists exhaustively annotated 120 frames (300 x 300 pixels) on test samples from a dataset not used in model development (N=536; resections and biopsies) to produce consensus ground truth cell labels. Model predictions were compared with pathologist annotations in these frames using Pearson correlation, precision, recall, and F1 metrics. Only those classes with greater than 50 consensus cells identified were evaluated.

Results:
CNN predictions of tissue and cell classes within H&E breast cancer WSIs showed concordance with manual pathologist consensus labels. The weighted average Pearson correlation (across the relevant cell types) between the model and consensus was 0.75, comparable to the correlation of 0.81 between pathologists and consensus. Classification metrics for each cell class are reported in Table 1. Reduced performance of the model relative to the average pathologist performance may be due to heterogeneous slide characteristics and
infrequency of some cell types in the data. For prediction of tumor bed area, CNN model predictions showed moderate correlation with pathologist consensus (Pearson r=0.65, 95% CI: 0.38-0.81).

Conclusions:
CNN model classification of cell types and tissue regions across entire H&E breast cancer WSIs shows concordance with pathologist consensus. Model predictions of tumor bed area also show concordance with pathologist assessment and can be used to derive the RCB score. These models can be reproducibly applied to quantify diverse histological features in large datasets, potentially enabling improved standardization and efficiency of pathologist evaluation of the breast cancer TME and neoadjuvant response.

Classification Metrics for Individual Cell Classes

<table>
<thead>
<tr>
<th>Cell Class</th>
<th>Precision (Model)</th>
<th>Precision (Pathologist)</th>
<th>Recall (Model)</th>
<th>Recall (Pathologist)</th>
<th>F1 Model</th>
<th>F1 Pathologist</th>
<th>Cell Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Epithelial Cell</td>
<td>0.436</td>
<td>0.513</td>
<td>0.556</td>
<td>0.587</td>
<td>0.526</td>
<td>0.6</td>
<td>550</td>
</tr>
<tr>
<td>Fibroblast</td>
<td>0.446</td>
<td>0.492</td>
<td>0.644</td>
<td>0.35</td>
<td>0.527</td>
<td>0.467</td>
<td>462</td>
</tr>
<tr>
<td>Plasma Cell</td>
<td>0.333</td>
<td>0.558</td>
<td>0.496</td>
<td>0.423</td>
<td>0.596</td>
<td>0.76</td>
<td>75</td>
</tr>
<tr>
<td>Lymphocyte</td>
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<td>0.721</td>
<td>0.648</td>
<td>0.553</td>
<td>0.771</td>
<td>0.628</td>
<td>1364</td>
</tr>
</tbody>
</table>

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Variations in diagnostic practice of Ki67 scoring suggest standard guidelines needed for pathological assessment: survey results of global Ki67 testing methods

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BACKGROUND The cell proliferation biomarker Ki67 is expressed during every phase of the cell cycle and has long been used as a diagnostic tool for cancer prognosis, especially for hormone receptor positive breast cancer (HR+ BC). More recently, Ki67 has emerged as a companion diagnostic to select patients for the medicines targeting high risk HR+ BC. We report survey results of local Ki67 immunohistochemistry (IHC) testing practices across 99 pathology labs in 11 countries supporting clinical trial sites in 2020-2021 for the coopERA Breast Cancer clinical study in neoadjuvant HR+ BC (NCT04436744). METHODS The survey was disseminated to pathology labs across five continents to assess local Ki67 IHC staining, analysis, and scoring methodologies. Metrics included pre-analytical considerations (e.g. sample type and requirements) and analytical considerations (e.g. test validation status, antibody, scoring methods, reporting). RESULTS All pathology labs reported requiring formalin-fixed, paraffin-embedded (FFPE) tissue for local Ki67 testing with 89% using sections with thickness of 2-5 microns. For the Ki67 test, the majority (65%) reported using an in vitro diagnostic assay, 23% used a validated test, and 8% utilized a research-use-only assay. Ki67 antibody selection varied among the labs with 46% using the MIB-1 mouse monoclonal (Dako Agilent), followed by 33% using the 30-9 rabbit monoclonal (Ventana) and 12% reporting the SP6 rabbit monoclonal (Thermo Fisher). A majority (65%) reported using single pathologist visual assessment for scoring, and 17% reported using two or more pathologists. Use of automated digital image analysis (ADIA) was reported by 18% of labs, either alone or in combination with pathologist visual assessment. A significant portion (75%) reported using the International Ki67 in Breast Cancer Working Group (IKWG) recommendations, whereas 7%
reported using only digital image analysis (e.g. Ventana Virtuoso). A minority (7%) indicated neither and instead described variations of "eyeball" or "hot spot" visual estimates. Most labs (65%) reported counting at least 500 cells with 15% of these counting more than 1000 cells. Remaining labs (30%) counted less than 500 or no cells. Predominantly, 85% reported counting cells in at least 3 or more high power fields. Most labs (96%) report Ki67 scores as a percentage of positive nuclei and the remaining minority reported using other methods (e.g. ranges [< 10%, 10-20%, etc.] or H-score [0-300]). CONCLUSIONS The survey results suggest high global variability of local Ki67 testing practices with the highest variability observed in the test validation status, Ki67 clone, and scoring methods. Despite efforts by the IKWG to harmonize and increase the clinical validity of Ki67 as a biomarker, many labs indicating IKWG compliance had survey answers that were discordant with the specific guidelines set forth by the working group. Taking into account the totality of all answers provided by each respondent, only 51% of the surveyed labs fully conformed to the IKWG recommendations. Moreover, a small fraction conducts global estimations without specific cell counting or use "hot spot" scoring methods, despite the high variability and low reproducibility of these scores both intra- and inter-lab. This study demonstrates the benefits of using a central assay in clinical studies to reduce the variability of local Ki67 results in identifying high risk HR+ BC patients and suggests more work is needed to streamline the analytical practices of local Ki67 methodologies, which may directly impact clinical decisions such as the use of neoadjuvant therapies in HR+ BC.

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Recurrence Prediction in Ductal Carcinoma In Situ (DCIS) Patients from Tissue Microarrays (TMAs)

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Recurrence Prediction in Ductal Carcinoma In Situ (DCIS) Patients Using Generative Adversarial Network (GAN) Augmented Deep Learning Model

Background: DCIS patients have an excellent overall survival rate and over-treatment is always a cause for concern due to potential side-effects. Standard clinicopathological factors (age, growth pattern, tumor size, margin status and grade) have been shown to have limited value in predicting recurrence and segregation of high and low risk patients. Early and accurate recurrence prediction would facilitate a more aggressive treatment policy for high-risk patients (mastectomy or adjuvant radiation therapy), and simultaneously reduce over-treatment of low-risk patients. In this work, we have developed a deep learning (DL) classification framework that predicts recurrence in DCIS patients from Tissue microarrays (TMAs) hematoxylin and eosin (H&E) images using a generative adversarial network (GAN) augmented deep learning (DL) classification model. A GAN is a class of DL models, in which two adversarial neural networks, generator and discriminator contest among each other to generate high quality images. During the adversarial training process, the generator learns to synthesize realistic images similar to those in the training set while the discriminator learns to distinguish between real and generated images. In recent years, high quality medical images have been generated by GAN models. To the best of our knowledge, this is the first time a GAN model has been used to generate H&E images to
train a DL classification model to predict recurrence in DCIS patients. Materials and methods: The cohort was comprised of 68 DCIS patients, aged between 35-89 years, lesion size of 5-90 mm, with a mix of low (15%), intermediate (35%) and 50% high grade cases. Patients were treated with mastectomy and/or a combination of lumpectomy, radiation and hormone therapy. TMAs were constructed from 2mm cores (1-3 cores per patient) in consultation with a breast pathologist to create hematoxylin and eosin (H&E) images for further analysis. The cohort was split into independent training (n=50 patients, 10 with recurrences at 5years) and validation groups (n=18 patients, 6 with recurrences at 5years). TMA (H&E) images were divided into smaller image patches of size 256x256 to train a GAN to generate image patches. A DL classification network (Resnet-Inception v2) was trained using TMA image patches and aggressive image patches generated by GAN to predict recurrence. The ability to generate synthetic image patches of aggressive lesions permitted training of a large DL classification network and predict recurrence in DCIS patients. Importantly, manual annotation was not necessary for the process. Results: The DL classification model trained with both TMA and GAN generated image patches predicted recurrence with an AUC of 0.87, sensitivity of 0.83 and specificity of 0.91 in the validation dataset. The DL classification model trained with image patches from TMAs only predicted recurrence with an AUC of 0.81. Conclusions: The use of a GAN model to generate H&E images circumvents the needs for a large cohort and accurate labor-intensive manual annotation of histopathological images, which is often required for training a large DL classification model. The use of GAN generated aggressive image patches during training significantly improves recurrence prediction accuracy of the DL classification model. Validation in independent larger cohorts is ongoing, and if successful, could provide a novel assay for risk prediction that does not waste precious tissue samples.

Disclosure(s):
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Sunil Badve, MD: Indiana/Emory University: Receipt of Intellectual Property Rights / Patent Holder (Ongoing)
Improved quantitative fibrosis indices reveal diverse survivals of triple negative breast cancer patients

Background: The ability of cancer cells to metastasise influences the mortality rate of patients with cancer. Extracellular matrix (ECM) from stromal organization is associated with tumorigenesis and metastasis in breast cancer. It is proposed that morphological features of collagen, based on second harmonic generation (SHG) microscopy, within the tumour environment can be a quantitative image-based biomarker for to predict the survival rate of triple-negative breast cancer (TNBC) patients. To this, we have developed quantitative fibrosis indices by combining multiple collagen features in breast tumour to reveal the diverse survivals of TNBC patients.

Method: The patients (n = 216) in this study were diagnosed with TNBC in Singapore from 2003 to 2015. Disease-free survival (DFS) and overall survival (OS) were defined as time from the point of diagnosis to recurrence or to death/the date of the last follow-up, respectively. The constructed tissue microarrays (TMA) of breast tumours were scanned by the SHG microscope (Genesis, HistoIndex Pte. Ltd., Singapore). 33 collagen parameters were quantified from each sample. These collagen parameters were used to build disease free survival (DFS) index, overall survival (OS) index for prediction of early recurrence (DFS< 1 year) and early death (OS< 4 years), respectively. Kaplan-Meier survival analysis was further performed to assess long-term survival of TNBC patients with high and low risk as stratified by the indices, tumour grade and tumour size. The indices were validated using leave-one-out method.

Results: Both DFS-index and OS-index were created using 10 collagen parameters chosen by sequential selection methods. Due to insufficient follow-up time, 12 patients and 81 patients were excluded from the early recurrence analysis and early death analysis, respectively. The DFS-index could differentiate low-risk patients with DFS≥1 year (n=179) and high-risk patients with DFS< 1 year(n=25) (training p< 0.001; validation p=0.157) with a cut-off value DFS-index=0.880. The OS-index could differentiate the low-risk patients with OS≥4 years (n=101) and high-risk patients with OS< 4 years (n=34) (training p< 0.001; validation p=0.011) with a cut-off value OS-index=0.703. The log-rank test showed DFS-index (training p = 0.001; validation p=0.025) and OS-index (training p < 0.001; validation p=0.011) could be used for the prediction of disease-free survival and overall survival. Kaplan-Meier survival analysis revealed tumour size>20mm (DFS, p=0.605; OS, p=0.136) and tumour grade=3 (DFS, p=0.328; OS, p=0.768) had poor predictive value in this study.
Conclusion: Quantitative assessment of fibrosis in breast cancer correlates with long-term survival of TNBC patients. This study used DFS-index and OS-index combined complex morphological collagen features and obtained better prediction results than tumour size and tumour grade.

Table: The difference between low and high risk groups differentiated by developed indices, tumour size and tumour grade. Low-risk group has a longer DFS and OS months based on DFS-index and OS-index.

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<th>High-risk group</th>
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<tr>
<td></td>
<td>Patient number</td>
<td>DFS/OS months</td>
<td>Patient number</td>
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<tr>
<td></td>
<td>Mean (std)</td>
<td>Mean (std)</td>
<td></td>
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<tr>
<td>DFS-index</td>
<td>Training 79</td>
<td>68.1(45.8)</td>
<td>125</td>
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<tr>
<td></td>
<td>Validation 78</td>
<td>64.6(47.0)</td>
<td>126</td>
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<tr>
<td>OS-index</td>
<td>Training 79</td>
<td>94.3(40.0)</td>
<td>56</td>
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<td></td>
<td>Validation 81</td>
<td>88.9(41.3)</td>
<td>54</td>
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<tr>
<td>Tumour size</td>
<td>DFS 55</td>
<td>52.0(43.1)</td>
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<tr>
<td></td>
<td>OS 54</td>
<td>57.8(42.1)</td>
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<tr>
<td>Tumour grade</td>
<td>DFS 38</td>
<td>51.3(42.5)</td>
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<tr>
<td></td>
<td>OS 38</td>
<td>55.7(43.9)</td>
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Disclosure(s):

**Yayun Ren, n/a:** HistolIndex Pte Ltd, Singapore: Salary (Ongoing)

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Differential diagnoses of breast biopsies by spatial parametric modeling of histological structures and explainable AI

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Background: Pathologists typically diagnose the breast tissue slides under a microscope by examining: (i) lumen and ductal morphology, (ii) nuclei size, shape, and spatial arrangement and their combinations, (iii) intraductal architecture, and (iv) textural properties. These features may be subtle and can overlap between diagnoses which contribute to inter- and intra-observer variability. We aim to mitigate this arbitrary nature of breast diagnoses with an exemplar-driven precision pathology pipeline based on spatial parametric modeling of histological structures.

Methods: For our study, we consider a broad spectrum of breast biopsies including: (i) invasive breast cancer, (ii) three high-risk benign lesions: ductal carcinoma in-situ, atypical ductal hyperplasia (ADH), and flat epithelial atypia (FEA), and (iii) three low-risk benign lesions: usual ductal hyperplasia, columnar cell change and Normal; where the risk is indicated by the relative chance of developing breast cancer. We build spatial parametric models for a dictionary of histological structures that pathologists frequently use (also documented in the standard reference book from WHO on the classification of tumors) in making complex diagnostic decisions. These models enable our precision pathology pipeline to simultaneously identify distinct exemplar images to account for inter-class heterogeneity, and learn the relative importance of lumen/ductal morphology (LD), intraductal structures including nuclei morphology and spatial arrangements (ID) and textural features (T) from automatically identified exemplar images in assigning diagnostic labels. In doing so, we assert that the assignment of relative importances to LD, ID, and T features is driven by similar looking ducts (‘exemplars’) which were previously encountered during pathology training or clinical practice.

Results: We evaluated the inferential power of our exemplar-driven precision pathology pipeline on two separate breast core biopsy image datasets, i) dataset containing 4539 regions of interest (ROIs) images extracted from 387 whole slide images (WSIs, 40x), and ii) dataset containing 1237 ROI images extracted from 93 WSIs (20x). Our precision pathology pipeline shows significant improvement (~20%) in the overall classification performance compared to state-of-the-art black box deep learning methods (e.g., graphical neural networks) on both datasets. In particular, while our performance in detecting invasive lesions is comparable to baseline methods, we show a significant improvement (p< 0.01) in detecting diagnostically important high-risk ADH and FEA ROIs compared to the baseline methods, where inter- and intra-observer variability is a problem.

Conclusions: A key highlight of our method is in its ability to provide pathologist friendly diagnostic explanations without largely compromising on the classification performance. The strategy outlined in this work can be generalized to other tissue histologies from other organs as defined in the WHO Classification of Tumors books. Further, our approach can facilitate a
communication platform between pathologists and computational scientists to interact and develop AI-driven algorithmic tools that can enhance patient care in a clinical setting. Our framework provides pathologist-friendly explanations paving the way for better, transparent, and trustworthy diagnostic tools.

Differential diagnoses of breast biopsies

The precision pathology pipeline optimizes the identification of a broad spectrum of breast biopsies (invasive, DCIS, benign), including difficult borderline cases (e.g., ADH, FEA, etc.). It provides pathologist-friendly explanations integrated into a clinical workflow for better, transparent, and trustworthy diagnostic aid. This approach addresses the limitations of standard black-box AI in building trust with pathologists.

Disclosure(s):
Akif Burak Tosun, PhD: SpIntellx, Inc.: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing)
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Centralized adequacy assessment of ductal carcinoma in situ samples for the COMET study (AFT-25)

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Introduction COMET (Comparing an Operation to Monitoring, with or without Endocrine Therapy) is a phase III clinical trial randomizing patients diagnosed with low-intermediate grade DCIS to either active monitoring or surgery. The study has a planned accrual goal of 1200 patients and is enrolling until 12/31/22. The protocol requires agreement between two pathologists (who do not need to be at the same institution) that a case fulfills COMET eligibility criteria. If there is disagreement, a third pathology review is required. As per protocol, tissue blocks or unstained slides of biopsies containing DCIS from enrolled patients are sent to a designated central location. While central pathology review is not a pre-requisite of the study, a retrospective review of received materials was performed to determine adequacy for correlative molecular and spatial profiling studies. Methods Sites submit either a tissue block or twenty (20) sequentially numbered, unstained, serial five-micron tissue sections from a diagnostic biopsy of DCIS to the Alliance Foundation Trials (AFT) central biorepository, a CAP-accredited biobank. All submitted biospecimens are de-identified (coded) and investigators are blinded to arm assignment and primary study outcomes. To evaluate the adequacy of specimens for subsequent correlative science studies, one unstained slide from each submitted slide set was stained with routine hematoxylin and eosin by the biobank, scanned at 40X magnification with an Aperio scanner, and provided to one of two expert breast pathologists for adequacy review. Slides were rated as “DCIS present”, “DCIS absent”, or “possible DCIS.” To conserve tissue, submitted tissue blocks are held in abeyance pending future correlative science planning. Results As of May 2022, tissue has been submitted from 789 of 856 eligible patients enrolled in the trial, demonstrating a very high level (92%) of case submission compliance. Despite the limiting size of such lesions and general clinical center hesitancy to release blocks for clinical trial research, tissue blocks were received from 376 of 789 (48%) of cases. Among 359 cases involving slide-only submissions that have been retrospectively reviewed to date, 294 were definite DCIS (82%), 25 (7%) were classified as possible DCIS, and 40 cases (11%) were classified as no DCIS present in the section reviewed. In no case was high grade DCIS or invasive breast cancer observed. Of the cases considered possible DCIS, atypical cells were present, but the lesions were too small or incomplete to confirm DCIS. The small percentage of cases that lacked DCIS or definite DCIS could be attributed to the receipt of a different block or subsequent (deeper) section from the same block used for the initial diagnosis. These cases were previously known to the submitting institutions. Conclusion Interim analysis at 71% accrual demonstrates both the feasibility of obtaining diagnostic biopsy material of limited size and the adequacy of these samples for subsequent correlative science studies that aim to improve pathology diagnostics and patient management.

Disclosure(s):
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<th>Name</th>
<th>Financial Relationships</th>
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Comparison of next-generation sequencing and real-time PCR for PIK3CA testing in hormone receptor-positive/HER2-negative breast cancer on metastatic and matched primary tumor samples

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Introduction: Based on the SOLAR-1 study, the PI3Kα-specific inhibitor alpelisib has been approved in combination with fulvestrant for postmenopausal women, and men, with HR+/HER2-, PIK3CA-mutated, advanced or metastatic breast cancer (BC). Despite PIK3CA mutations occurring in ~40% of HR+/HER2- BC, PIK3CA molecular testing is a new task to be carried out in clinical practice. Adopting the most appropriate testing strategy (RT-PCR vs. NGS) on the most appropriate biological sample is of capital significance in oncologic pathology. Here, we sought to assess the concordance rate for PIK3CA molecular analysis between different technical platforms in both metastatic and matched primary tumors. Methods: From our Institutional registry, n=16 HR+/HER2- metastatic BC, which were found to harbor PIK3CA mutations via next-generation sequencing (NGS) assays [custom panel and Oncomine Comprehensive Assay (OCA) v3 (Thermo Fisher Scientific, Waltham, MA, USA)], were selected. In half of the cases (n=8), matched primary tumors were available and were subjected to PIK3CA testing with NGS. The analytical performance between NGS and a semi-closed RT-PCR (EasyPGX®, Diatech Pharmacogenetics, Italy) was assessed in 13/16 (81.3%) metastatic samples for which archival slides and blocks and/or residual extracted DNA were available, and all the primary tumors. Results: Overall, upfront testing of PIK3CA mutational status with NGS detected genetic alterations in exons 7, 9, and 20. A concordance rate of 100.0% was observed between primary and metastatic tumors. On the other hand, the analysis of primary tumors (n=8) and 13/16 (81.3%) metastatic samples with RT-PCR revealed a concordance of 42.9%. Analytical performance comparison showed that the two technologies were concordant in 7/13 metastatic cases (53.8%). In two of the discordant cases (15.4%), RT-PCR did not identify the PIK3CA mutations due to their absence from its reference range. Interestingly, visual inspection of the RT-PCR raw data increased the concordance to 76.9%. In primary tumors, consensus between the two testing methods was observed in 5 (62.5%) cases. Discussion: The concordance rate analysis shows that upfront PIK3CA molecular testing with NGS appears to be more efficacious compared with RT-PCR. Our data suggest that primary tissues reflect the PIK3CA mutational status when tested with NGS. RT-PCR is simpler with a shorter turnaround time, and less expensive than NGS approaches, however, trained personnel are required for accurate results interpretation. In addition, the limited reference range of this testing method should be taken into account for potential false negative results. Conclusion: In terms of PIK3CA molecular testing, NGS should be the preferred method in comparison with RT-PCR. Primary tumors represent a valid biospecimen to be used for this analysis in the absence of the metastatic sample.

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Introduction: Tertiary lymphoid structures (TLSs) and tumor-infiltrating lymphocytes (TILs) in breast carcinomas are prognostic for survival and predictive of certain therapy responses. The presence of TLSs and TILs are identified by manual pathological examination; however, this method often lacks reproducibility, limiting its use in routine clinical practice. Here, we demonstrate that morphological evaluation of whole slide images (WSIs) using an artificial intelligence (AI)-based analytic workflow comprised of convolutional neural network (CNN)
deep learning models that accurately and reproducibly characterizes TILs, measured as the lymphocyte immune-infiltrated area (LIIA), and TLSs in the tumor microenvironment (TME) of breast carcinomas. Methods We collected a cohort of 445 TCGA breast cancer H&E WSIs, including clinical and sequencing data, and divided this cohort into luminal invasive lobular carcinoma (ILC) (n = 192), HER2-enriched (n = 110), and basal-like (n = 143) molecular subtypes. After 55 samples were excluded due to artifacts or incomplete clinical annotation, a total of 390 samples were analyzed. A combination of CNN-based deep learning models was used to detect and classify the tumor area, TLSs present in the TME, TLS density (number of TLS per mm² of tumor), and lymphocyte-rich regions. The LIIA was calculated as the area of the stromal and TIL components of the TME. Validation was performed by manually annotating 10 random WSIs from the dataset. Spatial model predictions of the tumor and TLSs were combined to identify TLS locations. Each model’s predictions were verified by univariate (Kaplan-Meier) and multivariate (Cox regression) survival analyses, and the log-rank test was used to calculate overall survival. Additionally, the relationship between TLSs and LIIAs with CD274 expression (PD-L1) and a high tumor mutational burden (TMB > 10) was analyzed. Statistical analyses included Spearman’s rank correlation and Mann-Whitney tests. Results TLS were detected in 53% (n = 207) of the samples, with a mean density of 26.02 TLS/mm² (Q3 = 5.53 TLS/mm²). TLS density was higher in basal-like subtype samples compared to luminal and HER2-enriched subtypes. While LIIA and TMB-high samples exhibited a significant relationship (p = 0.00001), no significant association was found between TME and TLS quantities or density. PD-L1 gene expression exhibited weak to moderate correlations with predicted LIIA in basal-like (r = 0.38, p = 0.00001) and HER2-enriched subtypes (r = 0.38, p = 0.0001). The luminal subtype had no significant correlation between PD-L1 expression and predicted LIIA. As a result, LIIA and TLS were characterized as positive prognostic factors for the basal-like subtype. After adjusting for age, stage, and grade, the LIIA and TLS density were found to be significant independent positive prognostic overall survival factors for the basal-like subtype (LIIA HR: 0.02, p = 0.003; TLS-high group HR: 0.09, p = 0.002). For the HER2-enriched subtype, TLS density was also a significant predictor (HR: 0.05, p = 0.035), while LIIA was not a statistically significant prognostic factor (HR: 0.0002, p = 0.08). Associations were not observed between the TLSs and LIIA between the ILC subtypes and survival outcomes. The same result was observed for univariate analyses. Conclusion The developed analytic pipeline accurately identified the presence of LIIA and TLS on H&E slides, demonstrating the potential of CNN for automated characterization of the breast cancer TME. AI-based TLS and LIIA quantification can be a robust tool for pathology processes, offering additional information to help in clinical decision-making. This approach can be used to detect features of immune morphology biomarkers in other cancer types.

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Background Computational pathology-based methods, eg, Quantitative Continuous Scoring (QCS) [Gustavson, SABCS 2020], are built to provide objective and quantitative methods to
assess HER2 expression in breast cancer (BC). For accurate HER2 quantification, it is important to exclude non-invasive epithelium from analysis since HER2 overexpression could be more frequent in ductal carcinoma in situ (DCIS) and pleomorphic lobular carcinoma in situ (PLCIS) than in invasive BC [Lari, J Cancer 2011]. Generally, computational pathology-based approaches require experts to delineate the invasive BC regions of interest for analysis and exclude all benign/non-invasive epithelium. Developing a tool that delineates the invasive BC regions automatically without human intervention to avoid subjectivity of manual annotation by pathologists is ideal. We developed a novel, deep-learning-based system, called DualScaleNet, to perform Automated Region segmentation of Tumor (ART) by automatically identifying the invasive BC regions and excluding benign/non-invasive epithelium on HER2-stained digitized images. Identification and diagnosis of these regions, especially the in situ tumors are a challenge as they can mimic benign and invasive lesions causing wrong HER2 evaluation. Additional stains (eg, p63 for myoepithelial cells or laminin for basement membrane) are often required for diagnosis [Pinder, Mod Pathol 2010] but were not available for this study.

Methods DualScaleNet works simultaneously on HER2-stained immunohistochemistry (IHC) image patches at 2 different resolutions. The target branch uses a higher resolution RGB image (0.5 μm/pixel) to learn accurate local details; the context branch uses a lower resolution image (4.0 μm/pixel) to incorporate more context in visual learning. The algorithm generates 4 output image layers representing probabilities of 4 classes: invasive tumor, ductal/lobular carcinoma in situ, benign epithelium, and other tissue. The final segmentation result is generated by assigning each image pixel the class with the largest probability value. The algorithm was trained using ground truth (GT) annotations generated by 5 pathologists using 6157 square field of views (FOVs), 200-500 μm in size. These FOVs were collected from 850 whole slide images (WSI), spanning 9 commercial BC sample cohorts stained with different HER2 assays and scanned by several versions of the Aperio AT2 scanner. The samples included a mixture of biopsies and resections and covered different BC histologies and HER2 staining intensities. To evaluate the reproducibility of tumor area detection by human pathologists, an interpathologist comparison in detection of invasive tumor regions was performed using 225 FOVs annotated by multiple pathologists. Results Analysis generated an average Dice/F1 Score of 81.6% among different pathologists for invasive cancer. On the same sample set (independent of the ART training set), the invasive cancer detection by the ART algorithm was on par with human pathologists, achieving a similar average Dice/F1 score of 80.7%. Conclusions Novel deep learning-based ART algorithm provides accurate segmentation of invasive cancer on HER2-stained IHC images. The performance was verified against the GT annotations provided by multiple pathologists. Since the algorithm is trained using annotations from multiple pathologists, it is not possible to generate higher accuracy with computational pathology than is achievable between independent pathologists. Importantly, the same WSI read by the ART will consistently output the exact same tumor region identification result thus removing the inherent human subjectivity and variability, while improving the turnaround time for analysis. This development serves as the necessary foundation upon which a computational pathology-based diagnostic can be built.

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High Intra- and Inter-block concordance of HER2 immunohistochemistry (IHC) scores across breast cancer samples and impact of decalcification procedures

Background & Objective: Trastuzumab deruxtecan is effective in HER2-positive (IHC3+ or ISH-positive) and HER2-low (IHC1+; IHC2+/ISH-negative) breast cancer. We assessed consistency of HER2-positive and HER2-low categorization by IHC across and between breast cancer samples with a range of HER2 expression. The impact of decalcification procedures on HER2 IHC staining was also assessed to determine whether HER2 expression is likely to be compromised in decalcified samples from metastatic bone disease.

Methods: Three non-consecutive tumor sections (approximately 100 μm apart) from 50 commercially obtained breast cancer resections (2 blocks/resection) and 20 biopsies (sections ~40 μm apart) representing a range of HER2 IHC expression, and with known ISH status, were stained using the VENTANA anti-HER2/neu 4B5 IHC assay, scored per ASCO-CAP (2018) guidelines and intra-block/inter-block concordance reported for HER2-positive and HER2-low categorization. To investigate the impact of decalcification, four resection samples were formalin-fixed, divided into four pieces, of which three were pre-treated with either 10% formic acid, Decal STAT or Richard Allan Scientific<sup>TM</sup> Decalcifying Solution before processing and staining with the 4B5 IHC assay. Results: A single pathologist reviewed all samples. Intra-block agreement for HER2-low (proportion of blocks in which 3 of 3 sections had identical status) was 89.5% for biopsies (17/19) and 80.6% for resection samples (n=79/98). Inter-block agreement (proportion of resections in which two independent blocks had the same majority status for HER2-low) was 91.7%. Intra and inter-block agreement for HER2-positive was >90%. Exposure to Decal STAT or Richard Allan Scientific<sup>TM</sup> Decalcifying Solution caused a significant reduction in HER2 IHC1+ and IHC2+ staining in breast cancer samples. 10% formic acid had no apparent impact on HER2 IHC staining in all four samples tested. Conclusion: There was high HER2-positive and HER2-low agreement within breast cancer biopsies and resection blocks and highly consistent HER2-positive and HER2-low categorization between different blocks from tumor resections. Our results suggest HER2 staining heterogeneity does not impact determination of HER2-positive and HER2-low status in the majority of cases. Accurate
assessment of HER2 IHC1+ and IHC2+ status was observed to be compromised by Decal STAT and Richard Allan decalcification solutions. Decalcification of bone metastasis samples for HER2-positive and HER2-low status determination may be possible using formic acid, but this would require further validation.

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Rapid diagnosis of breast biopsies with open-top light-sheet microscopy

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Intro: Detection of breast cancer is achieved through a diagnostic work-up that involves specialized breast imaging, image-guided biopsy, and pathological assessment. Pathology results typically require ~ 3 business days before a diagnosis is rendered, creating avoidable anxiety in women presenting with a breast abnormality. We describe a solution to deliver a rapid preliminary diagnosis within 30 minutes of biopsy. This rapid preliminary diagnosis has the potential to reduce anxiety, streamline patient care workflows, and reduce healthcare costs.

Methods: Fresh 14 gauge breast biopsies in normal saline were received directly from the breast imaging clinic and immediately stained using the nuclear marker SYBR Gold (Invitrogen) and pan-protein marker Atto 655 NHS Ester (Sigma) prepared in dimethyl sulfoxide, washed, and cleared for imaging at a refractive index of 1.46 using 2,2'-Thiodiethanol (Sigma). The full process requires approximately 14 minutes for staining and clearing. After staining, we placed the biopsy in a custom-built specimen holder and imaged a 100-micron cross section along the full length of the biopsy using our custom open-top light-sheet microscope. Images were subsequently converted computationally to a standard hematoxylin and eosin (H&E) color format using Fiji and Aivia (Leica) software and were ready for evaluation by a pathologist on the same day they were collected. Results: Using the protocol above, we demonstrated the ability to stain, clear, image, and visualize needle core biopsies within 30 minutes of receiving the tissue sample. Processing the data and converting to the H&E color palette required
additional time, often requiring 60-90 minutes, surpassing the overall 30 minute turnaround time goal. The images contained identifiable stroma, epithelial cells, immune cells, and duct structures to a depth of 100 microns. Discussion: We describe a method to obtain a microscopic image for preliminary diagnosis within 30 minutes of receipt of tissue. The quality of the images produced by the method shows promise for preliminary diagnosis. Additional optimization is needed in sample preparation and data processing to meet the 30 minute turnaround time requirement. This optimization can be achieved by parallelization of the data processing on a cluster or cloud to reduce the time by an order of magnitude, which is currently under investigation by our team. The imaging and data processing will also be accelerated by multi-resolution imaging, which will decrease the time of imaging and dataset size for processing. A diagnostic study, comparing the preliminary light-sheet-based diagnosis to the final formalin fixed paraffin embedded (FFPE) pathology, is underway.

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Engaging pathologists in a social peer-to-peer learning collaborative to discuss the emergence of HER2-low breast cancer

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Introduction: Recent advances in research have shown clinical effectiveness when targeting the lower range of HER2 expression (ie, HER2-low) in patients with metastatic breast cancer. American Society for Clinical Pathology worked in collaboration with Q Synthesis to develop a peer-to-peer learning collaborative to proactively prepare pathologists for HER2-low and to discuss the clinical implications around this emerging classification. This CME project was supported by an educational grant from AstraZeneca Pharmaceuticals LP and Daiichi Sankyo Inc. Methods: ASCP launched a peer-to-peer (P2P) learning collaborative (HER2 Breast Trailblazers) where small groups of pathologists met to discuss some of the practical implications associated with HER2-low. 38 pathologists from a mix of academic and community settings participated in this CME program. For foundational knowledge, learners completed online modules covering scientific updates on HER2-low. Through small-group, case-based discussions, learners reviewed operational challenges and opportunities to prepare for HER2-low. They applied this knowledge to lead projects at their own institutions focusing on the anticipated changes around HER2-low. ASCP also launched a series of peer-led Twitter Chats that were designed to reach a broad audience and foster open dialogue about the emerging science of HER2-low breast cancer. This approach engaged Twitter users who were eager to share and disseminate the education to their colleagues. Twitter Chats provided peer-to-peer feedback regarding ways to navigate obstacles, barriers, and other challenges affecting HER2 testing in breast cancer. Results: The learners identified the following challenges and opportunities: Defining HER2-low: Several learners had heard misconceptions around the definition of HER2-low. Recent studies have defined HER2-low as IHC 1+ or IHC 2+ with ISH-negative. Interobserver concordance with IHC 0 vs 1+: Several learners discussed the challenges around interpreting IHC 0 vs 1+. They felt that some pathologists may need guided feedback to improve their diagnostic skills. Use of IHC vs. ISH: Several learners only performed ISH for HER2 testing on all breast cancer samples. If HER2-low emerges as a third category, they would need to return to IHC. Implications for non-metastatic breast cancer: Recent HER2-low studies have focused on patients with metastatic breast cancer. If HER2-low emerges as a third category, it is unclear whether this designation will also be used in patients who have early-stage breast cancer. Leadership: As pathologists prepare for HER2-low, they have opportunities to lead projects to assess and improve IHC interobserver concordance, coach others on IHC interpretation, increase operational efficiency, strengthen communication skills, and build up the team by proactively anticipating challenges around HER2-low. Conclusions: HER2-low breast cancer appears to be emerging as a new classification and pathologists need to be prepared to ensure accurate testing and interpretation. Through a peer-to-peer learning collaborative, pathologists identified ways to proactively prepare and demonstrate leadership so
that cancer centers and laboratories may be ready to embrace a new paradigm of HER2 classification in breast cancer. A series of public Twitter Chats broadened this discussion and increased awareness among pathologists.
Employment status patterns in a cohort of young women with breast cancer in Mexico

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Background: Breast cancer diagnosis and treatment carries a disruption in multiple aspects in the life of women. For young women affected by this condition, the evidence of employment status and its change is limited. This study aims to document the first change in employment that may be experienced by young women with breast cancer and determine which factors could influence such patterns. Methods: Mexican women from the Joven & Fuerte prospective multicenter cohort, aged ≤40, diagnosed with stage I-III breast cancer between 2015-2021 with at least 6 months of follow-up were included. Participants with a documented recurrence, missing employment status information, diagnosis of a new primary breast cancer or a second type of cancer were excluded from the analysis. Patients completed surveys at baseline, 6 months, and yearly for up to 5 years to assess sociodemographic characteristics, employment
status, medical and treatment data. Women were categorized on a scale of employment status as follows: full-time > part-time > student > medical leave > unemployed. Subsequently, an increase or reduction in employment status was considered whenever a participant moved up or down a category, respectively. Only the first employment status change was analyzed. The Kaplan-Meier failure estimate was employed to calculate the increase or decrease in employment status at 1 year and 2 years post-diagnosis. Competing risk regression models were undertaken to explore variables associated with a decrease in employment status.

Results: A total of 142 women with a median age at diagnosis of 36.5 years (IQR 33-39) and median follow-up of 17 months were included in the analysis. Baseline employment status for these patients was: employed - full time (27%), employed - part time (14%), student (1%), medical leave (4%) and unemployed (54%). At 12 months, 18.5% of participants had a reduction in their work activities (95% CI 12.8 - 26.4%) and this proportion further increased to 25.8% at 24 months (95% CI 18.7 - 34.8%). In contrast, 11.8% (95% CI 7.3 - 19.0%) and 23.2% (95% CI 15.9 - 33.2%) of participants exhibited an increase in their work activity at 12 and 24 months, respectively. The most common patterns in first employment status change were from unemployed to employed - full time (19%), employed - full time to employed - part time (13%) and employed - full time to unemployed (13%). Age, education, monthly income, number of people who contribute to the household, number of children, being financially responsible for another person, mastectomy, chemotherapy, radiotherapy and endocrine treatment were not associated with an increase or reduction in work activity. Postmenopausal status at 1 year postdiagnosis was associated with a higher hazard for experiencing a reduction in work activity (SHR=3.05, 95% CI 1.38 - 6.72, p=0.006). Conclusion: The results from the present study appear to be in line with those of a European cohort. Further studies are needed to identify other potential factors that influence employment status trajectories. The development of interventions that tackle actionable characteristics of young patients with breast cancer at risk of employment disruption is imperative.

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Cynthia Villarreal-Garza, n/a: AstraZeneca: Contracted Research (Ongoing); Lilly: Consulting Fees (e.g., advisory boards) (Ongoing); Myriad Genetics: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing); Roche: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing)
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PRESENCE OF BRCA MUTATIONS AND PRE-CHEMOTHERAPY SERUM ANTI-MULLERIAN HORMONE LEVELS PREDICT RISK OF AMENORRHEA IN WOMEN WITH BREAST CANCER

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KUTLUK H. OKTAY, MD, PHD, PROFESSOR - DEPARTMENT OF OBSTETRICS, GYNECOLOGY, AND REPRODUCTIVE SCIENCES, YALE UNIVERSITY SCHOOL OF MEDICINE

OBJECTIVE: The likelihood of post-chemotherapy (ChT) amenorrhea is still empirically determined. Our aim was to determine the predictors of amenorrhea risk post-ChT in women with breast cancer (ca). As acute amenorrhea (< 12mo post-ChT) can be temporary, we used amenorrhea status 12 and 18 months post-ChT as the primary endpoint.

MATERIALS AND METHODS: 102 women aged 18-44, with regular cycles and stage I-III breast ca were prospectively and longitudinally followed for their menstrual pattern changes at 6, 12, and 18mo after the completion of adjuvant ChT with an Anthracycline-Cyclophosphamide-based (AC) or Cyclophosphamide-Methotrexate +5-Fluorouracil regimen on an IRB-approved protocol. Prior ChT, ovarian surgery, pelvic RT, family history of POI, and infertility diagnosis were the exclusion criteria. AMH was measured pre- and immediately post-ChT. Amenorrhea was defined as no bleeding for 4 consecutive cycles. Preand/or post-ChT AMH levels, age and BMI at the onset of ChT, BMI, tamoxifen use, regimen type (AC-based vs. not), and BRCA mutation (m) status (positive vs. not) were evaluated for the prediction of
amenorrhea risk. 
RESULTS: In multivariable-adjusted logistic regression models, age (p=0.03) and AMH (p=0.03) were significant predictors of amenorrhea at 12mo, and BRCAm status (p=0.03) at 18 mo; these models yielded areas under the ROC curve of 0.77 and 0.76, respectively. An undetectable AMH post-ChT was best predictive of amenorrhea with shorter follow-up, but not at 18mo. In longitudinal analysis (with data at 0, 6, 12, and 18 months) estimating 'time-trends', a baseline AMH < 2.0 ng/ml (optimal cut-off from ROC curve) and BRCAm status were associated with the risk of amenorrhea. The baseline AMH ≥2.0 group showed attenuated time-trend vs. the AMH < 2.0 ng/ml group (ratio of ORs=0.91, 95% CI=0.86-0.97, p=0.002), while the BRCA-positive group showed a steeper time-trend in the odds ratio (OR) of amenorrhea, compared to the non-positive group (ratio of ORs=1.12, 95% CI=1.04-1.20, p=0.003) (Table 1). Sensitivity analyses demonstrated the robustness of these findings, for example, yielding an 8-10% increased risk of amenorrhea for BRCAm carriers, with p-values of 0.008- 0.04. CONCLUSIONS: Age, pre- and post-ChT AMH levels, and BRCAm status are potential predictors of amenorrhea at 12 and 18mo post-ChT. These predictors may help better guide fertility preservation decision-making in women with breast ca. The higher likelihood of amenorrhea in women with BRCAm suggests that they may be more prone to lose their ovarian function post-ChT and should be accordingly counseled.
Table 1. Longitudinal analysis at 0, 6, 12 and 18 months for the difference in amenorrhea trend between groups dichotomized by baseline factors

<table>
<thead>
<tr>
<th>Difference in time trend between 2 groups (per 1 month)</th>
<th>Multivariable-adjusted model Ratio of Odds Ratios (95% CI), p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference group</td>
<td>0.98 (0.89, 1.08), p=0.65</td>
</tr>
<tr>
<td>AMH at baseline: &gt; vs. ≤2.0*</td>
<td>0.91 (0.86, 0.97), p=0.002</td>
</tr>
<tr>
<td>Age: &gt; vs. ≤40</td>
<td>1.03 (0.99, 1.11), p=0.14</td>
</tr>
<tr>
<td>BMI: &gt; vs. ≤25</td>
<td>1.05 (0.99, 1.11), p=0.09</td>
</tr>
<tr>
<td>Tamoxifen vs. not</td>
<td>1.05 (0.96, 1.14), p=0.31</td>
</tr>
<tr>
<td>CMF vs. AC-based regimen</td>
<td>1.02 (0.95, 1.11), p=0.57</td>
</tr>
<tr>
<td>BRCA positive vs. not</td>
<td>1.12 (1.04, 1.20), p=0.003</td>
</tr>
</tbody>
</table>

*Cut-off was suggested from ROC curve in Figure S1.

Ratio of odds ratio–1 indicates null value, i.e., no difference in time-trend between 2 groups, measured by odds ratio (of 1 month increase and outcome) in each group separately.

Longitudinal data were fit via a Generalized Estimating Equation (GEE). Sensitivity analyses (e.g., based on Generalized Linear Mixed effects model (GLMM)) are presented in Table S3.

Disclosure(s):

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KUTLUK H. OKTAY, MD, PHD: No financial relationships to disclose
Introduction: Breast cancer is the most common cancer diagnosed in women in the United States with primary treatment consisting of a combination of surgery, systemic therapy, and radiation. Breast reconstruction has been shown to improve quality of life in women and utilization is increasing with time. There is a large amount of evidence demonstrating the complications of radiation therapy on implant-based breast reconstruction including but not limited to, capsular contracture, infection, and reoperation. However, the majority of these studies have examined populations consisting primarily of non-Hispanic white patients with breast cancer. In general, hispanic populations are not well represented in research studies or Phase II/III clinical trials. Therefore, the goal of this study was to analyze the impact of radiation therapy on post mastectomy implant-based breast reconstruction complications in self-identified Hispanic patients.

Methods: We retrospectively reviewed patients who underwent mastectomy with implant reconstruction between January 1, 2017 and December 1, 2019. The inclusion criteria included female patients 18 years or older who self-reported as Hispanic or Latino. Exclusion criteria included patients who did not undergo mastectomy, did not undergo tissue-expander or implant reconstruction, or did not self identify as Hispanic descent. Outcomes needing antibiotics, capsular contracture Baker grade II-IV, and implant loss. Statistical analysis was performed using Chi-squared analysis.

Results: A total of 258 patients of Hispanic or Latino women were included in the study. This included 343 total number of breasts, with 228 breasts that underwent mastectomy with
reconstruction due to breast cancer and 115 breasts that underwent prophylactic mastectomy with reconstruction. The median age at time of initial mastectomy was 49 years (range 19-86). 46 total breasts received adjuvant postoperative radiation and 296 breasts did not receive radiation. Median radiation dose to the chest wall was 50 Gy (range 42.56 - 60) in 2Gy (range 1.8 - 2.66) fractions. All patients who received postoperative radiation had at least 1 complication. The rate of complications and comparison between radiated breast compared to non-radiated breasts is demonstrated in table 1.

Conclusion: The goal of this study was to analyze the impact of radiation therapy complications on post-mastectomy implant-based breast reconstruction surgeries in patients of Hispanic descent. We demonstrate that the rate of capsular contracture is significantly higher after radiation therapy and the rate of overall complication after radiation therapy is higher (even though non statistically significant) compared with patients who do not undergo radiation. While these results are comparable to similar studies done in non-Hispanic groups, this is the first study to our knowledge that has looked at post-mastectomy complications focusing specifically on a Hispanic population. Mastectomy and subsequent implant reconstruction, radiation, and complications can have negative psychological effects on patients and can manifest differently with varying cultural backgrounds. It is imperative to understand the complications associated with race to better allow practitioners to cater treatment and support for a diverse patient population with breast cancer.

Table 1: Complications

<table>
<thead>
<tr>
<th></th>
<th>With Radiation</th>
<th>No Radiation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection needing antibiotics</td>
<td>6/46 (13%)</td>
<td>23/296 (7.8)</td>
<td>0.467</td>
</tr>
<tr>
<td>Capsular contracture Baker II-IV</td>
<td>11/46 (23.9%)</td>
<td>31/296 (10.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Implant loss</td>
<td>14/46 (30.4%)</td>
<td>43/296 (14.5%)</td>
<td>0.081</td>
</tr>
</tbody>
</table>

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Brianna Conte, n/a: No financial relationships to disclose
Caroline Shermoen, n/a: No financial relationships to disclose
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Patterns in palliative care use and their impact on survival in the elderly metastatic breast cancer (MBC) population: a National Cancer Database (NCDB) Analysis

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Country: United States
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Country: United States

Background: About 6% of patients diagnosed with breast cancer (BC) will have metastatic disease at time of diagnosis. In this case, treatment is palliative and focused on systemic therapies. Both American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend early integration of palliative care (PC) for patients with metastatic disease to improve symptom management and quality of life while potentially decreasing mortality. However, the frequency by which elderly patients with metastatic breast cancer (MBC) receive PC is unknown. This is especially relevant as improvements in health care have allowed for longer life expectancy and an increase in America’s aged population. The goal of this study was to use the NCDB to describe national patterns in PC use in elderly patients over 75 years of age with MBC and evaluate differences in overall survival (OS).

Methods: Women with a diagnosis of BC at age >/= 75 years and with metastases at time of initial diagnosis from 2010 to 2019 were identified from the NCDB. Patients were stratified into age subgroups of 75-79, 80-84, and >/= 85 years. Chi-square tests were used to compare categorical variables. Kaplan Meier curves were used to determine OS distributions for patients by age and receipt of PC. Log-rank tests and multivariable cox proportional hazards modeling was performed to assess the difference in OS between patients who received and did not receive PC.

Results: Of 17,325 eligible women included in the final analysis, 39.4% were 75-79, 30.1% 80-84, and 30.4% >/= 85 years of age. Overall, 20.5% of patients utilized PC. The table below describes the baseline characteristics of patients who received PC versus those who did not.
Rates of PC utilization varied among the age subgroups, with the lowest utilization in the >/= 85 years of age group, p< 0.0001. Performance status as measured by Charlson-Deyo Score did not impact rates of PC use, p=0.3196. Use of PC varied across races with higher use in Non-Hispanic White patients and lower in Hispanic and Non-Hispanic Black subgroups, p< 0.0001. In the overall population, the use of PC increased from 17.9% in 2010 to 23.2% in 2019, p=0.0003. This was primarily driven by the statistically significant increase in the 75-79 age group (18.4% to 26.8%, p=0.0003). Although there were numeric increases in PC use from 2010 to 2019 in the 80-84 (20.9% to 24%, p=0.2899) and >/= 85 (13.9% to 17.9%, p=0.1082) age groups, these differences were not statistically significant. Palliative care receipt did not
impact overall survival. Three-year OS rates were 27.8% (CI: 26.1-29.5) and 27.8% (CI: 27.0-28.7), for patients who received PC compared to those who did not, respectively, p=0.512.

Conclusions: Over the last decade, we observed an increase in PC utilization in patients >/= 75 years with MBC. However, significant increases were only seen in the 75-79 age group. Palliative care use was lower among patients >/= 85 years compared to those 75-79 or 80-84 years of age. Performance status did not influence receipt of PC. There were no differences in OS between elderly patients who received PC versus those who did not. Future follow up analyses will be needed to determine the impact of PC on OS in this population. Clinicians should be encouraged to integrate PC into the treatment of elderly patients with MBC, particularly those >/= 85 years, as this can improve symptoms and quality of life.

Table 1. Patient Baseline Characteristics by Palliative Care Receipt

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N=17,705 (%)</th>
<th>No Palliative Care N=13,705 (79.5%)</th>
<th>Received Palliative Care N=3,960 (20.5%)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>70-79 yrs</td>
<td>6,834 (39.4)</td>
<td>5,376 (39.1)</td>
<td>1,458 (41.0)</td>
<td></td>
</tr>
<tr>
<td>80-84 yrs</td>
<td>5,218 (30.1)</td>
<td>4,076 (30.6)</td>
<td>1,142 (32.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;/= 85 yrs</td>
<td>5,273 (30.4)</td>
<td>4,373 (31.3)</td>
<td>900 (27.1)</td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6,521 (36.6)</td>
<td>5,452 (40.4)</td>
<td>1,069 (26.9)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>13,014 (73.4)</td>
<td>9,252 (68.6)</td>
<td>3,762 (93.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>597 (3.4)</td>
<td>517 (3.9)</td>
<td>80 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>652 (3.7)</td>
<td>538 (4.0)</td>
<td>114 (3.4)</td>
<td></td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
<td></td>
<td></td>
<td>0.3196</td>
</tr>
<tr>
<td>0</td>
<td>12,271 (70.6)</td>
<td>9,770 (71.6)</td>
<td>2,502 (70.5)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3,177 (18.0)</td>
<td>2,486 (18.5)</td>
<td>691 (17.6)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1,141 (6.4)</td>
<td>899 (6.7)</td>
<td>242 (6.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;/=3</td>
<td>176 (1.0)</td>
<td>61 (0.4)</td>
<td>115 (3.0)</td>
<td></td>
</tr>
</tbody>
</table>

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Rima Patel, MD: No financial relationships to disclose
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Patient-reported outcomes, perceptions, and knowledge about recurrence in women with high-risk hormone receptor-positive (HR+) breast cancer (BC)

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Background: Over half of HR+ BC recurrences occur >5 years (y) from diagnosis (dx). While the risk of late recurrence is constant and extends for at least 20y, little is known about concerns, perceptions, knowledge, and interest in risk reduction in longer-term HR+ BC survivors.
Methods: From 1/2021-1/2022, we prospectively identified patients (pts) at Dana-Farber Cancer Institute with a history of stage II/III, HR+/HER2- BC, ≥5y from dx, without recurrence. Pts were invited to participate in a study investigating circulating tumor DNA and risk of recurrence as well as a separate, 1-time survey that assessed physical/mental health (PROMIS), dx/treatment concerns (Brief Illness Perception Questionnaire), risk perceptions, knowledge, and interest in risk reduction. “Overestimation” was defined as estimating ≥20% risk based on the response to the question: “If 100 women with HR+ BC are treated according to recommended guidelines, about how many will have BC come back in the 5-10y following completion of active treatment.” Descriptive statistics included medians and proportions. Logistic regression identified factors associated with overestimation of 5-10y metastatic recurrence risk.

Results: Among 166 women (of 209 sent surveys, 79%), median age at dx was 51 (range 21-76), 4% were Hispanic and/or Black; 19% did not have a college degree. Approximately 30% had stage III disease, most received chemotherapy (72%) and radiation (81%) and over half (57%) a mastectomy. Median time from dx was 10 y (range: 5-23). Almost all (97%) reported prior (44%) or current hormonal therapy (14% tamoxifen, 39% AI). Median PROMIS anxiety (53; range: 37-73), physical (51, range: 32-68), and mental (51, range: 25-68) scores were similar to population norms (score of 50). On a 0 (not at all)-10 (extremely) scale, the median rating for concern about dx/treatment was 5; for emotional impact of dx/treatment, the median rating was 9. Regarding risk perceptions, participants estimated that on average, a median of 15 and 10 women (of 100 women) would develop a loco-regional or distant recurrence, respectively, in the 5-10y interval; 43% and 40% estimated the risk of loco-regional and distant recurrence as ≥20%, respectively, for this interval. Pts without a college degree were more likely to overestimate 5-10y distant recurrence risk (multivariable OR: 3.66, 95% CI: 1.56, 8.59); age, chemotherapy receipt, surgery type, stage, and grade were not associated with overestimation. When asked, on average, which women have a higher chance of BC returning after 5y, 17% correctly responded HR+; 42% responded triple negative and 41% responded the risk was the same for both. While >1/3 responded they believed alcohol in moderation may decrease the risk of BC coming back, most also responded that having a healthy weight, eating ≥5 fruits/vegetables a day, and exercise may decrease this risk, with over half reporting engagement in these behaviors (Table).

Conclusion: While most longer-term stage II/III HR+ BC survivors report mental and physical health commensurate to population norms, inaccurate knowledge and perceptions about recurrence are common. Strategies to effectively communicate risk (e.g., pictograms, decision/conversation aids) and risk reduction information can promote an accurate understanding of risk in the setting of longer-term HR+ BC survivorship, potentially mitigating emotional concerns which are prevalent ≥5y post-dx. The association between lower educational attainment underscores the importance of attention to literacy and numeracy when developing interventions to improve risk communication.

Table. Perceived impact of health behaviors on recurrence risk
<table>
<thead>
<tr>
<th>Belief that behavior affects recurrence</th>
<th>Healthy weight (%)</th>
<th>≥5 fruits/vegetables/day (%)</th>
<th>≥30 min moderate-vigorous exercise ≥5 days (%)</th>
<th>Alcohol in moderation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May increase chance</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Makes no difference</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>May decrease chance</td>
<td>82</td>
<td>89</td>
<td>91</td>
<td>37</td>
</tr>
<tr>
<td>Don't know</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Engaged in behavior because it decreases recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59</td>
<td>59</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>15</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>No but I want to</td>
<td>29</td>
<td>26</td>
<td>33</td>
<td>-</td>
</tr>
</tbody>
</table>

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**Shoshana Rosenberg, ScD, MPH:** Pfizer: Contracted Research (Ongoing)

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Patient-reported anxiety and fatigue in women enrolled in the RxPONDER trial (SWOG S1007) by menopausal status

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Introduction: Anxiety and fatigue have been reported by women undergoing cytotoxic and endocrine treatment (tx) for breast cancer and can have lasting effects on quality of life (QoL). The differential effects of menopausal (meno) status, tx allocation and duration of symptoms are not well established.

Methods: Participants (pts) with hormone receptor positive, HER2 negative breast cancer with 1-3 positive lymph nodes and an Oncotype DX recurrence score of 0-25 enrolled in the RxPONDER trial were randomly assigned to endocrine therapy (ET) alone vs chemotherapy followed by ET (CET). A subset of English speaking pts in the US at the start of the trial were invited to complete health-related QoL (HRQoL) questionnaires shortly after randomization (baseline; BL) and 6, 12, and 36 months after BL until accrual goal reached. BL surveys were completed in clinic; cognitive function results presented separately. Standardized T scores (mean 50; SD 10) were computed for anxiety (PROMIS Emotional Distress – Anxiety Short Form 7a) and fatigue (PROMIS Fatigue Short Form 7a). Higher T scores indicate more anxiety or fatigue. The primary endpoint of this exploratory analysis was to compare mean anxiety and fatigue T score by tx arm by meno status. Separately by meno status, a GEE model was fit to the three follow-up timepoints adjusting for BL to estimate the difference between tx arms and whether there was a time trend over the three follow-up measures.

Results: The accrual exceeded the goal of 500 pts with 74% of pts participating voluntarily until
the QOL invitation was removed from the protocol (12/1/12). A total of 139 pre and 432 postmenopausal pts completed the anxiety questionnaire at BL. There was no difference in anxiety between tx arms [Table 1]. Mean anxiety score difference between CET and ET over time in the premenopausal cohort was -0.63 (p=0.63) and in the postmenopausal cohort was 0.59 (p=0.45). Although anxiety scores decreased over the three follow-up times, the change was not statistically significant.

A total of 139 pre and 429 postmenopausal pts completed the fatigue questionnaire at BL. Fatigue mean T scores in both the pre and postmenopausal cohorts were higher over time in the CET vs ET arm [Table 2]. Fatigue scores were 2.85 points higher for CET vs. ET over time in the premenopausal cohort (p=0.02) and 1.82 points higher in the postmenopausal cohort (p=0.007). Fatigue scores decreased over time for premenopausal (p=0.01), but not for postmenopausal (p=0.62) pts.

Dropoff occurred over time with 79%, 76%, 60% of pts at BL participating at 6, 12, and 36 months. Endocrine treatment adherence data are not yet available at each timepoint.

Conclusions: CET had a clinically significant negative effect on mean fatigue scores compared to ET alone in both pre and postmenopausal pts over time. Scores improved over time but did not return to BL. Pts had lower mean anxiety scores during tx compared to BL, but differences in scores between CET and ET groups out to 3 years did not significantly differ. Future therapeutic studies must continue to include HRQoL assessments to broaden our understanding of the full impact of chemotherapy and for the development of preventative and therapeutic strategies to manage these toxicities.

Table 1. Comparisons of mean Anxiety score by treatment arm and menopausal status

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>Assigned Arm</th>
<th>Randomization</th>
<th>Timepoint</th>
<th>CET vs. ET Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 mos</td>
<td>12 mos</td>
<td>36 mos</td>
</tr>
<tr>
<td>Pre</td>
<td>CET</td>
<td>57.05</td>
<td>50.83</td>
<td>51.62</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>54.97</td>
<td>50.92</td>
<td>49.68</td>
</tr>
<tr>
<td>Post</td>
<td>CET</td>
<td>56.09</td>
<td>50.99</td>
<td>51.40</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>54.54</td>
<td>50.50</td>
<td>48.86</td>
</tr>
</tbody>
</table>

Table 2. Comparisons of mean Fatigue score by treatment arm and menopausal status

<table>
<thead>
<tr>
<th>Menopausal status</th>
<th>Arm</th>
<th>Randomization</th>
<th>Timepoint</th>
<th>CET vs. ET Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 mos</td>
<td>12 mos</td>
<td>36 mos</td>
</tr>
<tr>
<td>Pre</td>
<td>CET</td>
<td>48.11</td>
<td>52.46</td>
<td>51.64</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>49.58</td>
<td>50.30</td>
<td>49.87</td>
</tr>
<tr>
<td>Post</td>
<td>CET</td>
<td>49.99</td>
<td>53.75</td>
<td>52.84</td>
</tr>
<tr>
<td></td>
<td>ET</td>
<td>50.29</td>
<td>51.68</td>
<td>50.88</td>
</tr>
</tbody>
</table>

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Oncologic outcomes of pregnancy after surgical treatment of breast cancer 35 years old or under

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Purpose: Recent advances in the treatment of breast cancer has led to the improvement of breast cancer patient's survival. With prolonged survival of these patients, pregnancy became an important issue, especially in those of young cancer patients aged 35 or under. Increased hormone levels during pregnancy, however, raises concerns of elevating the risk of cancer recurrence. The aim of this study was to validate the notion of increased risk associated with pregnancy after breast cancer treatment in young patients.

Methods: From January 2009 to December 2020, newly diagnosed breast cancer patients of 35 years old or under who underwent curative surgery in Korea University Guro Hospital were enrolled in this study. Patients were categorized into 3 groups: nulliparous, pregnancy prior to treatment of breast cancer, and patients with pregnancy after breast cancer treatment. Their overall survival and disease-free survival were evaluated. Results: A total of 126 patients was enrolled in this study. Seventeen patients (13.4%) conceived and successfully delivered. The mean age of enrolled patients was 32.0 years old (± 3.1), and the mean follow up period after surgery was 56.8 months (± 34.2). There was no significant difference in overall survival (p=0.490) and disease-free survival (p=0.740) among different groups. Among 22 patients with re-diagnosis of breast cancer, 2 of them (9%) had breast cancer on their contralateral breast.

Conclusion: In young patients, pregnancy after treatment for breast cancer did not affect their overall survival or disease-free survival as compared to nullipara or previously delivered groups. Therefore, pregnancy counseling should not be prevented in young breast cancer patients of 35 years old or under.

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Yong Yeup Kim, M.D.: No financial relationships to disclose
Metastatic breast cancer (MBC) is an incurable disease that affects over 168,000 women in the US. Family caregivers play a critical role in patients’ adjustment to MBC by providing practical and emotional support. However, the extensive involvement of caregivers in patient care places them at increased risk for clinically significant psychological distress symptoms. In fact, research has shown that distress is as prominent for caregivers as it is for patients and that it can adversely affect caregiver support to the patient. Distress screening with appropriate triage and follow-up for psychosocial concerns is recognized by the Institute of Medicine (IOM) and National Comprehensive Cancer Network (NCCN) as critical for ensuring high-quality comprehensive cancer care. However, clinical tools to assist with recognizing caregiver distress are sparse, creating a practical barrier for caregivers to obtain needed psychosocial support. The NCCN Distress Thermometer (DT) is a validated single-item self-report measure that was developed to screen for cancer patient distress. It is often used with the NCCN 42-item Problem List (PL) which identifies sources of distress to help guide providers in making appropriate referrals. Although the DT has been validated for use with caregivers, most adult oncology practices have yet to establish protocols for identifying caregivers with high distress levels. Part of the problem is that many PL items ask about physical and other concerns that are related to either having or undergoing treatment for cancer. Developing a caregiver-focused PL could thus not only improve clinical uptake of distress screening for cancer caregivers, but also enable greater integration of family-centered support services as part of routine cancer care. With these goals in mind, this mixed-methods study sought to inform development of a PL to address the unique concerns of cancer caregivers. Methods: Caregivers of MBC patients completed a short survey containing sociodemographic questions and the NCCN DT. They also participated in semi-structured interviews about their role in symptom management, psychosocial impacts of cancer, and unmet needs. Interviews were audio-recorded and transcribed. The five NCCN problem domains (i.e., physical, emotional, family, practical, and religious/spiritual concerns) that have been identified as sources of distress were used to guide thematic analysis. Results: Nineteen caregivers (63.2% female; 47.4% racial/ethnic minorities) participated. Most were middle aged (M = 54.4, SD = 16.4) and either spouses (42.1%) or adult children (31.6%). Surveys revealed that caregivers had moderate distress levels (M=4.4 out of 10, SD=3.1); 53% exceeded the DT cut-off of 5, warranting further psychological evaluation. In the interviews, caregivers reported an average of 7.7 concerns (Range = 0 to 17 concerns). The most common issues were worry (63.2%), coping with the patient’s emotions (57.9%), providing emotional support to the patient (52.6%) and assisting with activities of daily living (47.9%). Caregivers also expressed problems coordinating care with other family members, feelings of guilt, and unmet needs for information. Caregivers reporting more concerns reported significantly (p<.05) higher levels of psychological distress. Conclusion: Many of the concerns raised by MBC caregivers did not align with the NCCN PL, suggesting that development of a
caregiver-specific PL is warranted. Additional study is needed to determine whether such a PL could help to efficiently route caregivers to information and resources matching their needs and ultimately help to alleviate their distress.

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Cardiovascular Risk Evaluation for Breast Cancer Survivors: A Pilot Study

Introduction
Breast cancer (BC) is the most common cancer in women in the United States (US). With advances in screening and treatment, there are increasing numbers of BC survivors. Preexisting or emerging cardiovascular (CV) risk factors and some cancer therapies put BC survivors at risk for long-term CV disease (CVD). ASCO clinical practice guidelines for prevention and monitoring of cardiac dysfunction recommend treatment of CV risk factors in cancer survivors, however, the application of these guidelines in clinical practice presents several challenges. In this pilot study, we describe the feasibility of performing CVD risk assessment in a cohort of BC survivors in a single institution in an urban area that serves mostly Black/African American (AA) populations.

Methods
We identified patients with early-stage BC treated between 2015 and 2022. Patients underwent CVD risk assessment including vital signs, hemoglobin A1c, lipid panel, transthoracic echocardiogram (TTE), 6-minute walk test (6MWT), troponin T, and B-type natriuretic peptide...
(NT-ProBNP). The primary objective of the study was to describe the feasibility of performing a CVD risk assessment.

Results
Out of 69 eligible patients who were approached for the study, 50 were enrolled and completed the CVD risk assessment (72%). Among 19 patients who did not enroll or complete the risk assessment, time constraints to complete the work up was the predominant factor. The median age was 60.5 years (SD = 13.65; range 34-86), 76% self-identified as Black/AA, 14% as White, and 95% as Non-Hispanic. Half of the patients had hormone-receptor-positive BC, 34% human epidermal growth factor receptor 2 (HER2) positive disease (and received HER2-targeted therapies), and 28% triple-negative breast cancer (TNBC). In terms of treatment, 34% received anthracycline-containing regimens. CVD risk assessment results are shown in Table 1. Twenty-four (48%) of the patients had metabolic syndrome defined as the presence of 3 out of 5 CV risk factors (waist circumference, hypertension, low HDL, high triglycerides, insulin resistance). Although all patients had an ejection fraction (EF) above 55%, 7 patients (14%) had an abnormal global longitudinal strain (GLS). The median number of meters in the 6MWT was 369 (SD 94.46, range 67-531); 74% of patients walked a shorter distance than predicted by age and body mass index, indicating significant physical impairment. All patients had a troponin T value below the 99th percentile. The most frequent modifiable CVD-risk factors included obesity and hypertension.

Conclusion
Performing a low-cost CVD risk assessment in a population of mostly Black/AA BC survivors was feasible in this pilot study. We identified a high prevalence of CVD risk factors, with 48% of patients meeting metabolic syndrome criteria and the majority of patients demonstrated a very high level of functional impairment measured by 6MWT. Our findings underscore the importance of survivorship care focused on CVD risk in BC survivors. Limitations include the small sample size, single-institution study, and lack of CV and BC-related outcomes. The higher incidence of TNBC could be explained by a selection bias of patients receiving cytotoxic chemotherapy and the higher incidence of TNBC in the Black/AA population. Future research will focus on implementing this assessment in the survivorship clinic and establishing interventions to decrease CVD risk in cancer survivors.
Table 1: Clinical Measurements & Outcomes (n=50)

<table>
<thead>
<tr>
<th>Outcome or characteristic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-existing conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16</td>
</tr>
<tr>
<td>Current or previous smoking</td>
<td>38</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 18.5 (underweight)</td>
<td>2</td>
</tr>
<tr>
<td>18.6-25 (normal weight)</td>
<td>16</td>
</tr>
<tr>
<td>25.1-29.9 (overweight)</td>
<td>26</td>
</tr>
<tr>
<td>≥ 30 (obese)</td>
<td>46</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 130 and/or ≤ 80 mmHg</td>
<td>40</td>
</tr>
<tr>
<td>&gt;130 and/or &gt;80 mmHg</td>
<td>60</td>
</tr>
<tr>
<td><strong>LDL (mg/dl)</strong></td>
<td></td>
</tr>
<tr>
<td>≤110</td>
<td>54</td>
</tr>
<tr>
<td>111-129</td>
<td>18</td>
</tr>
<tr>
<td>≥ 130</td>
<td>28</td>
</tr>
<tr>
<td><strong>HDL (mg/dl)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;45</td>
<td>84</td>
</tr>
<tr>
<td>40-45</td>
<td>10</td>
</tr>
<tr>
<td>&lt;40</td>
<td>6</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;74</td>
<td>36</td>
</tr>
<tr>
<td>75-99</td>
<td>20</td>
</tr>
<tr>
<td>&gt;100</td>
<td>44</td>
</tr>
<tr>
<td><strong>Hemoglobin A1c (mg/dl)</strong></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;5.7)</td>
<td>46</td>
</tr>
<tr>
<td>Prediabetes (5.8-6.5)</td>
<td>34</td>
</tr>
<tr>
<td>Diabetes (&gt;6.5)</td>
<td>16</td>
</tr>
<tr>
<td><strong>Cardiac Biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal NT-proBNP (&gt;125 pg/mL)</td>
<td>12 (range 133-523)</td>
</tr>
<tr>
<td><strong>Echocardiogram</strong></td>
<td></td>
</tr>
<tr>
<td>Global longitudinal strain &lt; -18 %</td>
<td>23 (range -14.4 -17.9)</td>
</tr>
</tbody>
</table>

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An international survey on invasive lobular breast cancer (ILC) reveals gaps in knowledge and top priority research areas

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Background:
There is growing awareness of the unique etiology, biology, clinical presentation and progression of Invasive lobular breast cancer (ILC), but additional research is needed to assure translation of findings into management and treatment guidelines. We performed a survey to: 1) analyze the landscape of the current understanding of ILC, and 2) identify consensus research questions on ILC.

Methods:
The IRB-approved survey was developed with input from representatives of three major stakeholder groups - breast cancer clinicians/researchers, laboratory-based researchers, and advocates/patients. We fielded the survey from March to May 2022 using targeted email and via social media.

Results:
1,774 participants answered at least one question and 1,310 finished the survey. Participants are from 66 countries from all continents (except Antarctica). Respondents self-identified as clinicians (mostly medical oncologists and surgeons) (N=413), researchers (N=376), and breast cancer patients (1,121), with some belonging to more than one category. 26% of the patients who participated in the survey belong to advocate groups.

Only 46% of clinicians reported being confident in describing the differences between ILC and no special type (NST) (invasive ductal) breast cancer. Knowledge of histology was seen as important (73%), affecting their treatment decisions (51%), and refined treatment guidelines
would be valuable for patients with ILC in the future (76%). 85% of clinicians have never powered a clinical trial to allow subset analysis for histological subtypes, but the majority would consider it. 88% would participate in a consortium to conduct clinical trials on ILC. The top two most important research questions were: 1) determining mechanisms of endocrine resistance, and, 2) identifying novel therapeutic targets, repurposing existing drugs and progressing them to clinical trials.

Of the researchers, 48% reported being confident in describing differences between ILC and NST. They reported that ILCs are inadequately presented in large genomic data sets (52%), and that ILC models are insufficient (42%). Only 13% of respondents have inadequate access to tissue or blood from patients with ILC. The top two most important research questions identified by the laboratory researchers overlapped with those identified by the clinicians, i.e. understanding of endocrine resistance and identifying novel drugs that can be tested in clinical trials.

The majority of patients (52%) thought that their health care providers did not explain unique features of ILC, and that in general communication was limited. When asked about top research question, they chose: 1) Improvement of ILC screening/early detection, and, 2) Identifying new and specific imaging tools for ILC.

When comparing top priority topics across six research domains, there was a high degree of consistency, especially among clinicians and researcher, but less so when compared with the breast cancer patients (Table 1).

Conclusion:
In summary, we have gathered timely and representative information from an international community of clinicians, researchers, and patients/advocates that we expect will lay the foundation for a community-informed collaborative research agenda, with the goal of improving the management and personalizing treatment for patients with ILC.

TABLE 1: Ratings by all three stakeholder groups of the most critical and impactful ILC research topics. Top box scores between stakeholder groups were compared using chi-square analysis.
<table>
<thead>
<tr>
<th>Most Critical and Impactful Research Questions</th>
<th>Clinicians</th>
<th>Lab Researchers</th>
<th>Patients/Advocates</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology and Risk Reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy, Treatment Resistance and Disease Progression</td>
<td>43</td>
<td>50</td>
<td>60</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Identifying strategies to improve ILC screening/early detection</td>
<td>68</td>
<td>73</td>
<td>93</td>
<td>&lt;.0002</td>
</tr>
<tr>
<td>Impact of obesity and lifestyle factors on risk of developing ILC and risk of relapse</td>
<td>38</td>
<td>38</td>
<td>50</td>
<td>0.0006</td>
</tr>
<tr>
<td>Diagnosis (Imaging and Pathology)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examining use of IHC to predict ILC prognosis</td>
<td>52</td>
<td>55</td>
<td>74</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Improving diagnosis and understanding of ILC/ILC</td>
<td>50</td>
<td>56</td>
<td>65</td>
<td>0.0002</td>
</tr>
<tr>
<td>Understanding the use of artificial intelligence</td>
<td>41</td>
<td>37</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Role of genomic predictors for ILC prognosis and prediction of therapeutic response</td>
<td>75</td>
<td>78</td>
<td>76</td>
<td>0.6822</td>
</tr>
<tr>
<td>Identifying strategies to improve ILC screening/early detection</td>
<td>73</td>
<td>73</td>
<td>90</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Therapy, Treatment Resistance and Disease Progression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identifying mechanisms of metastasis</td>
<td>71</td>
<td>75</td>
<td>88</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Determining mechanisms of estrogen resistance in ILC</td>
<td>81</td>
<td>80</td>
<td>84</td>
<td>0.342</td>
</tr>
<tr>
<td>Identification of novel therapeutic targets and/or repurposing existing drugs for ILC</td>
<td>78</td>
<td>81</td>
<td>84</td>
<td>0.1775</td>
</tr>
<tr>
<td>Determining ability of immunotherapy in ILC</td>
<td>65</td>
<td>60</td>
<td>79</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Understanding value of liquid biopsies in patients with ILC</td>
<td>52</td>
<td>56</td>
<td>73</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Characterizing chemotherapy in ILC and understanding differences to IDC</td>
<td>74</td>
<td>67</td>
<td>77</td>
<td>0.0034</td>
</tr>
<tr>
<td>Determining mechanisms of dormancy and risk for late relapse</td>
<td>70</td>
<td>73</td>
<td>87</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Developing and testing lifestyle interventions</td>
<td>34</td>
<td>32</td>
<td>48</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimizing current breast cancer screening modalities</td>
<td>62</td>
<td>60</td>
<td>83</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Identifying new and specific imaging tools for ILC</td>
<td>65</td>
<td>68</td>
<td>92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Studying the importance of breast density</td>
<td>44</td>
<td>42</td>
<td>78</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Determining the utility of MRI</td>
<td>65</td>
<td>58</td>
<td>80</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Local therapy of the Primary Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determining how to reduce the high positive margin rates in ILC</td>
<td>66</td>
<td>60</td>
<td>76</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Characterizing further whether breast conservation/radiation is as safe as mastectomy</td>
<td>52</td>
<td>50</td>
<td>63</td>
<td>0.0003</td>
</tr>
<tr>
<td>Determining whether radiotherapy can replace axillary surgery in ILC</td>
<td>57</td>
<td>53</td>
<td>61</td>
<td>0.039</td>
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<tr>
<td>Characterizing differences in post-mastectomy radiation between ER+ IDC and ER- ILC</td>
<td>50</td>
<td>42</td>
<td>61</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Basic/translational research question</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determining cell of origin for ILC</td>
<td>39</td>
<td>43</td>
<td>73</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Development of a centralized ILC data and tissue registry</td>
<td>56</td>
<td>70</td>
<td>77</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Developing and characterizing ILC models</td>
<td>47</td>
<td>70</td>
<td>71</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Characterizing differences in the tumor microenvironment between ILC and IDC</td>
<td>54</td>
<td>71</td>
<td>72</td>
<td>0.0001</td>
</tr>
<tr>
<td>Understanding of LCIS as a precursor of ILC</td>
<td>43</td>
<td>46</td>
<td>60</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Characterizing subtypes of ILC (pleomorphic, mixed etc.)</td>
<td>47</td>
<td>51</td>
<td>63</td>
<td>0.0001</td>
</tr>
<tr>
<td>Understanding of the unique etiology of ILC</td>
<td>46</td>
<td>49</td>
<td>66</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Green: Highest rating within domain by stakeholder group
* Med: Highest 2 ratings by group across all domains

Disclosure(s):

Steffi Oesterreich, PhD: Astrazeneca: Contracted Research (Ongoing); Ocean Genomics: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing); puma: Contracted Research (Ongoing); UPMC Enterprise: Employee (Ongoing)

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Active surveillance versus conventional treatment in low-risk DCIS; women’s preferences in the LORD trial

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Background: Ductal carcinoma in situ (DCIS) is a potential precursor to breast cancer. Its incidence has increased multifold with the introduction of breast cancer screening and makes for 20% of all malignant breast lesions in women. DCIS has the potential to progress into invasive breast cancer. However, the majority of DCIS lesions are indolent and will never progress during the patient’s lifetime. Consequently, there is a growing concern of
overdiagnosis and overtreatment for women with DCIS. The LORD trial is a non-randomized, patient preference trial comparing active surveillance to conventional treatment (i.e., breast conserving surgery with or without radiotherapy or mastectomy). The primary outcome of this trial is the percentage of women without an occurrence of ipsilateral invasive breast cancer after 10 years of follow up. Within the patient preference design, women are free to opt for either treatment arm. In addition to active surveillance of the DCIS, quality of life (QOL) of women included in the LORD trial is also actively monitored. The aims of this study were to: a) describe the distribution of participants within the treatment arms, b) identify women’s motives to opt for their preferred treatment arm, and c) assess factors associated with a preference for either treatment arm. Methods: Data from the baseline patient QOL questionnaire was collected. This questionnaire was completed after the women’s diagnosis and first consultation with their physician. Descriptive statistics were used to assess the distribution in both treatment arms. Thematic analyses were used to describe self-reported reasons for treatment selection derived from the open-ended question about treatment preference. Multivariable logistic regression analyses were used to assess associations between the patient characteristics and their preferred treatment arm. Results: In total 384 women completed the baseline questionnaire, of which 376 entered their final treatment decision. Of these women, 287 (76%) opted for active surveillance and 89 (24%) for conventional treatment. Most frequently cited reason for opting for active surveillance was that treatment was not yet necessary (55%). Also, patients’ reasons for preferring active surveillance alluded to a high level of trust in the active surveillance plan (24%) and that disease progression could be picked up and treated in a timely manner (14%). Furthermore, 11% of patients cited the advice of their healthcare professional as a reason for opting for active surveillance and 8% cited reasons relating to altruism. Most reported reasons for opting for the conventional treatment arm were avoiding unnecessary risks (26%), avoiding cancer worry (18%), the notion that what doesn’t belong, should be removed from the body (18%) and a need for closure (13%). In multivariable logistic regression analyses, high level of education (OR 2.17; 95%CI 1.09-4.38) and higher knowledge score (OR 1.8; 95%CI 1.07-3.02) were associated with a preference for conventional treatment. Furthermore, women opting for active surveillance more often reported the decision to be a shared decision between them and their healthcare professional (OR 2.30; 95%CI 1.18-4.47) compared to women who chose conventional treatment, who more often reported decision-making to be patient-driven. Age and tolerance of uncertainty were not significantly associated with treatment preference. Conclusion: The LORD trial is the first to actively offer women with low-risk DCIS a choice between conventional treatment and active surveillance. Within this trial, most women opt for active surveillance, even though clinical guidelines still recommend treatment for all women with DCIS. Women with low-risk DCIS report high levels of trust in their physicians and the safety of active surveillance. Their preferences also highlight the necessity to proof that de-escalating treatment of low-risk DCIS is safe.

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Understanding Patient Perspectives on Window of Opportunity Clinical Trial Participation in Breast Cancer

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Background: Window of opportunity (WOO) clinical trials take advantage of the waiting period between a patient’s cancer diagnosis and standard treatment (usually surgery) to evaluate novel cancer therapies and their biologic effects in vivo. These types of trials are being increasingly harnessed in the clinical setting for the safe and rapid evaluation of novel therapeutic strategies in treatment naive patients, thereby expediting drug development. Distinct from neoadjuvant trials, no therapeutic benefit is envisaged and the patient’s standard treatments are not intentionally delayed. The purpose of this study was to understand the
patient motivations and perspectives for participating in WOO trials. Methods: This study was conducted at an academic cancer center where two breast cancer WOO trials were ongoing (NCT04781725 and NCT04676516). Eligible patients with newly diagnosed operable invasive breast cancers participating in either of these WOO trials were recruited to this separate study. Patients were provided with a questionnaire that surveyed their motivation and perspectives for participation or lack of participation in the WOO trial Results: From April 2021- May 2022, the study recruited 89 patients with age ranging from of 40-78 yrs with tumors ranging from 1.5-4.3 cm. Surgical wait times ranged from 2-8 weeks. Of the 83 patients that participated in a WOO trial, the most common reasons for participation included (a) the potential to benefit other patients in the future (90%) (b) trust in their treating doctor (88%), (c) desire to contribute to scientific research (62%) and (d) a belief that they may benefit from the therapy (39%). For these patients, 49% reported that the possibility of a repeat biopsy would not deter them from trial participation; whereas 11% said that it definitely would. Of the 6 patients that chose not to participate in a WOO trial the most common reasons included (a) travel or transportation issues (50%) and (b) lack of belief of potential benefit to them (33%). For these patients, when asked whether the participation of a cancer patient in the design of the WOO trial would change their mind, all reported that it would not make a difference. Conclusion: WOO trials are becoming increasingly common in oncology research. Understanding patient perspectives for WOO trial participation is useful to inform trial design and communication approaches in future WOO trial efforts.

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Gregory R. Pond, PhD PStat: Astra-Zeneca: Consulting Fees (e.g., advisory boards) (Terminated, March 1, 2021); Merck: Consulting Fees (e.g., advisory boards) (Terminated, July 1, 2021); Profound Medical: Consulting Fees (e.g., advisory boards) (Ongoing); Roche: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing); Takeda: Consulting Fees (e.g., advisory boards) (Ongoing)
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The Psychological Impacts of COVID-19 on Breast Cancer Patients in China

Background: Approximately 30% to 50% of breast cancer patients experienced mental distress prior to the advent of COVID. The delayed access to cancer treatment due to the outbreak of COVID-19 pandemic posed a unique challenge to breast cancer patients and caused a significant level of mental distress among them. In the current research, we examined the psychological impacts of COVID on breast cancer patients in China using Symptom Checklist-90-R (SCL-90-R).

Method: Participants were breast cancer patients at the outpatient clinic of Xijing hospital. The study was conducted virtually, and the questionnaires were distributed via Wenjuanxing, the Chinese alternative of Qualtrics. The researchers were healthcare workers affiliated with Xijing hospital, and the survey was sent to a breast cancer patient support group which included 1399 cancer patients and 6 healthcare workers. The initial sample consisted of 199 participants who signed an informed consent form to participate in the study. The inclusion criteria were as follows: 1) diagnosed with breast cancer, 2) aged 18 years or above, and 3) had no history of cognitive impairment or previous diagnosis of psychiatric disorders. The validated Mandarin version of the SCL-90-R (Wang, 1984) was then given to the participants to evaluate their psychological status. Categorical variables were summarized as numbers and percentages; continuous variables were described as mean (M) ± standard deviation (SD). Data were analyzed using IBM SPSS Statistics Version 26.

Results: Participants (N = 195) filled out the SCL-90 questionnaire in February, 2020. All participants were female breast cancer patients treated at Xijing hospital, among which 16.41%, 36.41%, 19.49%, and 28.21% had respectively received treatment for less than a year, 1-3 years, 3-5 years, and 5 years or more. 64.62% of the patients were at stage I; 0.77% were at stage II and III; 4.62% were at stage IV according to TNM classification. The molecular type of participants...
is as follows: 47.2% of ER+ HER2-, 31.8% of HER2+, and 21.0% of Triple negative. Participants whose treatments continued to be delayed, on average, reported an elevated general psychopathology score ($M = 1.48$, $SD = 0.47$) compared to participants whose treatments were resumed ($M = 1.30$, $SD = 0.34$), and the difference was statistically significant, $t(193) = 2.96$, $p = .003$, $d = 0.44$, 95%CI [0.06, 0.30]. The one-way ANOVA revealed a marginally significant effect of length of treatment delay on general psychopathology score, $F(4, 190) = 2.09$, $p = .08$, $\eta^2 = .04$. Follow-up multiple comparison analysis showed that participants who had their treatment delayed for 3 weeks to 1 month ($M = 1.70$, $SD = 0.70$) reported significantly higher general psychopathology scores than participants whose delay in treatment was less than 1 week ($M = 1.34$, $SD = 0.40$), $p = .05$. General health status ($p < .001$) and current treatment status ($p = .02$) are the only two variables that were statistically associated with general psychopathology score. Poorer perceived health status and current delay in treatment were associated with higher general psychopathology score. Additionally, younger age was associated with higher interpersonal sensitivity ($p = .01$) and hostility ($p = .006$).

Conclusions:
We found that breast cancer patients at an advanced stage were more likely to experience psychological symptoms with longer treatment delay, and whose treatments continued to be delayed reported elevated psychological symptoms than individuals whose treatment were resumed, regardless of treatment type. Additionally, a treatment delay of more than three weeks might have exacerbated breast cancer patients’ psychological symptoms, whereas a short-term delay of less than three weeks was less likely to have a significant effect on one’s mental well-being.

Table 1: Demographic Characteristics and Health Status of The Participants
<table>
<thead>
<tr>
<th>Marital Status</th>
<th>Number of Patients</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>177</td>
<td>90.8</td>
</tr>
<tr>
<td>Single, widowed, or separated</td>
<td>18</td>
<td>9.2</td>
</tr>
</tbody>
</table>

| Education                      |                    |                        |
| Middle school or below         | 109                | 55.9                   |
| High school or above           | 86                 | 44.1                   |

| Occupation                     |                    |                        |
| Unemployed or self-employed    | 44                 | 22.6                   |
| Employed for wage              | 80                 | 41.0                   |
| Retired                        | 71                 | 36.4                   |

| Age                            |                    |                        |
| ≤ 45                           | 55                 | 28.2                   |
| 46-55                          | 95                 | 48.7                   |
| 56-65                          | 32                 | 16.4                   |
| > 65                           | 13                 | 6.7                    |

| General Health Status          |                    |                        |
| Excellent                      | 31                 | 15.9                   |
| Great                          | 105                | 53.8                   |
| Fair                           | 51                 | 26.2                   |
| Poor                           | 8                  | 4.1                    |

| Length of Treatment            |                    |                        |
| Less than a year               | 32                 | 16.4                   |
| 1-3 years                      | 71                 | 36.4                   |
| 3-5 years                      | 38                 | 19.5                   |
| 5 years or more                | 54                 | 27.7                   |

| Length of Delay                |                    |                        |
| Less than a week               | 82                 | 42.1                   |
| 1-3 weeks                      | 27                 | 13.8                   |
| 2-3 weeks                      | 13                 | 6.7                    |
| 3 weeks to 1 month             | 14                 | 7.2                    |
| More than 1 month              | 59                 | 30.3                   |

| Breast Cancer Stage            |                    |                        |
| Stage I                        | 126                | 64.6                   |
| Stage II and III               | 60                 | 30.7                   |
| Stage IV                       | 9                  | 4.7                    |

| Molecular Type                 |                    |                        |
| ER+ HER2+                      | 92                 | 47.2                   |
| HER2+                          | 62                 | 31.8                   |
| Triple negative                | 41                 | 21.0                   |

Table 2A: Multiple Regression analysis for SCL-90 dimensions
Table 2B: Multiple Regression analysis for SCL-90 dimensions

<table>
<thead>
<tr>
<th>SCL-90 dimension</th>
<th>General Index</th>
<th>Sensation</th>
<th>Obsessive-Compulsive</th>
<th>Interpersonal Sensitivity</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>β</td>
<td>SE</td>
<td>β</td>
</tr>
<tr>
<td>Age</td>
<td>-0.13</td>
<td>0.04</td>
<td>0.54</td>
<td>-0.12</td>
<td>0.54</td>
</tr>
<tr>
<td>Education</td>
<td>-0.05</td>
<td>0.07</td>
<td>-0.01</td>
<td>1.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Occupation</td>
<td>-0.06</td>
<td>0.02</td>
<td>0.31</td>
<td>-0.04</td>
<td>0.31</td>
</tr>
<tr>
<td>General Health</td>
<td>0.34***</td>
<td>0.04</td>
<td>0.15**</td>
<td>0.64</td>
<td>0.27***</td>
</tr>
<tr>
<td>Breast Cancer Stage</td>
<td>-0.01</td>
<td>0.05</td>
<td>-0.10</td>
<td>0.80</td>
<td>0.04</td>
</tr>
<tr>
<td>COVID effect on City</td>
<td>-0.05</td>
<td>0.06</td>
<td>-0.004</td>
<td>0.89</td>
<td>-0.11</td>
</tr>
<tr>
<td>Current Treatment Status</td>
<td>-0.17**</td>
<td>0.06</td>
<td>-0.19***</td>
<td>0.94</td>
<td>-0.14</td>
</tr>
<tr>
<td>Length of Delay</td>
<td>-0.004</td>
<td>0.02</td>
<td>0.65</td>
<td>0.27</td>
<td>-0.007</td>
</tr>
</tbody>
</table>

*p ≤ .05, **p ≤ .01, ***p ≤ .001

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The association of sleep quality with anxiety, depression and social support in breast cancer patients with chemotherapy

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Background: Chemotherapy has side effects on breast cancer patients, and sleep disturbance is one of the common psychological symptoms. Purpose: This study aimed to examine the incidence of sleep disorders and investigate the relationship between anxiety and depression, hope, social support and sleep disorders in breast cancer patients with chemotherapy in China. Results: Total 350 patients were administered questionnaires, and 329 patients completed the questionnaires. The recovery rate was 94%. The majority of participants reported clinically significant sleep disturbance prior to chemotherapy (67.8%), during chemotherapy (71.8%), and after chemotherapy (72.2%). Pearson correlation analysis showed that the higher the direct support, emotional support, social interaction support, informational support and total social support score, the lower the total PSQI score of breast cancer patients (r = -0.212, -0.292, -0.236, -0.271, and -0.195 p< 0.01, respectively). Multifactorial model analysis showed that direct support, anxiety and age were the three main factors that affected sleep quality in breast cancer patients. Conclusions: Social support may provide a powerful tool to reduce anxiety and improve sleep quality in breast cancer patients with chemotherapy.

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Hui Yang, n/a: No financial relationships to disclose
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Jun Guo, n/a: No financial relationships to disclose
Jinnan Gao, n/a: No financial relationships to disclose
Background: Breast cancer patients are faced with treatment choices that can involve complex preference-sensitive decisions. The National Quality Forum initiated a "Call to Action" to integrate shared decision-making (SDM) processes into practice where clinicians and patients work together to make healthcare decisions that align with what matters most to patients. Projects In Knowledge, @Point of Care, Dartmouth and Yale collaborated to develop a pilot educational initiative to address and improve patient-centered care and SDM processes in the institutional cancer care setting.

Methods: Training materials co-developed for the Yale Breast Cancer multidisciplinary team
(N=11: oncologists, nurses/NPs, pharmacist) address SDM, CDK4/6 Inhibitor treatment of metastatic HR+ HER2- breast cancer, and clinician-patient role play methods implementing SDM in treatment discussions/decisions with patients. Reinforcement training, based on interim interview and case role play assessments, was customized to meet specific needs of the team. Qualitative semi-structured interviews and simulation case role play observational methods, using a two-rater system, were used to assess improved SDM performance. Baseline pre-intervention interviews and case role play assessments were compared to interim post-intervention and end of pilot (EOP) post-reinforcement training intervention interviews and case role play assessments (using a Likert scale 0-4 rating score: 0=0%; 1=25% 2=50%; 3=75%; 4=100%). Following the training and assessments, a focus group of team members provided insights into the performance of the group, assessed the acceptability, feasibility, and repeatability of the program, and informed future education.

Results: Semi-structured interview findings revealed that clinicians learned about nuances of CDK 4/6 inhibitors, crystallized their understanding of SDM through reinforcement training (customized in real time), and felt they were better able to implement SDM as a result of their case role play assessments. Training empowered the Yale Breast Cancer team to show pre-to post-education improvement in SDM case role play scenarios, ranging from 16% to 39%. Areas of greatest improvement: 1) determining decision style preference (+36%); 2) determining patients’ risk/burden tolerance (+32%); 3) determining patients’ activation, engagement, and self-efficacy (+34%), 4) determining trade-off decisions with patients (+39%), and 5) determining patients’ readiness to make a decision (+32%). Future research should explore how best to integrate SDM into the real world time restricted clinical practice.

Conclusions: Educational training improved SDM skills for the multidisciplinary Yale Breast Cancer team, which can lead to improved clinician-patient decision-making and patient-centric care. The training process also facilitated team building and encouraged ongoing participation in SDM.

Overall Yale Breast Cancer SDM Pilot Case Study Role-Play Assessments
(Data reflect findings for 11 participants who completed their case role play)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline: Percentage of SDM Domains Addressed (N=11)</th>
<th>End of Pilot: Percentage of SDM Domains Addressed (N=11)</th>
<th>Improvement Baseline vs EOP % Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasonable Options</td>
<td>59%</td>
<td>75%</td>
<td>16%**</td>
</tr>
<tr>
<td>Decision Style Preference</td>
<td>28%</td>
<td>65%</td>
<td>36%**</td>
</tr>
<tr>
<td>Knowledge</td>
<td>47%</td>
<td>71%</td>
<td>24%**</td>
</tr>
<tr>
<td>Risk/Burden Tolerance</td>
<td>33%</td>
<td>63%</td>
<td>32%**</td>
</tr>
<tr>
<td>Activation, Engagement, Self-Efficacy</td>
<td>15%</td>
<td>48%</td>
<td>34%**</td>
</tr>
<tr>
<td>Trade-Off Decisions</td>
<td>32%</td>
<td>71%</td>
<td>39%**</td>
</tr>
<tr>
<td>Readiness</td>
<td>46%</td>
<td>78%</td>
<td>32%**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.005

(Data reflect findings for 11 participants who completed their case role play)

Disclosure(s):
Elaine Rudell, n/a: No financial relationships to disclose
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EMD Serono: Contracted Research (Ongoing)
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Inadequate social contacts and loneliness, often referred to as social isolation (SI), are associated with increased mortality from many diseases, including breast cancer. Up to 41% of breast cancer patients have been identified as feeling socially isolated. Moreover, socially isolated breast cancer survivors have a 43% higher risk of recurrence than socially integrated survivors. To prevent increased mortality, biological mechanisms which mediate the effects of SI on cancer need to be identified. One unexplored, but possible mechanism is through the gut microbiota. Through bidirectional interactions, the gut is affected by stress and the gut microbiota in turn can modulate stress response, host immunity and metabolism. Here we tested the hypothesis that SI induces gut dysbiosis. In our study, repeated in four separate experiments, adult female mice were divided into two groups – those kept group housed (GH, 4 mice per cage) and those housed singly in SI for 4 weeks. Several differences in the gut microbial family, genus and species levels were seen, but the differences were mostly unique to each of the four experiment. Beta-diversity was increased in three of the four studies in SI mice. Since beta-diversity is increased by aging, SI may accelerate the aging process. At the genus level, SI significantly suppressed the abundance of Akkermansia in all four studies and increased Acetatifactor in three studies. These two bacterial changes are expected to disrupt mitochondrial oxidative phosphorylation (OXPHOS), most likely by suppressing the short-chain fatty acid production. Further, low Akkermansia and high Acetatifactor are expected to increase inflammation. In a separate study, we discovered that SI impaired OXPHOS and activated inflammatory pathways in the mammary gland. We also have assessed immune cells in the spleen. SI increased the frequency of pro-inflammatory CD4+RORy+ cells, and the immunosuppressive Treg (CD4+Foxp3+) and PMN-MDSCs cells. In addition, SI increased PD1 expression in Foxp3+ cells, suggesting that anti-PD1 therapy might adversely affect socially isolated breast cancer patients by invigorating Treg cells. We are currently studying if the changes in the gut microbiota in SI mice are causally linked to their impaired mitochondrial metabolism, immunosuppression and increased mammary cancer mortality. We also plan to investigate if dietary modifications can reverse gut dysbiosis in SI mice and prevent their increased mortality from mammary cancer.
Disclosure(s):

**Fabia de Oliveira Andrade, n/a**: No financial relationships to disclose

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**Vivek Verma, n/a**: No financial relationships to disclose

**Maddie McDermott, n/a**: No financial relationships to disclose

**Chris Staley, n/a**: No financial relationships to disclose

**Leena Hilakivi-Clarke, PhD**: No financial relationships to disclose
Recruitment challenges in a UK surgical de-escalation study: preliminary qualitative research findings from the SMALL trial

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Background SMALL (ISRCTN 12240119) is a novel UK phase III multicentre randomised trial comparing vacuum-assisted excision (VAE) to surgery for small screen-detected breast cancers with biologically favourable characteristics. Acceptance by the clinical community and recruitment to SMALL was anticipated to be challenging as it involves randomisation, surgical de-escalation and minimally-invasive percutaneous treatment (VAE). A QuinteT Recruitment Intervention (QRI) has therefore been integrated throughout SMALL’s recruitment period, with the aim of optimising recruitment and informed consent. Methods The QRI in SMALL has involved the analysis of: a) screening log data b) written views from recruiters on the two treatments and their advantages/disadvantages c) in-depth semi-structured interviews with members of the Trial Management Group (TMG) and clinician-recruiters and d) audio-recordings of recruitment discussions with potentially eligible patients. Recruitment challenges were identified and addressed through the provision of written recruitment tips documents, and group and individual feedback sessions with recruiters. Results There was widespread support for the concept of the SMALL trial within the clinical community. Recruiters recognised the pioneering role of SMALL as the only current surgical de-escalation randomised trial in screen-detected breast cancer. Key recruitment challenges revolved around i) healthcare professionals (HCPs) who met patients early in the pathway providing information indicating that they were being referred for surgery (without mentioning SMALL or VAE), ii) concerns around the balance of de-escalation/escalation of different treatment modalities (e.g. some clinicians may prefer to de-escalate radiotherapy in preference to surgery in low-risk patients), iii) challenges in articulating equipoise in a surgical de-escalation trial, iv) patient preferences (primarily for surgery) and recruiter discomfort in exploring/addressing such preferences and v) fewer eligible patients than anticipated. QRI actions to overcome these issues included developing a tips document for HCPs meeting patients early in the pathway, highlighting the need to refrain from making treatment recommendations. A more generic tips document was also developed emphasising the importance of the early introduction of the study, provision of balanced information about both treatments, encouraging recruiters to engage with patients’ concerns and preferences, and adequate explanation of randomisation. Group and individual feedback sessions focussed on two key areas – articulating equipoise through balanced information provision, and considering optimal ways to explore patient preferences where they are expressed. Despite the many set-up and recruitment challenges that arose from opening at the start of the pandemic, SMALL has recruited 142 patients to date from 23 sites, with an approached to randomised patient ratio of ~50%. Conclusion SMALL is a novel surgical de-escalation study in breast cancer, which will provide critical evidence to support reductions in treatment of good prognosis disease. Using a range of qualitative methodology, the QRI has identified both broad support for the study within the clinical community, but has also identified barriers to recruitment at both clinician and patient level. These challenges have been addressed employing a range of methods, and the recruitment level and approach/randomised ratio shows the overall acceptability of this study to patients. Further work will involve interviews with patients, with a focus on their views on de-escalation, and further recruiter feedback sessions. Taken together, these data will help inform the development and design of future de-
escalation and treatment optimisation studies in breast cancer. SMALL is funded by the UK NIHR HTA programme, award 17/42/32

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Background: Developing countries like India share higher burden of deaths due to breast cancer, despite having lower incidence than the west. Greater proportion of patients presenting with advanced stages of cancer is one of the reasons for this disparity. Since the factors leading to such delay have not been well studied in Indian patients, we decided to perform this study.

Methodology: This was an observational study conducted from Jan 2021 to July 2022. Purposive Non-Random sampling was used and patients who had stage 3 or 4 breast cancer and were between 18-80 years of age were recruited. Interview was done on a one-to-one basis in a secluded area. Descriptive statistics were used, and chi-square was used to study the association of socio-demographic and clinical variables with the delay status of the breast cancer.

Results: A total of 75 participants were enrolled in the study with mean age of 52.5 years and SD of 12.5 years. Out of these, 74 had lump as their first symptom. Only 14 of these 74 presented early i.e., within 3 months of onset of symptoms. Rest 60 participants presented late (more than 3 months after onset of symptoms). Between these two groups, difference in incidences of pregnancy associated lumps (0% in < 3 months vs 13.1% in ≥ 3 months, p=0.002), patients being afraid of treatment related complications (0% in < 3months vs 6.6% in ≥ 3 months, p=0.039) and their inability to decide because of lack of knowledge (0% in < 3months vs 6.6% in ≥ 3 months, p=0.039) were statistically significant. To our surprise, the thought that the lump was harmless and painless, embarrassment, limited access to healthcare and distance from the nearest healthcare facility, financial limitations, educational status, socio-economic status, family history of breast cancer, fear of mutilating surgeries and use of traditional medicine or spiritual care didn’t have significant effect on whether the patients presented within or after 3 months of onset of symptoms. On the question of COVID pandemic related delay, only 16% of all patients cited this as an additional reason for delay and this was again, not different between the patients who presented within or after 3 months of onset of symptoms.

Conclusions: Health promotion in terms of proper evaluation of pregnancy related lumps and awareness about the management options of breast cancer may help patients to present earlier to healthcare facilities and may help in improving breast cancer related outcomes in developing countries like India.
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R N NAGA SANTOSH IRINKI, MS, General Surgery: No financial relationships to disclose
Background: Older adults with pre-existing health conditions such as cancer are at higher risks of COVID-related morbidity and mortality. Moreover, the pandemic has triggered new sources of anxiety and stress impairing their quality of life (QoL), such as fear of infection, financial challenges, and social isolation. The goal of this study is to evaluate the changes in QoL of breast cancer patients and survivors during the pandemic and assess whether racial/ethnic minority patients were disproportionately affected. As the COVID-19 vaccines become available, another goal of the study is to examine the vaccination rate and symptoms after vaccination among patients of different racial/ethnic groups.

Methods: Two waves of surveys were sent out to the breast cancer patients registered in the Chicago Multiethnic Epidemiologic Breast Cancer Cohort (ChiMEC) via RedCap in the summers of 2020 and 2021 with response rates of > 48%. To measure anxiety and stress, we calculated an overall score (ranging from 0-44) using 11 questions on a 5-point Likert scale, with lower score representing better QoL. The questions were adopted from existing item banks, and the items showed good internal consistency (Cronbach’s α = 0.84). The second survey also contained questions on vaccination status, concerns, and symptoms after
Results: In the first wave of survey in 2020, no significant racial differences were found in the anxiety/stress scores among the 1300 breast cancer patients. In the second wave of survey in 2021, 1348 patients responded, with 66% of them also respondents of the previous survey. Compared to 2020, the average anxiety/stress score in 2021 decreased from 13.2 to 12.2 for White patients, while increased from 12.8 to 13.6 for Black patients. Mixed effects models showed that the scores worsened significantly for Black patients while improved significantly for White patients. Compared to Whites, Black patients were significantly less confident to find medical help and keep up with work/home responsibilities, while significantly more likely to feel isolated and overwhelmed, and more frequently worried about being sick and going to hospitals. The racial differences in the anxiety/stress scores became insignificant after adjusting for annual household income in multivariate linear mixed effect models. In terms of Covid-19 vaccination, 92.2% of the respondents got vaccinated, with no significant racial/ethnic difference. However, there were more Black patients who had not decided yet or did not respond to this question (Table). The major concerns for patients were the long-term and short-term side effects of the vaccines. In terms of symptoms after vaccination, the most reported symptoms were pain at injection site (62.0%), tiredness (50.2%) and muscle or body aches (30.8%).

Conclusions: Through a longitudinal study, we found that although the anxiety/stress scores of our patients remained moderate, White patients were having improved QoL while Black patients were doing worse. A third wave of survey is planned in the summer of 2022 to further examine this trend. In our study, the vaccination rates were very high among all racial/ethnic groups and the symptoms after vaccination were similar to the ones demonstrated in the general population. We hope that this information can proactively address some patients’ concerns about getting vaccinated.

Table. Summary of the Second Wave of Survey by Racial/Ethnic Groups
Table. Summary of the Second Wave of Survey by Racial/Ethnic Groups

<table>
<thead>
<tr>
<th></th>
<th>Whites (n= 942)</th>
<th>Blacks (n= 304)</th>
<th>Others* (n=102)</th>
<th>p-value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL score, mean (sd)</td>
<td>12.2 (5.9)</td>
<td>13.6 (7.0)</td>
<td>14.2 (5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at diagnosis, mean (sd)</td>
<td>53.9 (11.3)</td>
<td>54.8 (12.8)</td>
<td>47.8 (10.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Years since diagnosis, mean (sd)</td>
<td>7.5 (5.2)</td>
<td>7.9 (5.1)</td>
<td>6.0 (4.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Vaccination status</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>851 (90.3%)</td>
<td>261 (85.9%)</td>
<td>94 (92.2%)</td>
<td></td>
</tr>
<tr>
<td>Not yet, but planned</td>
<td>5 (0.5%)</td>
<td>8 (2.6%)</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Not decided yet</td>
<td>30 (3.2%)</td>
<td>16 (5.3%)</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>No, not planned</td>
<td>32 (3.4%)</td>
<td>6 (2.0%)</td>
<td>3 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Did not respond</td>
<td>24 (2.5%)</td>
<td>13 (4.3%)</td>
<td>3 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Concerns for not getting vaccinated^c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term side effects</td>
<td>47 (75.8%)</td>
<td>16 (72.7%)</td>
<td>4 (100%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Short-term side effects</td>
<td>25 (40.3%)</td>
<td>7 (31.8%)</td>
<td>1 (25.0%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Do not trust government/ CDC</td>
<td>24 (38.7%)</td>
<td>6 (27.3%)</td>
<td>2 (50.0%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Doubt the vaccine’s effectiveness</td>
<td>18 (29.0%)</td>
<td>8 (36.4%)</td>
<td>1 (25.0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Do not know if it’s suitable</td>
<td>14 (22.6%)</td>
<td>5 (22.7%)</td>
<td>0</td>
<td>0.80</td>
</tr>
<tr>
<td>Already had COVID so not needed</td>
<td>8 (12.9%)</td>
<td>2 (9.1%)</td>
<td>1 (25.0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Do not feel affected</td>
<td>6 (9.7%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Not convenient to get</td>
<td>2 (3.2%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>13 (21.0%)</td>
<td>6 (27.3%)</td>
<td>0</td>
<td>0.43</td>
</tr>
<tr>
<td>Symptoms after vaccination^d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>538 (63.2%)</td>
<td>141 (54.0%)</td>
<td>69 (73.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Tiredness</td>
<td>455 (53.5%)</td>
<td>95 (36.4%)</td>
<td>56 (59.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Muscle or body aches</td>
<td>268 (31.5%)</td>
<td>64 (24.5%)</td>
<td>40 (42.6%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Headache</td>
<td>223 (26.2%)</td>
<td>47 (18.0%)</td>
<td>29 (30.9%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Chills</td>
<td>181 (21.3%)</td>
<td>26 (10.0%)</td>
<td>21 (22.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fever</td>
<td>121 (14.2%)</td>
<td>18 (6.9%)</td>
<td>19 (20.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td>105 (12.3%)</td>
<td>25 (9.6%)</td>
<td>9 (9.6%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td>85 (10.0%)</td>
<td>27 (10.3%)</td>
<td>8 (8.5%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Nausea</td>
<td>48 (5.6%)</td>
<td>11 (4.2%)</td>
<td>3 (3.2%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Itching at injection site</td>
<td>37 (4.3%)</td>
<td>21 (8.0%)</td>
<td>2 (2.1%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (0.6%)</td>
<td>3 (1.1%)</td>
<td>0</td>
<td>0.41</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>5 (0.6%)</td>
<td>1 (0.4%)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Others</td>
<td>46 (5.4%)</td>
<td>12 (4.6%)</td>
<td>8 (8.5%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

^a Other patients include 59 Asians, 40 Hispanics, 1 Native American and 2 unknown

^b p-values for the comparison between Black and White patients were estimated using t-tests for continuous variables and χ2 tests and Fisher’s exact tests for categorical variables

^c Patients who did not plan to get vaccinated or who had not decided yet can select multiple answers for their concerns, so the number (%) of patients selecting each option were shown

^d Patients who got vaccinated can report multiple symptoms, so the number (%) of patients selecting each option were shown

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Quitxt Mobile Cessation Service for Cancer Patients: Development and Implementation Process

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Background: Physicians have unparalleled access to smokers. It is estimated that over 70% of smokers visit a physician every year, which provides a powerful opportunity to promote tobacco cessation by asking about smoking behaviors and providing cessation advice and counseling to tobacco users at every visit. In general, smokers consider a physician’s advice to quit an important motivator to make a quit attempt. We adapted our Quitxt program to the patient population attending the Mays Cancer Center at UT Health San Antonio. Every patient is screened for tobacco use; if the patient is a tobacco user, healthcare providers (HCPs) advise them to quit, offer nicotine replacement therapy if needed, and recommend enrollment in the Quitxt program. Purpose: We present the development process and implementation of Quitxt, our evidence-based, bilingual mobile cessation service tailored to the patient population of the Mays Cancer Center (MCC). Methods: Tobacco screening was integrated into EPIC, and the Quitxt program was added to the BestPractice Advisories Banner. All patients are screened for tobacco use. If a tobacco-using patient is identified, the BestPractice Advisories Banner will appear, prompting HCPs to counsel patients to quit and encourage them to enroll in Quitxt. Selecting referral to Quitxt will activate our Patient Navigator (PNs) follow-up. PNs contact patients and provide support, positive reinforcement, and encouragement. They continue with monthly follow-ups for the duration of the program. The EPIC system also places instructions on how to enroll in Quitxt in the patients’ after-visit summary. The Quitxt library of messages was adapted to the patient population of the MCC. We also developed a news-style video for HCPs with peer modeling on how to approach patients and enroll them in Quitxt. Results: The program will be launched at the MCC on August 1st, 2022. We will present the development and implementation process and preliminary results related to patient enrollment characteristics, stages of change, smoking abstinence, and patient navigation support. Conclusion: This project will greatly increase the accessibility and utilization of a bilingual evidence-based smoking cessation service among primary care and cancer patients. Quitxt will also serve as a model that can be easily adapted and replicated by any organization or network interested in serving their patients with an evidence-based cessation program. Quitxt represents an affordable approach to reach tobacco-using patients, produce a public health impact, reduce health service costs, and reduce tobacco-related diseases and mortality.

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Background: Breast cancer (BC) is the commonest diagnosed cancer in Singaporean women. Increasingly, non-metastatic BC are treated aggressively with neoadjuvant therapy (NAT). Early identification and addressing supportive care needs of NAT treated patients is important for effective cancer care whilst maintaining optimal physical, psychological and social function. This project aims to explore the longitudinal trends of quality of life (QOL) of BC patients enrolled in a NAT program. Methods: This was a prospective cohort study of females aged ≥21 diagnosed with non-metastatic BC, referred to the NAT program at the SingHealth network of acute hospitals. The Functional Assessment of Cancer Therapy-Breast (FACT-B) was used as a health related QOL measure prior to NAT, within 2 months post definitive breast surgery and at 1-year post diagnosis. In older adults (OA) ≥65 years, the Attitude scale, Now vs Later as well as Health Outcome tool were also performed at baseline. Here we report pre-NAT baseline FACT-B and questionnaire results of OA patients recruited into the NAT program between Jun 2020 and Jun 2021. Results: Pre-NAT median FACT-B scores was 117 (IQR 102-126) for the entire cohort (n=119) and 116 (IQR 104-126) for OA (n=22). OA had significantly lower median Social Wellbeing score at baseline compared to patients < 65 years (p=0.01), while Physical, Emotional, and Functional Wellbeing were not significantly different. More than 50% of OA favoured QOL over quantity of life on the Attitude Scale. 68% of patients would rather have
QOL now than 1 year later with half expecting their QOL to reduce by 50% in this time period. When the time scale was extended to 5 years, 64% would rather have QOL 5-years from now instead of QOL now with close to 80% expecting their QOL to be lower in 5 years than presently. Of the 4 outcomes, maintaining independence scored the highest, followed by keeping alive, then reducing / eliminating pain and other symptoms. Conclusion: Our study suggests that OA with BC report similar QOL to younger patients at baseline prior to NAT. Majority of OA patients favoured QOL over quantity of life, and viewed the ability to maintain independence as more important than survival prolongation representing their unique attitude towards cancer treatment and outcomes.

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Multilevel, Multicomponent Intervention to Improve Informed Decision-Making about Clinical Trial Participation among Cancer Patients

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Background: Knowledge gained through cancer clinical trials (CTs) has been proven critical to preventing, diagnosing and treating the disease, and providing the evidence base for clinical
practice. Major advances in cancer treatment, which are essential for improving patients’ outcomes, come from investigations of new therapeutic agents in CTs. Despite the large number of available studies and improvements in public awareness about CTs, participation of underrepresented minorities in clinical research has been persistently low, with only 2 to 5% of Latinos and African Americans participating in cancer treatment trials. Barriers to participation are multilevel, complex, and multifactorial, including study design, healthcare system barriers, and patient- and medical team-related factors. Structural inequities, social determinants of health, distrust of government, patient-doctor communication, cultural and language barriers, and lower levels of health literacy have all been cited as common barriers for Latino and African American populations. Purpose: To improve informed decision-making about cancer CT participation among cancer patients and community members through a bilingual multilevel, multi-communication approach, including 1) a randomized controlled educational trial (clinic-based settings), and 2) a community education module (community-based settings). We will assess the impact of the intervention on awareness, attitudes, self-efficacy, and intentions to consider CTs as an appropriate treatment option for cancer and improve CT participation rates. Methods: The clinical setting includes a 2-group, parallel, randomized study with 400 patients from the Mays Cancer Center. The intervention group receives 1) a bilingual educational video on CTs, 2) a low literacy booklet, 3) support from a patient navigator (PN), and 4) an invitation to join our Salud America! network providing online/social media CT information. The control group receives a general fact sheet on CTs. All healthcare providers involved in clinical research will participate in Webinars to raise awareness of implicit bias and the importance of inclusive research. The community-setting intervention features a prospective single-group pre/post design, where participants (400) act as their own controls. They will receive an educational session on CTs provided by a community health educator + a low literacy booklet. Results: Focus groups guided the development of the video script, booklet, and educational materials. The short video features real cancer patients sharing their experience with CTs and how they overcame common barriers. Patient recruitment starts in August 2022. Preliminary results will be presented. Conclusions: Multilevel interventions involving culturally tailored decision aids (i.e., online video, low literacy booklet) in combination with care coordination by a PN can effectively address common barriers influencing patient decision-making regarding CTs, raise awareness, and increase positive attitudes and CT participation among specific groups with low participation in clinical research. Keywords: health equity, clinical trials, Latinos, underrepresented groups

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Introduction After a cancer diagnosis and treatment patients often experience chronic symptoms such as fatigue, mental problems, decreased quality of life, sexual problems, hot flashes, nausea and postoperative pain. The unmet needs of patients managing these symptoms, improve the demand for Integrative Medicine (IM), which is lifestyle and evidence based complementary care. The prevalence of IM use varies in the Netherlands, according to published data. Aim The first aim of the study was to evaluate the prevalence and associates of the use of IM by patients after a cancer diagnosis. The second aim was to gain insight into the need for guidance of cancer patients in a large Dutch teaching hospital. Methods A cross-sectional design with data collected through a structured, self-reporting questionnaire. This was created by combining a validated questionnaire to evaluate IM use in the Netherlands and a questionnaire on IM use developed by The Dutch Breast Cancer Association. Cancer patients diagnosed with breast cancer, colon cancer, prostate cancer or testicular cancer were invited to fill out the questionnaire. They were all and treated in the period of 2018-2019. Patients were included one to three years after completing treatment. Descriptive statistics and logistic regression analysis were used to analyze the results. Results 1850 patients received the questionnaire and 1028 patients responded to the survey (56%). 29.4% used complementary care such as self-care products (8.3%), physician-assisted self-care (9%) or self-help techniques (10.5%). 40.3% made one or more lifestyle changes during or after cancer treatment regarding food (33.8%), exercise (56.1%), relaxation (40.9%), social factors (35.6%), life purpose (23.7%) and sleep (37.8%). Associates of complementary care use were breast cancer, gender (women) and age. The information about IM was mostly obtained by patients through the hospital or internet. Patients reported a preferred way to receive information by treating physician (53.9%), specialized nurse (59.2%), primary care physician (25.1%) or hospital brochure (26.3%). 82.3% of the patients, including patients who did not use IM at all, placed great value on receiving reliable information from their doctors or nurses about IM. Conclusion Up to two thirds of the oncology patients are using a form of IM. Internet is one of the most important information source. For safety reasons and to meet the demand of most oncology patients for reliable information, it’s important to provide all oncology patients with evidence-based information regarding lifestyle and evidence based complementary care. The majority of patients place great value on receiving this information from their doctor of nurse.
Implementing System Solutions for Survivorship Care Plans

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Background: A survivorship care plan (SCP) is a detailed cancer care summary and future care plan that is generally given to a patient upon completion of adjuvant treatment for a cancer diagnosis. The initial goals of SCPS were to educate patients and other health care professionals about the treatments received, make them aware about potential long-term effects of therapy, and emphasize recommendations for future cancer screening and care (1).

Due to numerous barriers—scheduling, staffing, and lack of awareness—SCPs are not delivered to all eligible patients. To address this unmet need our multidisciplinary breast clinic (MDBC) established an Advanced Practice Professional (APP) Survivorship Clinic. With the acute impact of the COVID-19 pandemic, survivorship referrals decreased. We, therefore, developed and implemented system solutions to address SCP access. Methods: System solutions include partnering with the Cancer Registry to provide the list of patients potentially in need of survivorship visits, partnering with pharmacy to confirm patient eligibility, creating specifically designated telemedicine survivorship visits in our electronic scheduling system, prospectively scheduling persons identified, engagement of APPs across the MDBC, and establishing a single coordinating point. Numbers of SCPs delivered are tracked monthly and patient satisfaction is assessed through data collected Press Ganey surveys. Results: This presentation will share our process interventions and outcomes as they mature. Our early data demonstrate the efficacy of the workflow and appear promising. Conclusion: We anticipate that system-based solutions will provide more patients with SCPs and demonstrate patient satisfaction.

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Background: Adjuvant hormonal therapy (HT) is highly effective and appropriate for nearly all women with hormone receptor-positive tumors, making such treatment the most widely prescribed therapy for patients with this type of breast cancer. Despite its proven benefits in
reducing cancer recurrence and improving survival, HT adherence is suboptimal (less than 80%). About 33% of patients do not take their medication as prescribed and are at increased risk of disease recurrence and lower survival. 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 preliminary results of a pilot study to test the feasibility of an intervention consisting of a theory-based, bilingual, culturally tailored, and interactive mobile app + patient navigation to empower patients’ self-monitoring and management by facilitating patient education, self-efficacy, early identification and reporting of side effects, delivery of self-care advice, and timely feedback through direct communication between the patient and the oncology team. Methods: This is a 2-group parallel, randomized control trial recruiting patients (120) receiving hormone therapy treatment and attending the breast clinic at the Mays Cancer Center (MCC). The intervention group receives two components: 1) the HT Helper phone app; and 2) assistance from a patient navigator who will provide educational, psychosocial support and reinforcement, address common barriers, and facilitate the interaction with the medical team as needed. The control group receives the usual care and information provided by the MCC’s breast clinic to patients undergoing HT. The app and navigation support are based on Social Cognitive Theory and principles of motivational interviewing. Patients are assessed at baseline, three and six months. The primary outcome is HT adherence. Additional variables of interest include self-efficacy, social support, depression, side effects, anxiety, and quality of life. We also assess app usability and satisfaction. Results: We have recruited 108 patients, 56 in the intervention group and 52 in the control group. The mean age is 57.5 years, 58.3% are Latinas, 41.7% have less than high school education, 54.2% have a family income of less than $50,000/year and 52.8% have Medicare/Medicaid. In addition to descriptive data, we will present results of the 3-month and 6-month follow-ups. Conclusion: The anticipated outcome of this innovative, multi-communication study is a scalable, evidence-based, and easily adaptable intervention with potentially broad use to patients using oral anticancer agents. The intervention has the potential to improve breast cancer outcomes by reducing recurrence, improving quality of life and survival, and reducing healthcare costs. The ultimate goal of this innovative, multi-communication intervention is to improve overall survival and life expectancy, enhance quality of life, and decrease healthcare costs.

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WITHDRAWN
FEASIBILITY, SAFETY AND EFFICACY OF A COMBINED SUPERVISED PHYSICAL EXERCISE AND NUTRITIONAL PROGRAM IN A SELECTED POPULATION OF LUMINAL METASTATIC BREAST CANCER PATIENTS: ONCARE-01 PILOT STUDY

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Background: Supervised exercise programs (SEP) have demonstrated an improvement in quality of life (QoL), cardiovascular health, treatment tolerance and disease outcomes in early breast cancer patients. In metastatic breast cancer (MBC), previous data suggest SEP are safe but no impact on QoL and a low adherence to programs were shown. These studies included a heterogenous population in terms of type of treatments received, numbers of previous lines or comorbidities. From our perspective, MBC profile that could benefit most from SEP needs to be explored. Thus, we conducted a pilot study to assess adherence, safety and impact on QoL of a combined SEP and nutritional program (NP) in a selected population of MBC of patients treated with cyclin-dependent kinase 4/6 inhibitors (iCDK 4/6). Methods: This is a prospective, single center, single arm pilot study. SEP consisted in a 12-week intervention with twice a week in-person resistance exercise session. Patients also completed weekly aerobic exercise goals in self-managed sessions monitored with activity trackers. SEP was conducted by registered Physical Activity and Sports Science instructors that followed American College of Sports Medicine guidelines. In addition, participants had an initial nutritional assessment and personalized counselling by a qualified nutritionist. Adherence to treatment, biological variables and QoL assessments (FACIT-Fatigue and QLQ-C30 questionnaires) were collected at baseline (B) and week-12 (w12). Primary endpoint was global adherence (≥70% of attended sessions relative to scheduled sessions). Secondary endpoints included safety, changes in biological variables and QoL. Paired samples t-tests (Wilcoxon) were used to assess biological changes and QoL. Results: Patients (n=26) were recruited from October 2020 to November 2021. Median age was 47.5 years (45-55); 84.6% of patients were ECOG 0. 42.3% of patients were receiving Abemaciclib; 34.6% Ribociclib and 23.1% Palbociclib in first (73.1%) or second (26.9%) line treatment. Patients had bone (69.2%); visceral metastasis (57.7%) or both (30.8%). 2 patients did not start the intervention and additional 7 patients discontinued the program prematurely, the majority of them due to COVID-related concerns. Considering all patients who at least attended one session, global adherence was 66% (39-77.5%) and 45.8% of patients achieved an adherence of ≥ 70%. Patients reported an improvement in QoL [B global QLQ-C30 66.6 (50-75), w12 75 (66.6-83.3); p 0.0121] and fatigue [B FACIT-Fatigue 37 (30-44), w12 42 (38-48); p 0.0017]. Sit-to-stand repetitions in 30-second period also improved [(B 15 (12-17), 19 (15-23); p 0.0002]. Same benefits were seen in patients with adherence ≥ 70%. No statistically significant changes were seen in body fat or muscular composition and handgrip scores. Importantly, no safety issues related to study intervention were reported. Conclusions: Even though the study was conducted during COVID-19 pandemic, global adherence was 66%. For the first time in MBC, SEP and NP combined program demonstrated to be safe and improved QoL in patients with first or second line MBC treated with iCDK4/6. Further research is needed to identify strategies that improve QoL in MBC.

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Experience of Financial Toxicity and Distress Among Individuals Diagnosed with Triple Negative Breast Cancer: Findings from the Cancer Experience Registry

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Background: Financial toxicity associated with cancer and its treatment can negatively impact treatment adherence and quality of life. Individuals with triple negative breast cancer (TNBC) may be at increased risk for financial toxicity due to the aggressive nature of the disease and high rate of recurrence. The objective of this study was to characterize financial experiences of TNBC survivors, their descriptions of communication with providers concerning treatment costs, and correlations between financial toxicity and psychosocial distress. Methods: From July 2017 to August 2021, 94 individuals with TNBC took part in Cancer Support Community’s Cancer Experience Registry® (CER). Participants completed items related to financial distress, including COmprehensive Score for Financial Toxicity (COST), an 11-item (0=Not at all, 4=Very much) measure of financial well-being (range 0-44; lower scores indicate worse financial well-being), dichotomous (yes or no) items assessing patient-provider communication, and Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29 v2.0). Bivariate relations were assessed using Pearson’s correlation. Results: Participants were 81% non-Hispanic White, 6% Black, and 6% Hispanic. Mean age was 52 years (SD=11.3); 14 (15%) reported household income <$40K. Median time since diagnosis was 2 years; 15% (n=14) reported metastatic breast cancer and 36% were currently receiving treatment. Concerning out-of-pocket cancer-related costs, 56% of our sample reported spending >$250 per month; 32%
To reduce costs, 23% sometimes, often, or always postponed seeking psychological support, 19% delayed follow-up on recommendations, 6% postponed doctor’s appointments, and 5% skipped medication. The mean COST score was 23.0 (SD=12.3), indicating mild financial distress overall. Less than half of the sample (46%) indicated no financial toxicity (scores >25), 29% mild financial toxicity (scores 14-25), 22% moderate (score 1-13), and 3% severe (score of 0). The frequency of individual COST items showed 61% reported (somewhat, quite a bit, or very much) worry about future financial problems due to treatment costs; 14% were unable to meet monthly expenses; 49% reported concern about keeping their job or income; 47% reported frustration that they could not work or contribute as usual. COST scores were inversely correlated to PROMIS anxiety (r=-.45, p<.001), depression (r=-.44, p<.001), and sleep disturbance subscales (r=-.48, p<.001), such that lower financial well-being related to more symptomology. COST scores were positively associated with the social function subscale (r=.46, p<.001), so that better financial well-being related to higher social functioning. Regarding patient-provider communication, 70% reported their health care team did not discuss costs, 62% did not discuss impact of TNBC and treatment on work, and 59% did not discuss financial concerns. One-third (34%) wished they received more financial advice and assistance. Conclusion: In this sample of TNBC patients, average levels of financial toxicity were in the mild range. However, many reported moderate to severe toxicity (25%). Greater financial toxicity related to increased symptoms of anxiety, depression, sleep disturbance, and worse social functioning. Despite this, results indicate there is little patient-provider discussion about financial burden, with more than half of our sample reporting their health care team did not discuss costs, impact on work, or financial distress. One-third of participants indicated desire for more financial advice and assistance highlighting an opportunity to better serve TNBC patients, who may be at an increased risk of financial toxicity.

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Kara Doughtie, MA: No financial relationships to disclose
Erica E. Fortune, PhD: AbbVie: Contracted Research (Ongoing); Amgen Oncology: Contracted Research (Ongoing); Astellas Pharma: Contracted Research (Ongoing); AstraZeneca: Contracted Research (Ongoing); Bristol Myers Squibb: Contracted Research (Ongoing); Genentech: Contracted Research (Ongoing); Gilead Sciences: Contracted Research (Ongoing); Lilly Oncology: Contracted Research (Ongoing); Merck & Co., Inc.: Contracted Research (Ongoing); Sumimoto Dainippon Pharma Co: Contracted Research (Ongoing); Takeda Oncology: Contracted Research (Ongoing)
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Effects of a 12-Week Exercise Program on Breast Cancer Survivors’ Quality of Life

Previous studies have demonstrated that breast cancer survivors commonly experience a decrease in quality of life including an increased risk of depression, insomnia, cancer-related fatigue, and negative body image. Several studies have shown that exercise interventions, such as yoga, Pilates, water aerobics, and strengthening exercises, can improve survivors’ quality of life. We implemented a 12-week exercise program in breast cancer survivors and evaluated body composition and quality of life changes. Here we discuss our findings evaluating 5 quality of life questionnaires.

Methods:
We evaluated 22 participants who completed a baseline and post 12-week questionnaire assessments. All participants underwent a 12-week exercise program 3 times/week for 90 minutes/session. We calculated differences in baseline and post 12-week quality of life through 5 questionnaires: Functional Assessment of Cancer Therapy - General (FACT-G), Social Support, Insomnia Severity Index, Brief Fatigue Inventory, and Body Image after Breast Cancer (BIBCQ) and assessed the intervention's efficacy by comparing the baseline and post 12-week scores using paired t-tests.

Results:
The difference between baseline and post 12-week quality of life are presented in Table 1. 7/13 questionnaires showed statistical significance: FACT-G Emotional, FACT-G Functional, Insomnia Severity Index, BIBCQ Vulnerability Scale (VS), BIBCQ Body Stigma Scale (BSS), BIBCQ Limitation Scale (LS), and BIBCQ Body Concern Scale (BCS). Interestingly, 4/6 of the BIBCQ questionnaires showed statistical significance: BIBCQ VS, BIBCQ BSS, BIBCQ LS, and BIBCQ BCS.

Summary:
Our study showed improvement in all metrics evaluated in breast cancer survivors who underwent the personalized exercise program. Specifically, multiple questionnaires including body image were improved with exercise which further exemplifies the impact of lifestyle changes on quality of life measures and is an important adjunct to future cancer survivorship studies.

Table 1: Summary of questionnaires with overall significant improvements

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>n/22 (%) improvement</th>
<th>p-value (significant p&lt;0.05 in bold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G Physical</td>
<td>12/22 (54.5%)</td>
<td>0.097</td>
</tr>
<tr>
<td>FACT-G Social/Family</td>
<td>8/22 (36.4%)</td>
<td>0.612</td>
</tr>
<tr>
<td>FACT-G Emotional</td>
<td>12/22 (54.5%)</td>
<td>0.048</td>
</tr>
<tr>
<td>FACT-G Functional</td>
<td>12/22 (59.1%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Social Support</td>
<td>12/22 (54.5%)</td>
<td>0.577</td>
</tr>
<tr>
<td>Innomus Severity Index</td>
<td>14/22 (63.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Brief Fatigue Inventory</td>
<td>13/22 (59.1%)</td>
<td>0.138</td>
</tr>
<tr>
<td>BIBCQ VS</td>
<td>17/22 (77.3%)</td>
<td>0.004</td>
</tr>
<tr>
<td>BIBCQ BNS</td>
<td>15/22 (68.2%)</td>
<td>0.022</td>
</tr>
<tr>
<td>BIBCQ LS</td>
<td>18/22 (81.8%)</td>
<td>0.048</td>
</tr>
<tr>
<td>BIBCQ BCS</td>
<td>18/22 (81.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>BIBCQ Transparency Scale (TS)</td>
<td>14/22 (63.6%)</td>
<td>0.244</td>
</tr>
<tr>
<td>BIBCQ Arm Concern Scale (ACS)</td>
<td>13/22 (59.1%)</td>
<td>0.481</td>
</tr>
</tbody>
</table>

Disclosure(s):
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Ian Pagano, PhD: No financial relationships to disclose
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Early integrated rehabilitation helps smoking cessation in 467 breast cancer patients – a comparison between the intervention and control group in a prospective study

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Background: Tobacco related illnesses are important public health issues worldwide. Cigarette smoking affects cancer risk and cardiovascular risk. Smoking cessation confers substantial benefits on health. Our aim was to determine whether the early introduction of integrated rehabilitation from the beginning of cancer treatment is associated with the smoking cessation in breast cancer patients. Material and Methods: The subjects of our prospective study were 467 female breast cancer patients (29-65 (mean 52) years of age), who participated in the pilot study on the individualized integrated rehabilitation of breast cancer patients in 2019-2022 and were followed for at least one year. The control group included 282 patients and the intervention group 185 patients. The patients completed three questionnaires (EORTC QLQ C30, B23 and NCCN) before and one year after the beginning of cancer treatment. The control group obtained the same rehabilitation as was offered to all breast cancer patients in our hospital before the start of our prospective study. The multidisciplinary rehabilitation team reviewed the documentation of all the patients from the intervention group before and one year after the beginning of cancer treatment and recommended appropriate interventions according to the patient's difficulties. The integrated rehabilitation coordinator referred patients for additional interventions in compliance with the institute's clinical pathway (psychologist, general practitioner, clinical nutritionist, physical rehabilitation, kinesiologist-guided online exercises, gynecologist, analgesia, vocational rehabilitation). Smokers were referred to a smoking cessation workshop organized by a health promotion center within community health centres. Data on the patients' demographics, disease extent, cancer treatment and prevalence of tobacco smoking before and one year after the beginning of cancer treatment were collected and analysed using the chi-square and ANOVA test. Results: There were no differences between the control and the intervention group of patients in terms of age, education, disease extent, surgical procedures, systemic cancer treatment, or radiotherapy. There were no differences between the groups in the prevalence of smoking before the treatment. Before the cancer treatment, smoking was present in the intervention and control group in 22% and 27% (p=0.22), respectively. However, one year after the beginning of cancer treatment, smoking was less common in the intervention group in comparison to the control group of patients (p=0.004). Smoking was present in the intervention and control group in 10% and 20%, respectively. Conclusions: Early integrated rehabilitation helps the smoking cessation in breast cancer patients.

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Romi Cencelj-Arnez, MD: No financial relationships to disclose
Introduction: Place of death (PoD) studies are often used to motivate and monitor progress on health inequities for persons with cancer. It remains unclear whether aggregation of Asian race masks disparities in health equity for care at the end of life.

Methods: De-identified death certificate data were obtained via the National Center for Health Statistics. All adult (>18 years of age) breast cancer deaths from 2018 to 2019 were included. Multinomial logistic regression was used to test for differences in place of death associated with sociodemographic variables.

Results: From 2018 through 2019, 81,772 died from breast cancer in the United States. Overall, persons of Asian descent were less likely to die at home compared to White patients. Disaggregation noted significant differences in likelihood of hospice facility use. For example, Filipino race was approximately 5 times more likely to utilize hospice facilities (CI 3.764, 8.718; p< 0.001) compared to Whites, whereas Chinese race was significantly less likely (OR 0.49, 95% CI 0.307 to 0.627, p< 0.001). American Indian (OR 0.006), Asian Indian (OR 0.016), and Samoan (0.011) were the least likely to die in a nursing facility. While trends were overall similar when compared to White, Black and Hispanics, the likelihood of PoD among Asian subgroups were significantly different.

Conclusion: Our data highlights notable differences in PoD only apparent with disaggregation of Asian race. While this study remains exploratory in nature, and reasons to explain these disparities are necessary, disaggregation of the Asian Pacific Island category is imperative to unmask disparities to improve health equity among all indigenous populations.
Table 1: Number of deaths due to breast cancer in 2016 and 2019, by race. Odds ratios for the association between race and place of death from multivariable regression.

<table>
<thead>
<tr>
<th>Race</th>
<th>N</th>
<th>Hospital</th>
<th>Home</th>
<th>No Hospital</th>
<th>Nursing Facility</th>
<th>OR (% CI)</th>
<th>p</th>
<th>OR (% CI)</th>
<th>p</th>
<th>OR (% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>640</td>
<td>401 (62.8)</td>
<td>113 (17.4)</td>
<td>126 (19.8)</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
<td>0.326</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
</tr>
<tr>
<td>Black</td>
<td>1279</td>
<td>854 (66.5)</td>
<td>300 (23.2)</td>
<td>225 (17.3)</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
<td>0.326</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
</tr>
<tr>
<td>White</td>
<td>1336</td>
<td>897 (67.2)</td>
<td>307 (23.3)</td>
<td>232 (17.5)</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
<td>0.326</td>
<td>1.000 (1.000-1.000)</td>
<td>0.953</td>
<td>0.900-1.000</td>
</tr>
</tbody>
</table>

† Association between death in a given location compared to the reference category (Non-Hispanic White).

Disclosure(s):

Naveena Lall, MD: No financial relationships to disclose
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Qasim S. Hussaini, MD: No financial relationships to disclose
Amanda L. Blackford, ScM: No financial relationships to disclose
Arjun Gupta, MBBS: No financial relationships to disclose
Ramy Sedhom, MD: No financial relationships to disclose
Distress Reduction and Physical Activity Enhancement by Mobile Support Group in Breast Cancer Survivors: a randomized controlled study

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Purpose

Improving physical activity (PA) and reducing mental distress are important issues in the treatment of cancer survivors. This study aimed to investigate the effect of a mobile app-based community on enhancing PA and decreasing distress in breast cancer survivors.

Methods

We conducted a single-center, prospective, non-blinded, randomized controlled study. Subjects who got breast cancer surgery were allocated to a control group or a app-based community group (intervention) where members were able to share their daily physical activities. Daily walk steps and weekly distress scores using app-based Distress Thermometer (DT) questionnaires were collected from participants for 24 weeks. To examine the differences in levels of distress and weekly step counts for 6 months, we used a t-test method and multivariable regression modeling. Results

From Jan 2019 to Apr 2020, a total of 202 participants were enrolled in this study. The intervention group showed a significant increase in weekly steps by 4,496 for 6 months (p < 0.001). The participants in the intervention group showed a significantly lower rate of above mild distress (DT≥3, beta[B] = -0.731, p < 0.001) and above moderate distress (DT≥5, B = -0.558, p < 0.001) compared to those in the control group for 6 months. Conclusions

The mobile app-based community is an effective and less resource-intensive tool to increase PA and decrease distress in breast cancer survivors.

Disclosure(s):

Il-Yong Chung, M.D.: No financial relationships to disclose
Miyeon Jung, n/a: No financial relationships to disclose
Sae Byul Lee, M.D., Ph.D.: No financial relationships to disclose
Jong Won Lee, n/a: No financial relationships to disclose
Sei Hyun Ahn, M.D., Ph.D.: No financial relationships to disclose
Haekwon Chung, n/a: Swallaby Co.: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing)
Depression and Psychological Distress in Breast Cancer Patients

Introduction:
Patients with breast cancer are at increased risk for depression and suicide compared to the general population. Breast cancer is unique among other cancers in that some treatments aim to decrease levels of estrogen, a hormone that is intricately linked to mood regulation. The trauma of diagnosis, invasive treatments, and hormone dysregulation all possibly contribute to poor mental health outcomes. Understanding risk factors associated with depression and distress are important for timely interventions.

Methods:
We performed a retrospective chart review of breast cancer patients seen at Froedtert & MCW Cancer Center Breast Care Clinic between 2019 and 2020. The present study had two aims. The primary aim was to identify breast cancer patient populations at increased risk of depression and psychological distress. Patient populations were distinguished by tumor pathology, patient demographics, and types of treatment interventions. The secondary aim was to identify demographic and clinical variables associated with changes in self-reported distress and depression. Univariate and multivariate analysis of demographic and clinical variables was performed in relation to Patient Health Questionnaire (PHQ) and The National Comprehensive Cancer Network (NCCN) Distress Thermometer scores.

Results:
Data from 197 patients was analyzed. Patients with a history of depression scored significantly higher on distress screening (mean= 4.4 ± 3.0, p=0.004) versus patients without psychiatric history (mean 2.8 ± 2.9). Patients under 50 years old reported higher levels of distress than patients over 70 years old (p=0.031, beta= -1.0). Self-reported distress declined significantly with increased time from initial diagnosis (p=0.043; p=0.006 at 2 years). Distress was significantly higher prior to initiation of radiation versus during and immediately following therapy (p=0.028). A history of depression, younger age, passage of time, and temporal relationship to radiation treatment were not associated with significant differences in self-reported depression on multivariate analysis. Distress and depression screening scores were not significantly impacted by surgery or chemotherapy (p=0.5; p=0.11 respectively).

Conclusion:
Patients with a known history of depression and age less than 50 reported significantly higher levels of distress but not depression associated with diagnosis of breast cancer. Distress exhibited a greater downward trend than depression following initiation of oncologic intervention. The results of this study indicate that breast cancer patients are susceptible to significant fluctuations in psychological distress. In contrast, clinically relevant depression screening scores were less frequent and less subject to deviation.

Table 1: Multivariate analysis
Table 1: Multivariate Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Distress</th>
<th>PHQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Beta</td>
</tr>
<tr>
<td><strong>Age at dx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-50</td>
<td>157</td>
<td>-----</td>
</tr>
<tr>
<td>50-59</td>
<td>184</td>
<td>-1.0</td>
</tr>
<tr>
<td>60-69</td>
<td>144</td>
<td>-1.3</td>
</tr>
<tr>
<td>70+</td>
<td>76</td>
<td>-1.6</td>
</tr>
<tr>
<td><strong>Time since</strong></td>
<td>407</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Dx</strong></td>
<td>100</td>
<td>-1.0</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>144</td>
<td>-1.3</td>
</tr>
<tr>
<td>6 mo-1 yr</td>
<td>76</td>
<td>-1.6</td>
</tr>
<tr>
<td>1-2 yrs</td>
<td>97</td>
<td>1.3</td>
</tr>
<tr>
<td>2+ yrs</td>
<td>284</td>
<td>-----</td>
</tr>
<tr>
<td><strong>History of</strong></td>
<td>284</td>
<td>-----</td>
</tr>
<tr>
<td><strong>depression?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>284</td>
<td>-----</td>
</tr>
<tr>
<td>Yes</td>
<td>63</td>
<td>0.55</td>
</tr>
<tr>
<td>None/90+ days</td>
<td>21</td>
<td>-1.2</td>
</tr>
<tr>
<td>before 90 days</td>
<td>136</td>
<td>0.21</td>
</tr>
<tr>
<td>after 90 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI= Confidence interval

Dx= diagnosis. Significant p-values are bolded.
Cost-effectiveness of CDK4/6 inhibitors in the first-line treatment of HR+/HER2-
metastatic breast cancer in postmenopausal women in Panama.

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Country: United States

Background: 4/6 kinase-dependent cyclin inhibitors have been approved for use in combination with first-line aromatase inhibitors in patients with hormone-sensitive, Her2neu negative metastatic breast cancer. These agents have significantly improved progression-free survival compared to monotherapy aromatase inhibitors. The purpose of this study was to evaluate the cost-evaluation of each of these new agents (palbociclib, ribociclib, and abemaciclib) in the first line in Panama with the perspective of the National Oncological Institute. Methods: A partition survival analysis was carried out that includes three states (free of progression, progression, and death) with cycles of one month and a time horizon of 7.5 years. The efficacy data were taken from pivotal clinical trials, and the costs were estimated locally. A deterministic and probabilistic sensitivity analysis of the Monte Carlo was performed. Results: According to the base case, the update of each of these strategies involved an increase of USD 355,184 per additional QALY for ribociclib with Letrozole compared to Letrozole; USD 944,148 / additional QALY for Palbociclib plus Letrozole; and USD 223,956 for Abemaciclib plus Letrozole, when compared with Letrozole, all above the availability threshold to pay 50,000 / QALY. Conclusion: Despite the improvement in progression-free survival, none of the strategies have proved cost-effectiveness in our setting. Price negotiations, cost reduction, and risk-sharing agreements between pharmaceutical companies and payers might improve access to new drugs in countries with limited resources.

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Maria Lim, MD: No financial relationships to disclose
Lilian Montano, MD: No financial relationships to disclose
Cost-effectiveness of CDK4/6 inhibitors as a First line Therapy for Metastatic Breast Cancer. A Mexican Cohort.

BACKGROUND.
Breast cancer is the most frequent neoplasm worldwide, as reported by GLOBOCAN 2020, there were 2.2 million new cases per year and 680,000 deaths. In Mexico, it represents the leading cause of death from cancer in women, and therefore represents a public health problem in our country. The standard treatment for patients with hormone receptor-positive, her2-negative breast cancer is endocrine therapy with an aromatase inhibitor plus a CDK4/6 inhibitor (CDK4/6i+AI), however access to these therapies is difficult and limited resources in developing countries, lead to treatment strategies such as aromatase inhibitors alone (AI) or chemotherapy...
(ChT) still being used. However, management with ChT involves an increase in the use of reosurces due to cost per infusion, use of premedication and granulocyte colony-stimulating agents.

OBJECTIVE
The aim of this study was to provide an economic evaluation of CDK4/6i+AI compared with AI alone or ChT as a first line in MBC to better understand its value from the healthcare point of view in a developing country.

METHODS.
We designed a retrospective cost-effectiveness analysis of three different therapies CDK4/6i+AI, AI alone and ChT administered as first-line therapy for patients with MBC.

RESULTS.
A cost-effectiveness analysis was performed on a retrospective cohort of 150 MBC patients (March 2011 to April 2020) with a follow-up of at least 2 years. The median age at diagnosis was 55 years old. The utilization of health care resources was retrieved from clinical charts. Only direct costs associated with pre-progression, progression, and management of adverse events were considered and expressed on current USD.

Seventy-six percent were diagnosed with de novo stage IV disease, 66% were postmenopausal and 76% had ductal histology. The most common sites of metastasis were visceral 55% and 29% had only bone metastases. We identified 3 treatment groups: (1) CDK4/6i+AI, 18.66% (28/150), (2) AI, 48.66% (73/150) and (3) ChT, 32.66% (49/150). The median PFS of iCDK4/6 + TH was 32.10 months compared with 18.87 (95%CI: 16.4, 28.7) months for the AI group and 6.57 months for chemotherapy. The HR of iCDK4/6+TH vs HT was 0.357 (95%CI: 0.18-0.72) and that of iCDK4/6+TH vs chemotherapy was 0.09 (95%CI: 0.04-0.22). Median OS survival was not reached in any arm. The most frequent adverse events grade 3 were fatigue 10.71%, neutropenia 32.14%, diarrhea 7.14%, myalgias 3.57% and arthralgias 3.57% in the CDK4/6i + AI group, fatigue 2.74% and arthralgias 4.11% in AI group and fatigue 20.41%, neutropenia 18.37%, nausea 10.2%, diarrhea 6.12%, myalgias 2.4% and headache 2.4% with chemotherapy. PFS was used as the outcome for the cost-effectiveness analysis, with 5 years of follow-up, CDK4/6i+AI offer an incremental efficacy of 1.4 years in PFS compared with AI and 2.43 years with ChT, they are related to an incremental cost of $28,151.61 and $26,720.47 concerning AI and ChT, respectively. The ICER for CDK4/6i+AI compared to AI is $20,108.29 and $10,996.07 compared to chemotherapy.

CONCLUSION.
CDK4/6i+AI increase years of life gained when compared to AI and chemotherapy. Is a cost-effective treatment in our institution because it is less than two GDP per capita. CDK4/6i+AI is the standard treatment around the world even in developing countries like Mexico.

PFS 3 arms
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Comparing Changes in Depression and Anxiety Levels of Breast Cancer Patients throughout a Course of Radiation Therapy

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Country: United States

An estimated 32.2% and 41.9% of breast cancer patients experience depression and anxiety, respectively. However, due to differences in the understanding of radiotherapy and variability in the severity of side effects, responses of patients with breast cancer receiving radiation therapy may vary at different time points and differ in comparison to other patients with breast cancer. This study sought to describe the changes in levels of depression and anxiety experienced by English and Spanish-speaking patients throughout a course of radiation therapy for breast cancer along with the impact of different variables on these levels to better understand and quantify potential gaps.

Eligibility criteria included English and Spanish-speaking females, ages 18 or older, undergoing radiation therapy treatment for breast cancer at Boston Medical Center. Pre- and post-treatment surveys were completed before and after delivery of radiation therapy. Survey included sociodemographic questions along with the standardized PHQ-4 questionnaire, which uses a maximum total score of 12, to assess anxiety and depression. Results were analyzed using a least means square procedure.

A total of 60 participants completed pre- and post-treatment surveys. Total baseline distress mean (BDM) was 3.32 (SD= 3.55) and final distress mean (FDM) was 3.22 (SD= 3.78). English-speaking patients comprised 70% (n=42) of the sample and had a BDM of 3.40 with an adjusted change mean (ACM) decrease of 0.48. Spanish-speaking patients comprised 30% (n=18) of the sample, with a BDM of 3.11 and an ACM increase of 0.79, differences in ACM trended toward significance with a p-value of 0.083. Sociodemographic characteristics included: race, ethnicity, marital status, education level and longest residency. Additional variables surrounding social determinants of health included housing and food insecurity, which showed statistically significant increasing distress with increased insecurity at baseline.

While our study showed a higher BDM among English-speaking patients in comparison to Spanish-speaking patients, results showed that Spanish-speakers’ distress increased throughout treatment as opposed to English-speakers. Most of our patient population was English-speaking, though approximately one third Spanish-speaking and our participants were also primarily Black, non-Hispanic, never married, had a high school or associate level
education, and had their longest residence in the US. Although the majority did not report housing or food insecurity, both had increasing DM with increased insecurity, with statistically significant results. As the number of Spanish-speakers in the US continues to increase, it will be important to continue assessing potential differences in cancer care. In addition, an understanding of the changes of distress throughout radiation treatment could help inform future interventions that address these disparities.

Baseline distress values and adjusted change in overall score by sociodemographic factors

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (SE)</th>
<th>Overall</th>
<th>1 vs. 2</th>
<th>1 vs. 3</th>
<th>2 vs. 3</th>
<th>Adjusted Change Mean* (SE)</th>
<th>Overall</th>
</tr>
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<tbody>
<tr>
<td><strong>Language</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>42</td>
<td>3.40 (0.55)</td>
<td>0.772</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.48 (0.39)</td>
<td>0.083</td>
</tr>
<tr>
<td>Spanish</td>
<td>18</td>
<td>3.11 (0.84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79 (0.60)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1. White</td>
<td>16</td>
<td>3.13 (0.80)</td>
<td>0.965</td>
<td>0.961</td>
<td>0.988</td>
<td>0.994</td>
<td>-0.60 (0.63)</td>
<td>0.086</td>
</tr>
<tr>
<td>2. Black</td>
<td>28</td>
<td>3.43 (0.68)</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>-0.51 (0.48)</td>
<td></td>
</tr>
<tr>
<td>3. Other</td>
<td>16</td>
<td>3.31 (0.90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.12 (0.63)</td>
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<tr>
<td><strong>Hispanic identity</strong></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>49</td>
<td>3.25 (0.57)</td>
<td>0.839</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.59 (0.40)</td>
<td>0.038</td>
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<tr>
<td>Yes</td>
<td>20</td>
<td>3.46 (0.90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.56)</td>
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<tr>
<td><strong>Marital status</strong></td>
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<td></td>
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</tr>
<tr>
<td>1. Never married</td>
<td>22</td>
<td>3.82 (0.76)</td>
<td>0.376</td>
<td>0.987</td>
<td>0.393</td>
<td>0.494</td>
<td>-0.08 (0.50)</td>
<td>0.810</td>
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<tr>
<td>2. Married</td>
<td>20</td>
<td>3.66 (0.79)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.38 (0.59)</td>
<td></td>
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<tr>
<td>3. Divorced/Separated/Widowed</td>
<td>18</td>
<td>2.33 (0.84)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18 (0.63)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1. &lt; High School</td>
<td>12</td>
<td>3.25 (1.04)</td>
<td>0.897</td>
<td>0.981</td>
<td>0.972</td>
<td>0.889</td>
<td>0.65 (0.75)</td>
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<tr>
<td>2. High School/Associate</td>
<td>36</td>
<td>3.47 (0.60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.33 (0.44)</td>
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<tr>
<td>3. Bachelors/Masters/Doctorate</td>
<td>12</td>
<td>2.92 (1.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.17 (0.70)</td>
<td></td>
</tr>
<tr>
<td><strong>Country</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>United States</td>
<td>35</td>
<td>3.51 (0.60)</td>
<td>0.614</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.30 (0.44)</td>
<td>0.486</td>
</tr>
<tr>
<td>Foreign</td>
<td>25</td>
<td>3.04 (0.72)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18 (0.52)</td>
<td></td>
</tr>
<tr>
<td><strong>Housing worry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Never</td>
<td>30</td>
<td>2.13 (0.01)</td>
<td>0.007</td>
<td>0.384</td>
<td>0.001</td>
<td>0.190</td>
<td>-0.79 (0.48)</td>
<td>0.112</td>
</tr>
<tr>
<td>2. Sometimes</td>
<td>16</td>
<td>3.50 (0.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18 (0.64)</td>
<td></td>
</tr>
<tr>
<td>3. Always</td>
<td>14</td>
<td>5.64 (0.69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.07 (0.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Food worry</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Never</td>
<td>37</td>
<td>2.24 (0.54)</td>
<td>0.003</td>
<td>0.198</td>
<td>0.003</td>
<td>0.245</td>
<td>-0.54 (0.44)</td>
<td>0.194</td>
</tr>
<tr>
<td>2. Sometimes</td>
<td>13</td>
<td>4.08 (0.90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.08 (0.72)</td>
<td></td>
</tr>
<tr>
<td>3. Always</td>
<td>10</td>
<td>6.30 (1.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.30 (0.87)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: N= total number of respondents; SE= standard error
*The change in score from the first week of treatment to the final week was calculated as (final treatment score - first treatment score).

Disclosure(s):

Corina Beiner, BS: American Society of Clinical Oncology: ASCO Medical Student Rotation Award (Terminated, June 3, 2022)

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Ariel Hirsch, MD: No financial relationships to disclose

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Mammographic breast density (MBD) has been shown to be a strong, independent risk factor for breast cancer (BC) irrespective of race/ethnicity. Given the risk association of MBD and its potential to mask tumors on a mammogram, state and federal laws have mandated that women receive information regarding their personal MBD in their mammography reports. However, concerns have been raised regarding the impact of MBD notification on patient anxiety, especially written information for women who experience health disparities such as racial/ethnic minorities, lower health literacy, limited English proficiency and lower socioeconomic status. We performed a randomized controlled clinical trial to examine the impact of three different written and interpersonal approaches to MBD notification on patient anxiety, BC worry, and self-perceived BC risk, among Latinas receiving routine mammography screening at a federally qualified medical center (FQHC). We hypothesized that interpersonal education would reduce anxiety and worry, relative to the written notifications alone. The study was performed at the Baseline Clinic of Mountain Park Health Center, a FQHC in Phoenix, AZ. Women between ages 40 and 74 years presenting for screening mammogram were eligible. After providing signed informed consent, participants were randomized equally to usual care (UC- mailed notification letter); enhanced care (notification letter and MBD educational brochure designed for this study); interpersonal care (notification letter, brochure, promotora education via telephone). A stratified block randomization procedure was used with age > 50 years (yes vs no), ethnicity (Hispanic vs non-Hispanic), and language preference (Spanish vs. English) as strata. Study participants completed surveys at the time of enrollment/ pre-intervention (T0), at two weeks to six months after intervention was delivered (T1), and about one year after randomization (T2). Anxiety state was measured using the state anxiety subscale of the State-Trait Anxiety Inventory scale (STAI-S) (range from 20-80). BC worry was probed using the question: "How frequently do you worry about getting breast cancer someday". The self-perceived lifetime risk of BC was rated between 0% (no chance of BC) to 100% (definitely will get BC). The proportion of participants with an increase or persistence of higher level for each outcome between time points was compared between the three study groups. The study was approved by the Mayo Clinic Institutional Review Board. 1332 Latina women were enrolled and randomized between October 2016 and October 2019. All completed the baseline (T0) survey, 928 completed T1, 632 completed T2, and 516 completed both T1 and T2 surveys. At study entry, majority of the participants were young (64.1% between age 40-49 years), had no family history of breast cancer (81.0%), had less than high school education (68.8%), and were married or partnered (67.8%). At T0, the mean (SD) anxiety STAI score was 32.5 (11.1); 51.8% with moderate or severe anxiety (score > 30). With regard to BC worry, 41.3% reported worrying "sometimes", "often", or "almost all the time". Further, 25.4% reported a self-perceived lifetime risk of developing BC of >10% while only 6.6% had a Gail model estimated lifetime risk score of >10%. There was no significant difference in changes in anxiety, BC worry or self-perceived risk from T0 to either T1 or T2 surveys between the intervention groups. In summary, this study found high levels of baseline anxiety and BC worry (despite the majority being 40-49 years old and having no family history of BC) which persisted regardless of how notification and education were delivered. Future work is needed to improve the understanding of factors that could lower anxiety and BC worry and improve risk perception in this population.

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Bhavika K. Patel, M.D.: GRAIL Inc.: Contracted Research (Ongoing); Hologic Inc.: Contracted Research (Ongoing)
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Valentina Hernandez, M.S.: No financial relationships to disclose
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Vera Suman, Ph.D.: No financial relationships to disclose
Celine Vachon, PhD: NIH/NCI: Contracted Research (Ongoing)
The passage of H.R. 2116 (CROWN Act) prohibits hair texture and style discrimination based on race or national origin, thus, theoretically reducing structural barriers to economic mobility. Regardless, hair is synonymous with Black women’s identities. Possibly due to society’s afro-political ideologies of beauty, Black women tend to use more hair products compared to other racial groups. These standards include social structures that affect self-mediated worth, as well as structural and interpersonal racism based on appearance and societal status. The use of personal care products containing endocrine disrupting chemicals (EDCs) has been shown to increase Black women’s breast cancer risk. The Black identity, hair product use, and breast cancer scale (BHBS) was developed to measure the sociocultural constructs associated with Black women’s hair product use and perceived breast cancer risk. The purpose of this study was to validate the BHBS and examine hair product use among Black breast cancer survivors.
Methods: Participants (N=162) completed a 27-item survey between 2020 and 2022 via a community-based participatory research project—Bench to Community Initiative. Principal component analyses (PCA) and confirmatory factor analysis (CFA) were used to establish the underlying component structures and determine the model fit. Chi-square tests were used to determine associations between BHBS subscales and product use, with a p-value < 0.05 defined as statistically significant. Products evaluated included washout and leave-in conditioners, salon, and do-it-yourself (DIY) relaxers, and salon and DIY hair dyes. Response options were used daily through several times a year (daily–yearly), used but stopped, and never used. Results: Participants were African American (90%) and African or Caribbean (10%) Black breast cancer survivors. The mean age (standard deviation [SD]) and stage of diagnosis (SD) was 37.4 ± 8.8 and 1.9 ± 0.97, respectively. PCA yielded two components that accounted for 63% of the total variance in the model. Five items measuring sociocultural perspectives about hair and identity (subscale 1 [S1]) accounted for 28% of the total variance (α = 0.73, 95% CI 0.71, 0.82). Six items assessing perceived breast cancer risk related to hair product use (subscale 2 [S2]) accounted for 35% of the total variance (α=0.86, 95% CI= 0.81, 0.94). CFA confirmed the two-component structure (Root Mean Square Error of Approximation = 0.034; Comparative Fit Index = 0.93; Tucker Lewis Index = 0.89). On average, participants used hair products daily–yearly, including conditioners (64%), relaxers (32%), and hair dyes (33%). The use of salon relaxers was significantly associated with BHBS subscales (S1and S2). Similarly, salon hair dye was significantly associated with S2 of the BHBS. Discussion: The BHBS is a valid measure of sociocultural perspectives associated with hair product use and perceived risk for Black breast cancer survivors. Given that hair remains an important cultural expression within the afro-political confines of identity, the health impacts of hair products containing EDCs used to craft these identities should be considered in intervention planning.

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Dede Teteh, DrPH, MPH: No financial relationships to disclose
Aqua polo: Preliminary feasibility and efficacy study of a programme of adapted, supervised water polo to reduce fatigue and improve women’s psychological and social recovery after breast cancer treatment. A mixed-method design.

Introduction: Physical activity has been shown to have many benefits, including reducing cancer-related fatigue (CRF) and improving psychological and physical recovery from breast cancer. Some authors have shown the benefits of aquatic practice, while others have detailed the benefits of group and supervised practice. We hypothesise that an innovative sports coaching proposal could allow a significant adherence of patients and contribute to their health improvement. The main objective is to study the feasibility of an adapted water polo programme (aqua polo) for women after breast cancer. Secondary we will analyse the effect of such a practice on patients’ recovery and to study the relationship between coaches and participants.
The use of mixed methods will allow to question precisely the underlying processes. Methods and analysis: This is a prospective, non-randomised, monocentric study with a sample of 24 breast cancer patients after treatment. The intervention is a 20 week programme (1 session per week) of aqua polo in a real sports setting. The variables measured are patient participation, quality of life (QLQ BR23), CRF (R-PFS) and post-traumatic growth (PTG-I) as well as different variables to observe physical capacity (strength with dynamometer, step-test and arm amplitude). The quality of the coach-patient relationship will be evaluated (CART-Q) to explore its dynamics. Participatory observations and interviews will be carried out to report on the interactions between the coach and the participants during the sessions. Ethics and dissemination: Study procedures have been approved by the Institutional Review Board of the Institute (IPC 2019-028) and the National Ethics Committee (SI:20.01.20.54741). Consent is given in person to each participant. The information collected on the participants contain only a non-identifiable study identifier. The results of this protocol will be published in a scientific paper and communicated to the medical staff of the medical center. Trial registration number ID-RCB: 2019-A03003-54 Keywords: Quality of the relationship, Aquatic exercise, Quality of life, Sport

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Advocate-BREAST: Advocates and Patients' Advice to Enhance Breast Cancer Care Delivery, Patient Experience and Patient Centered Research by 2025

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Background: The high-level aims of the Advocate-BREAST study are to study and improve the overall experience of patients with breast cancer (BC) through education, shared decision making, and patient-centered clinical trials. Assessing areas of unmet need in care delivery and research as identified by patients with BC will direct future research and help us improve the patient experience. Methods: In April 2022, an electronic RedCap survey was circulated to 6,918 BC survivors (stage 0-4 disease) enrolled in the prospectively consented Mayo Clinic Breast Disease Registry (MCBDR), which includes rural-dwelling women often underrepresented in cancer care delivery research. The questionnaire asked about satisfaction with multiple aspects of cancer care delivery and the education and support patients receive(d) regarding practical, financial, emotional, societal and spiritual concerns linked to BC. Patients were also asked to rank potential Quality Improvement (QI) projects in order of the likelihood the proposal could improve quality of life for BC patients and their families. Questions regarding clinical trial participation, use of integrative medicine and perspectives on medical second opinions were also included. Responses were collected via anonymous local language questionnaires. Results: The survey received 2,451 responses from MCBDR enrollees. 13% of
respondents had Ductal Carcinoma in Situ (DCIS), 83% had early breast cancer (EBC) (Stage 1-3) and 4% had metastatic breast cancer (MBC). Mean age was 64 (SD 11.9), and mean time in months since diagnosis was 93 (SD 1.42). 69.3 % of patients received all care at Mayo Clinic; 24.7% at Mayo and another healthcare organization, and 6% at a non-Mayo site. Although the overall experience of care was generally good/excellent (> 90 %), gaps were perceived in terms of information provision, continuity of care (including survivorship care after 5 years), navigating care transitions, and timely access to mental health resources. The main severe symptoms patients recalled in year 1 were hair loss, eyebrow/eyelash thinning, hot flashes, sexual dysfunction and cognitive issues. The main concerns patients recalled in the first year following diagnosis were fear of BC recurrence and spread as well as of dying, practical and emotional concerns for family members if they were to die of BC, and their emotional health. Patients were most dissatisfied with information and support related to management of lymphedema, sexual dysfunction, eyebrow/eyelash thinning, and peripheral neuropathy. Respondents overwhelmingly voiced the need for the following QI projects: i) lifetime access to online patient educational resources: including summary “cheat sheets”; ii) educational, practical, emotional and holistic support programs for MBC patients, and iii) BC Wellness Programs for EBC and MBC patients (endorsed by 82.6%; 82.4% and 81.9% of respondents, respectively). Predictors in terms of age, time since diagnosis, and cancer stage that may account for satisfaction with care, concerns, or QI preferences will be reported at the meeting. Of 20% of patients who saw an Integrative Medicine provider, 85% were satisfied/very satisfied with the care received. Of ~40% of patients who received a second opinion regarding their BC diagnosis and treatment plan, 96% found this beneficial. 47% of respondents had participated in a clinical trial, which is higher than seen in the general population such that conclusions may not be generalizable. Of those who had not participated in a study, 30% reported that they were unsure if they would participate in a trial if offered, and 9% reported that they would decline same. Conclusion: Understanding the lived experiences of persons with BC is essential to improve quality of care. Patients with early and advanced BC desire holistic care, continuity of care, concise educational resources and early psychological support.

Disclosure(s):

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(Fluoroscopy-guided) Manual lymphatic drainage does not substantially improve the effect of decongestive lymphatic therapy in people with breast cancer-related lymphoedema (EFforT-BCRL trial): a multicentre randomised trial

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Importance: Although worldwide applied for the treatment of breast cancer-related lymphoedema (BCRL), the effectiveness of manual lymph drainage (MLD) remains unclear. Since 1930, traditional MLD is applied. Recently, the method of MLD has been optimised by making it patient-tailored (i.e. fluoroscopy-guided MLD). Objective: To investigate the effectiveness of fluoroscopy-guided MLD additional to decongestive lymphatic therapy (DLT), compared to traditional or placebo MLD, for the treatment of BCRL. Design: Multicentre, three-arm, double-blinded randomised controlled trial with concealed allocation and intention-to-treat analyses. Setting: Five hospitals in Belgium. Participants: 194 participants with unilateral chronic BCRL were enrolled. Four patients were lost to follow-up during the intensive treatment
Interventions: Participants were randomised into one of three groups, receiving standard DLT (consisting of education, skin care, compression therapy and exercises) either including fluoroscopy-guided MLD (n=63), traditional MLD (n=63) or placebo MLD (n=64). Participants received 14 sessions of physical therapy during the 3-weeks intensive phase and received 17 sessions during the 6-months maintenance phase. On the other days the participants performed self-management. Main outcome measures: Primary outcomes were 1) change in excessive volume reduction of the arm/hand, and 2) change in excessive volume accumulation at the shoulder/trunk. Primary endpoint was at the end of the intensive phase. Measurements were performed at baseline, after the intensive phase, after 1, 3, 6 months of maintenance phase, and after 6 months of follow-up. Results: In all three groups, excessive lymphoedema volume decreased significantly after three weeks of intensive treatment (p < 0.001). No differences between the fluoroscopy-guided MLD group (mean absolute reduction of 5.3 (95% CI: 3.9-6.7) percentage points of % excessive volume representing a relative reduction of 23.3%) and the traditional MLD group (mean absolute reduction of 5.2 (95%CI 3.8-6.6) percentage points of % excessive volume) were found. An increased fluid accumulation at the level of the shoulder/trunk was present in all three treatment groups, however, this was not significantly different between the groups (p>0.0125) (mean difference between the fluoro-MLD and traditional MLD group (95% CI): -3.6% (-6.4; -0.8), p= 0.013; mean difference between fluoro-MLD and placebo- MLD group (95% CI): -2.4% (-5.2; 0.4, p= 0.101)). Conclusions: In patients with chronic BCRL, evidence for a benefit of MLD in addition to the other components of DLT could not be demonstrated. There is no indication to still prescribe and include time-consuming MLD in the treatment of BCRL. Trial registration: clinicaltrials.gov identifier: NCT02609724, EudraCT Number 2015-004822-33

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Validity of EQ-5D-5L for women with breast cancer

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  Country: United States

Background: The EuroQol- 5 Dimension (EQ-5D) is a generic patient-reported outcome measure widely used to capture meaningful change in health-related quality of life between treatments to inform drug and health technology reimbursement decision making. We investigated the construct validity of EQ-5D-5L in women with breast cancer.

Methods: This study included adult women diagnosed with stage I to IV breast cancer, who completed the EQ-5D-5L and the Edmonton Symptom Assessment System (ESAS) during outpatient clinic visits at two academic cancer centres in Toronto. We evaluated construct validity through assessing known-group validity and convergent / divergent validity. For known-group validity, the primary analysis tested the hypothesis that EQ-5D-5L could adequately discriminate between patients with metastatic disease and early-stage disease; secondary analyses addressed utility values between women in breast-cancer associated health states. A suggested minimally important difference (MID) for the Canadian scoring of the EQ-5D-5L is 0.037; we evaluated whether the lower bound of the 95% confidence interval (95%CI) exceeded this value. In terms of convergent / divergent validity, the primary analysis tested the hypothesis that EQ-5D-5L mean utility values for each health state (HS) would be at least moderately correlated with ESAS total symptom distress score (SDS) (|r|>0.30) using Wilcoxon rank-sum tests and Spearman’s correlation tests. Construct validity was considered as acceptable if the hypotheses of the primary analysis are satisfied.

Results: We recruited 549 women, 406 (74%) with early-stage disease and 143 (26%) with metastatic disease (HS5), with a mean age of 57 (SD 12); 412 (75%) had been diagnosed with breast cancer in the 7 years prior to recruitment and were receiving active treatment for their cancer.

The mean utility value for early-stage breast cancer was 0.84 (95% CI 0.83-0.86) and for metastatic breast cancer (0.78, 95% CI 0.76-0.81). This difference was 0.060 (95% CI 0.036 to 0.085, p< 0.001) with the lower bound of the confidence interval slightly less than the prespecified MID (0.037). There was no significant difference between the mean utility value for women in the first year after primary breast cancer diagnosis (HS1), and women in their second to fifth year after a primary breast cancer treated with curative intent (HS3) or between women in HS1 and women in their sixth and following years after a primary breast cancer treated with curative intent (HS4). EQ-5D-5L also did not discriminate between women in HS3 and HS4.
For convergent / divergent validity, there was a negative correlation between utility values and ESAS physical, emotional and total SDSs. EQ-5D-5L and ESAS total SDSs correlation coefficients were higher than 0.30 for all health states. Conclusion: EQ-5D-5L met criteria for convergent/divergent validity in women with breast cancer. The tests for discriminant validity were equivocal, suggesting more research is needed for assessing construct validity with a larger sample size.

Table 1- EQ-5D-5L Utility Values

<table>
<thead>
<tr>
<th>Health State</th>
<th>N (%)</th>
<th>Mean (95%CI)</th>
<th>Std Dev</th>
<th>Median</th>
<th>Min-Max (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Study Population</td>
<td>549 (100)</td>
<td>0.83 (0.82-0.84)</td>
<td>0.13</td>
<td>0.87</td>
<td>0.13-0.95 (0.11)</td>
</tr>
<tr>
<td>Women with early-stage Breast cancer</td>
<td>406 (74%)</td>
<td>0.84 (0.83-0.86)</td>
<td>0.12</td>
<td>0.87</td>
<td>0.13-0.95 (0.10)</td>
</tr>
<tr>
<td>Women with metastatic breast cancer</td>
<td>143 (26)</td>
<td>0.78 (0.76-0.81)</td>
<td>0.14</td>
<td>0.81</td>
<td>0.29-0.95 (0.20)</td>
</tr>
<tr>
<td>Early-Stage Breast Cancer Health States</td>
<td>N (%)</td>
<td>Mean (95%CI)</td>
<td>Std Dev</td>
<td>Median</td>
<td>Min-Max (IQR)</td>
</tr>
<tr>
<td>First year after diagnosis primary breast cancer (HS1)</td>
<td>146 (27)</td>
<td>0.85 (0.83-0.86)</td>
<td>0.12</td>
<td>0.87</td>
<td>0.23-0.95 (0.08)</td>
</tr>
<tr>
<td>First after local recurrence or diagnosis new primary (HS2)</td>
<td>13 (2)</td>
<td>0.78 (0.65-0.90)</td>
<td>0.21</td>
<td>0.87</td>
<td>0.13-0.95 (0.12)</td>
</tr>
<tr>
<td>2nd to 5th year after a primary breast cancer (HS 3)</td>
<td>185 (34)</td>
<td>0.84 (0.83-0.86)</td>
<td>0.11</td>
<td>0.87</td>
<td>0.21-0.95 (0.10)</td>
</tr>
<tr>
<td>6th and following years after a primary breast cancer (HS 4)</td>
<td>62 (11)</td>
<td>0.86 (0.82-0.89)</td>
<td>0.14</td>
<td>0.90</td>
<td>0.36-0.95 (0.10)</td>
</tr>
</tbody>
</table>

N= number; Std Dev= standard deviation; IQR= interquartile range; CI= confidence interval

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Sofia Torres, n/a: No financial relationships to disclose
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Nicholas Mitsakakis, n/a: No financial relationships to disclose
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Background: Rates of contralateral prophylactic mastectomy (CPM) have more than doubled in the past decade amongst breast cancer patients irrespective of inherited genetic predisposition related to high penetrance genes. Increasing numbers of women with unilateral breast cancer are opting for removal of both the affected ipsilateral and unaffected contralateral 'normal' breast even when suitable for breast conserving surgery. Reasons for requesting CPM include prevention of recurrence, peace of mind and moving on after breast cancer. Some women seek CPM as a delayed procedure but factors influencing this are poorly understood. Methods: A retrospective analysis examined patients undergoing CPM as either an immediate or delayed procedure with or without breast reconstruction (BR) at a single tertiary referral centre between January 2009 and December 2019. 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 (1 = strongly disagree to 5 = strongly agree) with calculation of mean scores and standard deviation (SD). This questionnaire explored patient’s decision-making process in terms of timing of CPM and any BR and was supported by subjective free-text boxes to gauge qualitative and quantitative aspects of the patient-related decision-making process. Those patients who consented to participate were provided with access to an online questionnaire. Results: Amongst this cohort of 39 delayed CPM patients, there were 6 decliners and therefore questionnaires were issued to the remaining 33 patients. The response rate was 67% (22/33) and the most common reason for seeking delayed CPM was to allow completion of adjuvant treatment recommendations (including radiotherapy/chemotherapy) before surgery on the unaffected breast [mean score 2.91; SD 1.0]. This avoided risk of delay in commencement of adjuvant treatment consequent to potential complications of contralateral surgery (especially with BR). The second most important reason for choosing delayed CPM was unavailability of genetic test results at the time of therapeutic mastectomy [mean score 2.64; SD 1.4]. The third most common reason was a subsequent change in family history cancer history after their personal breast cancer diagnosis that often prompted genetic testing [mean score 2.55; SD 2.7]. Several patients cited a shorter recovery time as a strong reason for requesting delayed CPM. Conclusion: Factors determining delayed CPM are patient-driven and this accords with documented reasons for women seeking CPM in general. Patients tend to make decisions about CPM based on two main themes relating to either ‘fear’ of cancer or a desire to ‘take control’. Temporal factors are important in the context
of a delayed procedure and relate to subsequent availability of genetic test results and changes in family history in relatives who were otherwise unaffected at the time of initial diagnosis. Completion of all cancer treatments prior to delayed CPM (with BR) can be advantageous when implant-based BR is planned at the time of an immediate CPM. Radiotherapy can increase capsular contracture rates and surgical complications can delay start of chemotherapy. CPM should be offered as a potentially delayed option with informed discussion of risks and benefits.

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Providing Educational Resources during the Pandemic for Advanced Breast Cancer Patients

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Significance and Background: Metastatic Breast Cancer (MBC) or Advanced Breast Cancer (ABC) is multifaceted and requires high levels of support and resource utilization. The ABC Program at MD Anderson Cancer Center began in 2014 with a goal to increase the quantity and quality of life for patients living with MBC. It offers emotional support, personalized visits with a nurse practitioner navigator, access to clinical trials, specialty clinics, tailored patient education and innovative care projects. Prior to COVID-19, the ABC Program held a 90-minute quarterly town hall series featuring 2-3 presenters and topics of patient interest. In response to COVID-19, it pivoted to a weekly virtual 60-minute educational series called “ABCs of Healthy Living in Challenging Times” that is for patients with breast cancer, caregivers, faculty, staff, community members and advocates. Purpose: To address COVID-19 social-distancing related isolation and changes to healthcare, build community, empower patients, and educate on diverse topics including patient services, treatment, symptom management and quality of life. Interventions and Evaluation: The series was facilitated by a nurse practitioner navigator via Zoom. A distribution list created from town hall meetings was the basis for the series’ notices and has grown by referrals, word of mouth and marketing opportunities; it began with less than 150 people and has grown to more than 550 people. The facilitator offered a format where the attendees and speakers could interact visually and verbally with each other. From 4/2020 to 6/2022, 104 webinars were held for 2,546 attendees for an average of 24 attendees each week. Topics covered were side effect management/quality of life/healthy lifestyle (26%), patient education/empowerment (18%), treatment (19%), clinical trials/research (11%), quality of life related to COVID-19 (8%), COVID-19 (7%), innovation projects (4%), palliative/end of life care (7%), and financial/disability concerns (3%). The series was evaluated using the Qualtrics survey software (n=53). Respondents said that the series has positively influenced their interactions with healthcare providers (65%), how patients with MBC think about their cancer experiences (65%) and provided an opportunity to connect with others like themselves (65%). Respondents stated actions taken based on the series: shared the information with family/friends (77%), joined or remained in a support group (34%), spoke with a provider for
information and services (32%), requested an appointment with the ABC Program or other specialty clinics (26%), started a new healthy behavior (21%), joined a clinical trial (11%), or started using a patient reported outcome tool (9%). The series served mostly patients living with MBC (70%), established patients at MD Anderson (38%) or patients at MD Anderson as well as a community cancer center (17%). Most respondents indicated that they attended about half of the time, usually or always (60%) and are very or completely satisfied with the series (92%). Demographics of the respondents were White (77%), Black (13%), Asian (4%) and Hispanic (16%). Discussion: The ABC Program pivoted to COVID-19 by offering services virtually. The virtual series has allowed for more digestible patient education, varied presentations, and participation for those living outside of Houston, TX. Peer support and continuing education are imperative dynamics for patients to use their voice to impact their overall quality of life. The series has impacted attendees with a change in behavior when speaking with their clinical team, awareness and utilization of support resources, and starting healthy behaviors. While the series was created in response to demands of COVID-19, it effectively addressed psychosocial and educational needs and overall quality of life of MBC patients. The series was an easy intervention to initiate with lasting changes relative to the effort and resources required.

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Project SOAR (Speaking Our African American Realities): A qualitative study of the Strong Black Woman schema in the breast cancer context

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Background: Marked disparities exist for African American women, relative to non-Latina white women, in the five-year survival rate for breast cancer. Black women breast cancer survivors also demonstrate relative disadvantage in specific quality of life (QOL) domains, persisting through at least two years after diagnosis. Although Black women have higher QOL in the spiritual domain relative to white women, disparities include lower physical QOL, as well as more pronounced depressive symptoms, perceived stress, fear of dying, unmet supportive care needs, and financial distress, with younger Black women (< 50 years) particularly at risk. African American breast cancer survivors also report receiving too little information from their oncologists during diagnosis, treatment, and follow-up care. Sociodemographic and medical factors only partially explain the QOL disparities. The goal of Project SOAR (Speaking Our African American Realities), a community-academic partnership, is to interrogate the potential relevance of the Strong Black Woman (or Black Superwoman) schema in the breast cancer context. The schema involves historically grounded expectations to prioritize caregiving over self-care, suppress emotions, present an image of strength, decline support, and strive to achieve success without adequate resources. Method: Black women were recruited via relevant email listservs and flyers distributed at local breast cancer events to take part in a study “to understand the unique experiences of African American women and their views on the Strong Black Woman concept as it applies during their breast cancer experience.” Eligibility criteria were self-identification as being: 1) an African American woman (or a Black woman living in the United States); 2) diagnosed with breast cancer (any stage, any diagnosis duration); 3) at least 21 years old; and 4) able to communicate in English. Three Gatherings (i.e., culturally curated focus groups) were held as half-day experiences in intimate settings (e.g., private homes, a church) in three California cities (Sacramento, Oakland, Los Angeles). Gatherings provided an entirely Black women’s space to discuss the breast cancer experience and the relevance and consequences of the Strong Black Woman schema, break bread together, and engage in an inspiring activity. Reflexive thematic analysis was conducted on the Gatherings transcripts with
a critical realist, contextualist approach. Results: All participants (N = 37; age range = 30-94 years; M = 59 years) had heard of the concept of the Strong Black Woman. Reflexive thematic analysis yielded six themes: 1) historical legacy of Strong Black Woman; 2) navigating intersecting Strong Black Woman identities; 3) everyday challenges encountered on the battlefield by Strong Black Women; 4) Strong Black Woman in action during the breast cancer journey; 5) the complexities of seeking and accepting support; and 6) the liberated Strong Black Woman. Participants linked both negative and positive consequences with the Strong Black Woman schema. Negative consequences included the oncologic team and others expecting them to be strong and not to need support, as well as expectations of themselves to suppress emotions and to continue caring for others to the neglect of caring for themselves. Positive consequences included engaging in self-advocacy in the oncologic context, having a sense of resilience, and redefining strength to include expressing emotions and accepting help from others. Conclusion: Qualitative analysis revealed the relevance of the Strong Black Woman schema in the breast cancer context, as well as its negative and positive consequences. Future research can assess whether oncologic professionals’ awareness of the schema is useful in ensuring they offer support and refer Black women diagnosed with breast cancer to culturally relevant supportive resources.

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Preimplantation genetic testing for BRCA gene mutation carriers - the future of health care in Poland?

Introduction
Genetic background is rarely the cause of breast cancer incidence. Mutations in genes that increase the risk of breast cancer (most commonly BRCA1/2) are diagnosed in about 5-10% of patients. The lifetime risk of breast cancer in BRCA1/2 gene mutation carriers is 80%, and for ovarian cancer from 40-60%, while the chance of passing the mutation to offspring is 50%. The use of pre-implantation genetic testing (PGT-M) of the embryo during in vitro treatment prevents the transfer of mutated gene associated with an increased risk of cancer to the child. The significantly limited availability and high cost of PGT-M in Poland prevent its widespread use. The aim of the survey was to assess interest in PGT-M by female carriers of mutations in genes that increase cancer risk in Poland.

Material and Methods
The survey covered 103 persons, 102 with diagnosed mutations in genes that increase cancer risk. The questionnaire consisted of 22 questions regarding: age and gender of the patients, carriage of mutations in genes that increase the risk of cancer (age of mutation diagnosis, type of mutation, preventive measures taken, carriage of mutations in the family, incidence of cancer among relatives, and care of relatives during illness), and knowledge of pre-implantation diagnosis and attitudes regarding the use of PGT-M to avoid passing the defective gene to offspring.

Results
The study included 101 women (98.1%) and 2 men (1.9%), with a median age of 38 years (22-74). Fifty-two (50.5%) were diagnosed with cancer: 50 with breast cancer and 2 with ovarian cancer. Eighty-one subjects (78.6%) were diagnosed with a mutation in the BRCA1 gene, seventeen (16.5%) in the BRCA2 gene, three (2.9%) in the CHEK2 gene, two (1.9%) in the TP53 gene and one (1%) in the PALB gene. The median age of mutation diagnosis was 34 years (18-66). A significant proportion of patients took prophylactic measures, sixty-one (59.2%) underwent risk-reducing mastectomy (RRM), and forty-six (44.7%) risk-reducing salpingo-oophorectomy (RRSO). Ninety-five subjects (92.2%) declared regular visits to a genetic counseling center. Thirty-two persons (31.1%) had a family history of cancer (1-5 members in the family), mainly in 1st degree relatives – parents and siblings (about 60% of cases), the predominant cancers were breast cancer (106 cases), ovarian cancer (38 cases) and prostate cancer (7 cases); eighty-two family members died of cancer, seventy-five (72.8%) respondents accompanied family members in the dying process. Twenty-six individuals (25.2%) knew what PGT-M was, information was obtained from an oncologist (11), gynecologist (7), geneticist (6), other patients (6) and most often from the Internet (17). Seventy-four respondents (71.8%) had children. Thirty-three (32%) declared that information about carrying a mutation in a gene that increases cancer risk influenced their decision to have offspring. Sixty-eight (64.1%) of the respondents, with prior knowledge of PGT-M and with the availability of the method, would have used the diagnosis in combination with in vitro fertilization to avoid passing the defective gene to offspring. Fifty subjects (48.5%) were willing to cover the costs of this procedure.

Conclusions
PGT-M in combination with in vitro fertilization is a safe and effective method of preventing the transfer of a defective gene to offspring. Due to the lack of availability and high cost of the procedure, it is not available in daily clinical practice among carriers of mutations in genes that increase the risk of cancer in Poland. Their own incidence of cancer, multiple incidences in family members and involvement in the dying process may influence patients’ decisions to have offspring and motivate them to seek out centers offering PGT-M. The results of this survey indicate the need to offer pre-implantation testing to patients despite the lack of reimbursement and to increase its availability in Poland.
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Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Organon Polska Sp. z o.o.: Consulting Fees (e.g., advisory boards) (Terminated, March 11, 2022)
Perceptions About Breast Cancer in North Africa: A Social Listening Project

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Background
Social media platforms are a versatile platform used for exchange of information. It is increasingly being used by patients, caregivers, and physicians to interact and engage among themselves and with healthcare organizations. Breast cancer is the most commonly diagnosed cancer in the world, with ~2.3 million cases in 2020 alone. Hence, it is vital to understand the perceptions about breast cancer from a wider lookout to bridge the gaps in patient management.

The objective of this study was to understand the trends in social media conversations and current perceptions about breast cancer in the North African countries.

Methods
Artificial Intelligence (AI) technologies hosted by Brandwatch (a social analytics tool) were used to scan 100M websites to analyze publicly visible online conversations about cancer between November 1, 2018 and October 31, 2021. Conversations from 6 North African countries i.e. Algeria, Egypt, Morocco, Sudan, Tunisia, and Western Sahara were analyzed in 3 languages (Arabic, English, and French).

Conversations were filtered to isolate breast cancer and related mentions. To isolate the voice of breast cancer patients and their caregivers, manual review of all non-news content in which pronouns appeared within 7 words proximity of disease terms was carried out.

Results
A total volume of 53,354 conversations (43,785 Arabic, 6,161 English, and 3,408 French) on breast cancer were analyzed.

Breast cancer was the most discussed cancer type, contributing to 63% of Arabic, 61% of English, and 66% of French conversations among total cancer related conversations. Egypt led the volume of breast cancer related conversations in Arabic and English, followed by Sudan. Morocco led the volume of conversations in French, followed by Tunisia. For all 3 languages, the proportion of male authors dominated the volume of conversations as compared to female authors (60% of Arabic, 54% of English, and 56% of French). A total volume of 590 (347 Arabic, 158 English, and 85 French) conversations about breast cancer were identified as patient related. Twitter was the most popular platform for Arabic and English-speaking populations.

The most discussed topic about breast cancer was identified to be ‘Pink October’ or ‘Breast Cancer Awareness Month’.

Across all languages, impact on mental health and financial security was a significant patient concern. Many people reached out directly to the online community for financial support. In Arabic conversations, female patients expressed concern about impact on their relationship with their spouse (or future spouse) due to their condition. Patient conversations about the
Breast Cancer gene (BRCA) were also observed. However, there is little evidence about the extent of awareness among patients or their caregivers. There were scarce mentions about male/transgender breast cancer among conversations. Discussions about raising awareness, early detection, and self-checking of breast cancer were also identified.

Conclusion
Breast cancer was the most discussed type of cancer in North African countries. Patients and caregivers sought financial support on social media platforms. Based on types of conversations identified, it can be inferred that patients do not actively seek information about treatments and cancer management on social media.

These insights can be utilized to engage patients, caregivers, patient advocacy groups, and influencers to address concerns and disseminate accurate and simplified information for mass consumption.

Types of Patient Conversations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Conversation Category</th>
<th>Total</th>
<th>Arabic</th>
<th>English</th>
<th>French</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Financial impact</td>
<td>36</td>
<td>15</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Disease related</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Request for moral support</td>
<td>24</td>
<td>07</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Impact on mental health</td>
<td>34</td>
<td>05</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Impact on personal life</td>
<td>32</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Impact on social life</td>
<td>03</td>
<td>02</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Request for information</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Screening/ diagnosis conversation</td>
<td>80</td>
<td>44</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

Financial impact – This category included conversation in which patients and/or their caregivers have requested for financial support or have expressed concerns over the cost of treatment.

Impact on mental health – This category included conversations from patients about how breast cancer has affected their mental well-being and the associated emotions.

Impact on personal life – This category included conversations about impact of breast cancer on patients’ relationships with their spouse and their family. This category also included conversations about impact of breast cancer on marriage prospects.

Impact on social life – This category included conversations on the negative effect of breast cancer on patient’s social relations and social interactions.

* Retweets and reshared posts included

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Modeling a public-private grant initiative to address breast cancer care disparities at the community level

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Background: Breast cancer disparities between Black and White women have persisted in the US, with breast cancer death rates 40% higher in Black women compared to White women (American Cancer Society Cancer Facts & Figures for African American/Black People 2022-2024). Education and interventions at the community level can potentially reduce racial gaps, particularly in curbing late-stage diagnoses that disproportionately affect Black women with breast cancer. Together, the American Cancer Society (ACS) and Pfizer Global Medical Grants (Pfizer) developed a collaborative model to support health systems in engaging communities to reduce breast cancer disparities between Black and White women. This collaboration aimed to identify novel interventions and provide foundational support for these communities to advance their work in bridging the gap in breast cancer disparities. Methods: This collaborative grant program divided project responsibilities, in which Pfizer provided funding and ACS provided project oversight and technical support. An advisory committee provided input on the areas of most need, impact and project direction. Funding applicants were required to partner with local organizations to implement evidence-based initiatives for education and/or quality improvement within the respected community. The grant award selection committee comprised of experts in the field, including breast cancer survivors and individuals from racial/ethnic minority groups. In response to a Request for Proposals, over 100 applications were systematically reviewed based on the National Cancer Institute grant selection process. The committee selected 9 grantees with innovative proposals addressing breast cancer disparities for Black women along the cancer-care continuum. Bi-annual progress reports were used to measure progress, with a final report to mark projects’ impact and reach. The COVID-19 pandemic presented numerous obstacles during the project period and the ability to convene with partners virtually through web-based sessions helped to foster opportunities for collaboration and knowledge sharing among leaders in cancer disparities research. Results: The projects occurred from January 2020 to June 2022, with no-cost extensions given to accommodate COVID-19 pandemic delays. During this period grantees successfully completed project goals in one of three areas: screening, identifying areas of need and education. Approximately 10,000 patients and 200
healthcare professions were impacted among three projects focused on increasing mammography efforts in Black women during the project period. Three projects incorporated surveys and focus groups to identify novel areas for intervention/need and interviewed over 350 patients and over 60 health care professionals. The remaining three grantee projects that focused on education successfully implemented advertisement campaigns and lecture series to target patients and healthcare professionals. The projects selected under this model independently completed their goals within the project period while also laying a foundation to continue work in reducing disparities along the cancer care continuum with their enhanced community partner relations. Additionally, the project period also provided opportunities for external collaborations and discussion among all grantees through 8 ACS-coordinated online sessions and 3 summits. Conclusions: Projects selected by the public-private grant initiative model can enhance community relationships and provide infrastructure to continue work along the cancer care continuum. We believe this collaborative competitive grant program can be used for future efforts to address breast cancer and other health disparities at the community level. Similar collaborative funding projects related to prostate and pan-tumor disparities have been launched and are currently ongoing.

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Lobular Breast Cancer Alliance Inc. Survey of Individuals with Metastatic Invasive Lobular Carcinoma

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Background: The Lobular Breast Cancer Alliance Inc. (LBCA) is committed to raising awareness of the distinctive characteristics of invasive lobular carcinoma (ILC) and promoting and funding ILC research. Comprising 15% of all breast cancers, ILC tumors often form in a linear, sometimes diffuse fashion both within the breast and in metastatic sites, making them difficult to diagnose, monitor, and treat. LBCA surveyed individuals living with metastatic ILC (mILC) about their experiences with detection and monitoring of mILC. Methods: LBCA conducted an anonymous, online survey of persons living with mILC using SurveyMonkey. The survey was shared with LBCA newsletter subscribers, sister organizations, and via social media. Survey questions asked about metastatic site locations, imaging and monitoring modalities, and patient experience with disease progression and clinician discussions about mILC. An independent IRB review determined the study was exempt from full IRB review. Results: 241 people living with mILC completed the survey. 77% were from the US and Canada. 71% were between 35-64 years of age. 41% had been diagnosed with de novo metastatic ILC. Bone was the most common site of initial metastasis with 75% diagnosed de novo (DN) and 59% diagnosed with a distant recurrence (DR). GI metastases (including metastases to stomach, colon, bowel, peritoneum, or rectum) were reported by 11% of the DN and 14% of the DR groups, respectively. Unusual sites for breast cancer metastasis (to genitourinary organs, eye, or skin) were reported by 11% of the DN and 16% of the DR groups. Metastatic progression was reported by 47% of respondents including to bone (42%), to the liver (22%), and 40% reported progression within the initial metastatic site. 36% of individuals with DN mILC reported progression as compared to 54% among those with a DR. Both groups reported living with mILC for similar durations (on average 3.9 years for DN; 3.3 for DR). 36% of respondents reported that at least one imaging modality failed to visualize one or more of their metastatic sites at initial diagnosis of mILC. 54% of respondents with bone metastases and 19% of those with GI metastases indicated their metastases had not been visualized by standard imaging modalities. 48% of all surveyed stated their mILC was an unexpected or an incidental finding made during another medical procedure, of those, 64% were bone metastases. 25% of respondents whose metastases progressed indicated imaging failed to detect one or more of their sites of progression. In both the DN and DR groups, the most frequently utilized tests and/or procedures used to monitor for progression or changes in metastases were routine blood and tumor marker tests. Respondents with DN mILC reported an average 12 months between first report of symptoms and mILC diagnosis. Those with DR reported an average 8 months between symptom reporting and diagnosis. 42% of all respondents reported that a doctor had told them what symptoms to report at any time. 58% of respondents reported feeling that non-oncologists caring for them (primarily PCPs, radiologists, and gastroenterologists) needed to be better informed about ILC. Conclusion: Surveyed individuals confirmed the perception that mILC can occur in unique locations and be difficult to diagnose and that mILC may be challenging to monitor, and standard surveillance methods may fail to visualize mILC. While a large percent of respondents reported that their mILC diagnoses were unexpected or incidental findings during another medical procedure, this may be due to different understandings of “incidental.” This and the fact that more respondents with DR mILC reported progression than those with DN mILC warrant further study.

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Best Quality of Care from a Distance (BQual-D): Maintaining high quality care for hormone receptor positive (HR+) metastatic breast cancer (MBC) during the COVID pandemic, patient participation and satisfaction with the program.

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Background During the COVID pandemic, we designed and implemented a program, called BQual-D, to maintain high quality care for patients with HR+, HER2 negative MBC who were taking oral anti-cancer therapy and needed to shelter at home. This program augmented available clinical resources with (1) trained nurse coaches to manage side effects, improve adherence, monitor for cancer progression and screen for psychological distress via telehealth, and (2) a care coordinator to arrange blood testing at local labs to facilitate timely medication dose adjustments. BQual-D served patients from August 2020 through April 2021. Here, we describe survey results assessing patient (pt) satisfaction with BQual-D. Methods Pt's satisfaction surveys included questions rated on a Likert scale (1 “strongly disagree” to 5 “strongly agree”) with questions regarding the following: satisfaction with the quality of the nurse coaching calls; perception that the nurse coach listened to what they were trying to convey; whether or not their needs were met by the nurse coaching calls; whether they felt that they received adequate explanation regarding the nurse coaching calls; whether they would recommend the nurse coaching calls to a friend; perception of whether or not the nurse coach was negative or critical towards them; whether or not they would do it over (i.e., if they would return to the nurse coaching calls); whether or not they felt that the nurse coach was friendly or warm toward them; they were able to more effectively deal with care and symptoms; they felt free to express themselves; they were able to focus on what was of real concern to them; the nurse seemed to understand what they were thinking and feeling. Patients were also asked how much the calls helped with their care and symptoms. Descriptive statistics are reported (i.e., frequencies and means). Results 84 pts were screened and contacted for the BQual-D program. Of the 64 pts who responded, 52 (81.3%) were interested and enrolled in BQual-D; 12 (18.8%) declined. Among those who enrolled, 1 voluntarily withdrew, and 7 withdrew due to change in treatment. Participants had a mean age of 65 (range 36 – 88 yrs) and the following racial distribution - Caucasian/White (38, 73.1%), Black or African American (12, 23.1%), American Indian (1, 1.9%) and American Indian or Alaskan Native (1, 1.9%). Satisfaction surveys were received from 32 (50%) pts. Results of surveys regarding patient satisfaction with the nurse coach were generally positive. Pts agreed or strongly agreed that they were satisfied with the quality of the nurse coaching calls (94%), the nurse coach listened to what they were trying to convey (94%), their needs were met by the nurse coaching calls (91%), they understood the purpose of the call (90%), and they would recommend the nurse coaching calls to a friend (88%). The majority (74%) agreed or strongly agreed that they were able to more effectively deal with their care and symptoms after the nurse coach calls. When asked how much the calls helped their care and symptoms, 61% indicated that they made things a lot better, 19% indicated that they made things somewhat better, 16% indicated that they made no difference. One patient indicated that the calls made things somewhat worse. Conclusions During the COVID pandemic, when sheltering at home was encouraged, patient satisfaction with BQual-D, which provided additional health resources (nurse coaches, care coordinator) to support pts on oral therapy for HR+ MBC, was high. Resources needed to implement BQual-D should be explored as a way of providing additional support for pts to minimize the requirement for in-person visits. Funding: Supported by a grant from Pfizer.

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Addressing Healthcare Gaps and Disparities in Electronic Medical Record Messages: A Quality Improvement Project Among Breast Cancer Patients

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Introduction: Despite evidence that utilization of Electronic Medical Record (EMR) messaging positively impacts patients with cancer, there is little research on who uses EMR messaging and for what purpose.

Methods: Sociodemographic and MyChart usage data was collected from Epic to identify patterns of EMR messaging by patients at an academic breast center. Study eligibility included breast cancer patients who completed a visit and sent at least one message to a provider during the study period (May 2021- May 2022). Chi-square and t-tests were used to describe differences between users and non-users of EMR messaging. ANOVA and chi-square were used to describe differences between race/ethnicity. Analyses were performed in R version 4.2 and p< 0.05 was considered statistically significant.

Results: A total of 4069 patients who had MyChart account activated were included in the analysis sample. Of those, 3575 (87.9%) were messaging users and 494 (12.1%) were non-users. The mean age of users was significantly lower compared to the non-users (57.7 vs 61.2, p< .001). There were statistically significant racial/ethnic differences (p< 0.001) by user status with 83.9% and 9.5% of users being non-Hispanic White (NHW) and non-Hispanic Black (NHB) respectively. Among non-users 69.6% were NHW and 21.1% were NHB. There were also significant differences in preferred language (p< 0.001) and payor (p< 0.001) by user status. 99.2% of users were English speaking and 96.8% of non-users were non-English speaking. 54% and 38%, and 6.5% of users had Managed care, Medicare, and Medicaid respectively as their payor. Whereas 36.9%, 51%, and 10.5% of non-users had Managed care, Medicare, and Medicaid respectively. Lastly, there were statistically significant racial/ethnic differences in the types of messages sent among EMR users.

Conclusions: There are significant differences in race/ethnicity among EMR users and non-users, and racial/ethnic differences in the types of messages sent among EMR messaging users. We believe that these differences may be in part due to disparities in access or comfort in using EMR. Future directions include conducting interviews with minority patients who are users and non-users of EMR messaging to identify barriers and gaps in use.

Table 1. Patient Characteristics
Characteristics of users and non-users of EMR messaging. Chi-square and T-test for significance were performed to assess the difference between groups. P< .05 was considered significant.

Table 2. Message Type by Race/Ethnicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-User (N=494)</th>
<th>User (N=5575)</th>
<th>Total (N=5069)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE YEARS</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>61.188 (15.993)</td>
<td>57.710 (14.463)</td>
<td>58.132 (14.699)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>15 - 99</td>
<td>17 - 97</td>
<td>15 - 99</td>
<td></td>
</tr>
<tr>
<td>SEX</td>
<td></td>
<td></td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>Female</td>
<td>464 (98.0%)</td>
<td>3541 (99.0%)</td>
<td>4005 (98.9%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (2.0%)</td>
<td>34 (1.0%)</td>
<td>44 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>RACE/EThNICITY</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>344 (69.0%)</td>
<td>2998 (83.9%)</td>
<td>3342 (82.1%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>104 (21.1%)</td>
<td>341 (9.5%)</td>
<td>445 (10.9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (5.3%)</td>
<td>110 (3.1%)</td>
<td>136 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>COUNTY</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other Wi county/Out of State</td>
<td>69 (14.2%)</td>
<td>296 (8.3%)</td>
<td>365 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Milwaukee county</td>
<td>232 (47.8%)</td>
<td>1701 (48.0%)</td>
<td>1933 (47.9%)</td>
<td></td>
</tr>
<tr>
<td>Waukesha county</td>
<td>103 (21.2%)</td>
<td>503 (14.0%)</td>
<td>606 (14.9%)</td>
<td></td>
</tr>
<tr>
<td>Washington/Dane County</td>
<td>36 (7.4%)</td>
<td>279 (7.6%)</td>
<td>315 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>Racine/Xenosha County</td>
<td>45 (9.3%)</td>
<td>248 (7.0%)</td>
<td>293 (7.3%)</td>
<td></td>
</tr>
<tr>
<td>PREFERRED LANGUAGE</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>English</td>
<td>478 (96.8%)</td>
<td>3545 (99.2%)</td>
<td>4023 (98.9%)</td>
<td></td>
</tr>
<tr>
<td>Spanish</td>
<td>9 (1.8%)</td>
<td>12 (0.3%)</td>
<td>21 (0.5%)</td>
<td></td>
</tr>
<tr>
<td>Hmong</td>
<td>0 (0.0%)</td>
<td>4 (0.1%)</td>
<td>4 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Russian</td>
<td>2 (0.4%)</td>
<td>3 (0.1%)</td>
<td>5 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>American Sign Language</td>
<td>0 (0.0%)</td>
<td>2 (0.1%)</td>
<td>2 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.0%)</td>
<td>9 (0.3%)</td>
<td>14 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>INTERPRETER NEEDED</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>477 (97.0%)</td>
<td>3551 (99.3%)</td>
<td>4028 (99.9%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (3.0%)</td>
<td>24 (0.7%)</td>
<td>39 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>MAJOR</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Managed Care</td>
<td>180 (36.9%)</td>
<td>1922 (54.0%)</td>
<td>2102 (52.0%)</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>51 (10.5%)</td>
<td>230 (6.5%)</td>
<td>281 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>249 (51.0%)</td>
<td>1353 (38.0%)</td>
<td>1602 (39.6%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.6%)</td>
<td>51 (1.4%)</td>
<td>59 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>MEDICARE</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N</td>
<td>242 (49.0%)</td>
<td>2186 (62.1%)</td>
<td>2428 (59.7%)</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>252 (51.0%)</td>
<td>1389 (37.9%)</td>
<td>1641 (40.3%)</td>
<td></td>
</tr>
<tr>
<td>MEDICAID</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N</td>
<td>389 (78.7%)</td>
<td>3155 (88.3%)</td>
<td>3544 (87.1%)</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>105 (21.3%)</td>
<td>420 (11.7%)</td>
<td>525 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>DUAL COVERAGE</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N</td>
<td>445 (90.1%)</td>
<td>3417 (95.6%)</td>
<td>3862 (94.9%)</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>49 (9.9%)</td>
<td>158 (4.4%)</td>
<td>207 (5.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Types of message sent by race/ethnicity. ANOVA and chi-square were used to describe differences between race/ethnicity and type of message sent. P< .05 was considered significant.

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Science, Technology and Society have been related for many years with the goal of providing technological advances for the service of human development. Healthcare has not been immune to this influence and today there are numerous examples that promote the management of various diseases. Therefore, it is important to incorporate this technology into our daily lives, which will allow us to interact quickly and easily with various sectors of Peruvian society, regardless of their level of education or physical location. In this context, Technology and Innovation have become great allies in reinforcing health education and raising awareness of the importance of preventing and reducing the risks caused by cancer. By modifying some lifestyles for "healthy" ones, we would reduce the number of sick people. Knowing that in our country, 11 women die every day from breast and cervical cancer, totally preventable diseases that no one should die from; and that the government is completely overwhelmed in its preventive work, we decided to approach the mining industry. Together, we managed to create a "MOBILE CLINIC", an itinerant bus that will deliver medical care and perform oncological screening tests (Mammography, Ultrasound, Colposcopy and/or Laboratory Tests) to women from vulnerable populations in the communities that are within the area of influence of formal mining in Peru. Similarly, during these meetings all residents will be taught about the use of our Artificial Intelligence platform "MAUCHIS", (www.mauchis.org). Mauchis is the first and only free Platform available 24 hours a day, 365 days a year in Latin America for the prevention of cancer accessible from Whatsapp (+51 1 994003265) and/or Facebook Messenger. This service is free, no payment will be accepted and no institution or company is promoted.
"Clinical Trials are Space Travel": Moderators of Recurrence Stress among Breast Cancer Oncologists

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Background: Being an oncologist means accepting that some patients will have disease recurrence despite the most expert treatments. The universality of that experience, however, does not negate the potential for decisional regret and emotional distress on the part of the physician. The broad scale movement towards treatment optimization in medicine likely complicates this experience, as enrollment in de-escalation clinical trials inevitably means that the patient will receive less than the current standard of care. The objective of this study was to assess physician perceptions of potential emotional distress and decisional regret following patient recurrence through exploring the broad range of factors that either moderate or exacerbate those experiences. Methods: Physicians who treat breast cancer in academic and community settings across the United States participated in a qualitative interview designed to assess physician perspectives regarding patient enrollment in de-escalation clinical trials. Purposive sampling techniques were utilized to construct a balanced sample (sex, time in practice) of 39 participants. A subsection of the interview schedule centered on the experiences of decisional regret and distress surrounding patient recurrence. Interviews were recorded, transcribed, and analyzed in order to identify shared themes. Two independent coders performed a content analysis, identifying and recording factors that impact the level of distress that the physician may feel. Results: Thirty-six physicians provided in depth responses regarding their experience when a patient recurs. A total of 21 factors that affected recurrence stress were identified and spanned broad categories including patient features, disease biology, the design of the clinical trial, and characteristics of the physician. All participants expressed willingness to enroll patients in de-escalation-focused clinical trials. However, approximately half of the sample indicated that the experience would be worse after enrollment in a de-escalation trial than after a traditional intensification trial, and a quarter admitted that patient recurrence after a de-escalation trial would impact their decision making regarding future patient enrollment. Individuals not likely to experience distress emphasized having a strong trial rationale, informed patient consent, and engaging in shared decision-making, while greater distress centered on the fear of “not doing enough” and the patient missing out on necessary treatment. Conclusions: Many factors contribute to the experience of physician decisional regret and emotional distress after patient recurrence. Although most physicians recognize the importance of de-escalation focused clinical trials, a significant proportion indicated a greater potential for distress following patient recurrence in such trials and offered insight into how trial design and the process of patient enrollment can be improved to minimize potential distress. Disclosure(s):

Nicole L. Henderson, MPH, PhD: No financial relationships to disclose
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Financial Toxicity Outcomes on a Phase I 5-fraction Partial Breast Irradiation Protocol for Early Stage Breast Cancer

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Asal Rahimi, MD, MS, Associate Professor - University of Texas Southwestern Medical Center
Purpose/Objectives: Accelerated partial breast irradiation (APBI) has been shown to have both acceptable oncologic and cosmetic outcomes for early stage breast cancer following breast-conserving surgery (BCS). Given the demonstrated financial toxicity (FT) of conventional radiation treatments on breast cancer patients, we wanted to quantitatively assess the FT on patients treated with APBI in our phase I five fraction stereotactic APBI (S-PBI) trial, which could be generalized across APBI treatment regimens. Methods: A phase I dose escalation trial of S-PBI for early stage breast cancer following BCS was conducted. Women age > 18 years with in-situ or stage I-II (AJCC 7) invasive breast cancer < 3 cm following BCS with > 2 mm margins were treated with S-PBI in 5 fractions to a total dose of 30 to 40 Gy over 2.5 Gy increments (Clinical trials.gov ID NCT01162200). One month following completion of treatment, patients were asked to complete our novel “Patient Perspective Cost and Convenience of Care Questionnaire” developed at our institution. Results: Of 75 patients enrolled and treated, questionnaire data was available for 66 patients. Our trial encompassed a wide spectrum of annual household incomes, with 25.5% of patients (n=14/55) reporting income of less than $30k and 45.5% (n=25/55) reporting incomes of more than $80k. Educational status was also well represented with 53.1% completing at least some college (n= 34/64), 25% holding post graduate or professional degrees (n=16/64), and 21.9% patients reporting a high school equivalent or less (n=14/64). Overall 48.4% of patients (n=30/62) said that oncologic treatment did not present a financial burden; however, 29.0% (n=20/62) patients reported a somewhat to significant financial burden. Neither household income nor patient education status predicted perceived FT. Of the 6 patients (9.7%) who reported significant FT, 5 reported travelling at least 25 miles one way for treatment with 2 of these patient travelling over 175 miles. Half of the patients reported having private insurance for medication (49.2%, n=32/65), 33.8% had governmental coverage (n=22/65), 6.1% had both private and government coverage, 7.7% had no coverage (n=5/65), and 3.0% were unsure of their coverage (n=2/65). Only 1 of the 6 patients with significant FT had no coverage. Over half of the patients (54.2%, n=34/62) reported a co-pay during their treatment with a median out of pocket cost of $300 for treatment (range $10-10000, n=16). Over half of the patients were working full or part time during treatment (54.2%, n=32/59). All 26 patients that were working full time had to take time off work for treatment (median of 5 days, range 0.25 days – 10 days). Over a third of these patients (34.6%, n=9) had to use vacation time or unpaid time off. There was an additional patient who reported months off without pay. Additionally, 24.2% of patients (n=15/62) reported they had family or friends take time off work due to the patient’s treatment. Finally, patients were surveyed on the treatment related disruption to their daily activities and enjoyment of life rated on a scale 0-10, with 0 being no disruption, median values were 3 and 1, respectively. Patients also reported a median score of 10 (scale 0-10, 10 being most satisfied) on satisfaction with treatment time. Conclusions: In this cohort of patients, interestingly FT was significant primarily in the 10% of patients who traveled a significant distance for these treatments. However, despite this, and the fact that patients were undergoing cytotoxic cancer therapy, impressively, all patients were uniformly satisfied with treatment time (median score of 10), and most did not express significant disruption to their life. We plan to explore the impact of further reducing treatment fractions (with our single fraction S-PBI studies) on FT and quality of life in future studies.

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Objective: The aim of this study was to conduct a bibliometric and visual analysis of breast reconstruction related research at China and abroad published in the past five years, to understand the research status and development trend in this field, to discuss the focus of research in different countries and different disciplines, and to provide reference for other researchers. Methods: Relevant literatures about breast reconstruction were retrieved from the Web of Science Core Collection. The VOS viewer 1.6.15 software was used to extract the authors, countries, institutions and keywords to generate network maps of high-yield authors, institutions and high-frequency keywords clustering network. Results: 4,815 documents meeting the requirements were retrieved, which showed an upward trend in the past five years. Regarding the discipline, 838 documents (17.40%) were published by breast surgery and Cancer Surgery, 3308 (68.70%) were published by plastic surgery, and 669 (13.90%) were jointly published by both types of researchers. A total of 161 clinical trials were registered in the US clinical trial registry (ClinicalTrial.gov), of which intervention trials accounted for the highest proportion (107, 66.46%), followed by observational trials (54, 33.54%) and patient registry (4, 2.48%). Regarding country distribution, the United States conducted the largest number of breast reconstruction-related clinical trials (45, 27.95%), followed by China (22, 13.66%), Italy (12, 7.45%), France (11, 6.83%), the Netherlands (9, 5.59%). The top ten institutions
contributed 983 articles (20.41%), and the institution with the highest number of publications was MD Anderson Cancer Center (144, 2.99%), followed by Harvard Medical School (139, 2.89%), Sloan-Kettering Cancer Center (125, 2.60%), Stanford University (113, 2.35%) and University of Michigan (102, 2.12%). The author with the largest number of documents was Bernard T. Lee of Beth Israel Deaconess Medical Center (BIDMC), with 56 papers and 540 citations. The most cited author was Andrea L. Pusic of Brigham and Women's Hospital, with 48 papers and 1,332 citations. Chinese authors published 310 documents, accounting for 6.44%. There were differences in the disciplines of the main authors between China and abroad. In China, authors from breast surgery published a larger proportion of documents (138, 44.52%), while the number of documents published by authors of plastic surgery (129, 44.52%) and the joint publication of both types of authors (43, 13.87%) was relatively small. However, foreign documents mainly came from authors of plastic surgery (74.74%). There were more cooperative groups (155) formed by major foreign authors, and joint publishing between groups was more frequent; while Chinese author formed only 16 cooperative groups with less cooperation. Keyword cluster analysis showed that top five keywords were flap, implant, breast cancer, immediate breast reconstruction, tissue. In breast surgery publications, top five keywords were breast cancer, breast reconstruction, complications, implant, immediate breast reconstruction, while in plastic surgery publications top five keywords were flap, implant, tissue, breast cancer, infection. Authors from breast surgery focus more on oncology-related issues in breast reconstruction, while in plastic surgery, more attentions were paid on autologous tissue reconstruction. Conclusion: Breast reconstruction had gradually attracted the attention of Chinese and foreign researchers. Compared with foreign countries, there were problems such as lack of high-quality research and less cooperative research in China. There were differences in the research focus of breast reconstruction between China and abroad, which is mainly related to the differences in the disciplines of researchers.

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Developing and feasibility testing a web-based intervention (ePainQ) to support post-operative pain and symptom self-management following surgery for breast cancer

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Background: Breast cancer is the most commonly diagnosed women’s cancer with 2.3 million new global cases diagnosed in 2020. The global rise in survivorship has resulted in a significant health and economic burden on society. Breast cancer survivors report being overwhelmed physically and emotionally with treatment adverse effects. Recommendations include self-management support and personalised follow-up to meet patient needs. Persistent post-surgical pain (PPSP) is the most common negative consequence of breast surgery, often relating to inadequate acute post-surgical pain management. An unintended consequence of day surgery is reduced post-operative pain monitoring. There is a need to ensure appropriate support and pain monitoring alongside preparation, behavioural change and expectation management. Web-based interventions (WBI) could be a potential solution. A mixed-methods approach was used to develop a WBI to capture patient self-reported post-operative symptoms and provide individualised self-management advice. Methods: An audit and service evaluation revealed a 46% PPSP rate and identified opportunities where advice could support improved self-management. Developing the WBI (ePainQ) comprised a scoping review, systematic review, and development study with all results informing the development of ePainQ. ePainQ comprised two parts; a website containing supportive information and a post-operative symptom questionnaire. Intervention questions included pain, swelling, infection, functionality and QoL. Advice was generated for each question with different levels, based on CTCAE grading agreed with clinicians. A feasibility study prospectively tested ePainQ for acceptability, usability and perceived usefulness. Feasibility study aims were assessing uptake, retention, follow up and completion rates and acceptability of ePainQ. Study arms: usual care (cohort) or intervention (ePainQ). Intervention: daily online symptom questionnaire for 2 weeks commencing the day after surgery. Participants received immediate advice based on the severity of the reported symptoms, either self-management advice or in cases of clinical concern, advice to contact the hospital team. Reports were immediately available to HCPs as...
ePainQ was linked to the electronic patient record. Data collection: baseline, 2 weeks, 3 and 9 months post-operatively. Outcome measures: EORTC C30, and BR23, EQ-5D, HADS and BPI. Patient Activation was measured at baseline and 9 months. Results: 69 patients recruited over 8 months; 60 intervention and 9 cohort. Mean age: 57.7yrs (SD 9.8; range 38-82). Recruitment rate was 63%. IT issues prevented 12/60 using ePainQ but engagement of the 48/60 active participants was 89.6%. 40/48 completed a usability scale in which • 97.5% highlighted ePainQ as easy to use • 95% reported not needing any technical support • 90% felt very confident using ePainQ Outcome measures: 69/69 (100%) completion at baseline and 2 weeks. No active withdrawals with 13/69 passive withdrawals by 9 months. 67 participants (97.1%) consented to an interview invite with 14/67 interviews conducted. Participants were a mix of compliance rates to be reflective of the study and capture both positive and negative feedback. Feasibility study results demonstrated that ePainQ was perceived to be simple, easy to use and not requiring much learning to use effectively. All pre-set criteria for progression to a phase III RCT were met. Conclusion: ePainQ was designed in response to patient identified needs. The feasibility study established that ePainQ was accepted, used, and liked by participants who interacted with it. Even participants with limited use felt they had benefited from the advice. Results demonstrated patient positivity towards ePainQ suggesting recruitment rates could be increased if research capacity was improved and higher retention rates if IT issues were resolved and daily reporting duration was slightly reduced.

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Comparing Patient-Reported Outcomes for Same-day Discharge and Inpatient Admission After Mastectomy

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Background: Same-day discharge after mastectomy has been demonstrated to be safe in appropriately selected candidates. However, the association between same-day discharge after mastectomy and quality of life (QOL) is unclear. Patient-reported outcome (PRO) measures represent important indicators of QOL among patients undergoing treatment for breast cancer. In this study, we aimed to evaluate the effect of same-day discharge after mastectomy on PROs.

Methods: We performed a retrospective review of a prospectively collected, longitudinal PRO registry of female breast cancer patients treated at an academic breast center between June 2019 and June 2022. Patients were invited to complete the BREAST-Q module, a validated PRO questionnaire measuring QOL domains such as psychosocial wellbeing, physical wellbeing, satisfaction with their surgeon, and satisfaction with their medical team. Preoperative and 2-week postoperative questionnaire responses were analyzed in this study. Patients who had a mastectomy with or without reconstruction were included in this analysis. Those who underwent immediate reconstruction with autologous tissue were excluded as these operations are not conducive to same-day discharge. Patients were divided into two groups: the first was discharged on the date of surgery while the second was admitted to the hospital for a minimum of one night. Clinical and demographic factors were collected from a review of the electronic medical record. The primary endpoints were mean satisfaction scores as well as differences between postoperative and preoperative scores for the psychosocial and physical wellbeing domains. T-tests were used to evaluate differences between groups. A multiple regression model was fit to adjust for the effects of relevant clinical and demographic factors.

Results: A total of 104 patients within the registry underwent mastectomy during the study period and were offered questionnaires. Of these, 58 completed both the preoperative and 2-week postoperative questionnaire (56% response rate); 20 (34%) in the same-day discharge group and 38 (66%) in the inpatient admission group. The groups were similar in age, stage, American Society of Anesthesiologists’ classification group, body mass index, frequency of unplanned readmission or reoperation, and receipt of bilateral mastectomy, axillary lymph node dissection, post-mastectomy reconstruction, and neoadjuvant chemotherapy. Mean patient satisfaction scores and mean changes in psychosocial and physical wellbeing scores were similar between the groups 2 weeks after surgery (Table 1). After controlling for age, type of reconstructive operation, receipt of unplanned reoperation, and preoperative score, same-day discharge did not have a significant effect on satisfaction with the surgeon (Beta=-4.3, p=0.37), satisfaction with the medical team (Beta=0.2, p=0.97), physical wellbeing score (Beta=-0.1, p=0.99), or psychosocial wellbeing score (Beta=8.0, p=0.15).

Conclusions: Patients who are discharged from the hospital on the same day of a mastectomy display similar levels of satisfaction with their care team and similar short-term trends in physical and psychosocial wellbeing compared to those who are admitted to the hospital. While further data are being accrued, these early results suggest patients tolerate same-day discharge after mastectomy well.

Table 1
Patient-reported outcomes at 2 weeks after mastectomy for patients discharged on the date of surgery compared to those admitted inpatient

<table>
<thead>
<tr>
<th></th>
<th>Same-day Discharge</th>
<th>Inpatient Admission</th>
<th>Significance (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean change in score from baseline (SD)</td>
<td>Mean change in score from baseline (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=20</td>
<td>N=38</td>
<td></td>
</tr>
<tr>
<td>Satisfaction with Surgeon</td>
<td>87.5 (17.5)</td>
<td>90.0 (15.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Satisfaction with Medical Team</td>
<td>94.4 (12.8)</td>
<td>94.2 (12.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>Psychosocial Wellbeing – Change from Preoperative Score</td>
<td>-14.2 (27.4)</td>
<td>-5.8 (22.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Physical Wellbeing – Change from Preoperative Score</td>
<td>-28.4 (26.2)</td>
<td>-26.6 (31.4)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

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Early in the pandemic, cancer centers across the nation and Oregon canceled their cancer support programs as non-essential medical care. Breast cancer patients were forced to look elsewhere for essential assistance and community support to move along their cancer journeys.

Pink Lemonade Project (PLP), a Vancouver, WA based community based nonprofit, helped fill the gaps and expanded its local support for breast cancer patients. A virtual format allowed PLP to serve more individuals with our psychological, emotional and financial support programs. Next, PLP convened an informal coalition of all the local breast cancer support organizations including those that offer breast cancer support programs, community including dragon boating and rowing, and others that serve broader communities and more people of color.

Then, as Komen National announced its restructuring, and closed the Oregon-Southwest Washington affiliate in Spring 2021, Pink Lemonade Project stepped up again to maintain two locally-grown Komen programs that met critical community need--the MBC Dinner Series and the Treatment Access Program (TAP), a transportation assistance program that served all of Oregon and reduced the geographic barrier to care.

Through the coalition, PLP heard patients express concern that they were receiving outdated information and were struggling more to find needed support and resources from their providers. Understandably, nurse navigators and social workers could not maintain and/or
update patient resources while they assisted COVID patients. The goal of the coalition was to increase communication across the organizations and to share more event schedules for the ease of patients to understand what support programs are available.

This session, delivered by an all breast cancer patient panel, will give an overview of Pink Lemonade Project: its programs that helps with psychological, emotional, community and financial support for breast cancer patients, survivors and those living with metastatic breast cancer; and will highlight the results from the patient point of view of the systematic review of the contents of 6 regional health systems new patient binders and present recommendations for consistent, community-wide content for all future breast cancer patients.

The project’s main strength was that Pink Lemonade Project could draw upon on an existing coalition of local, community-based breast cancer organizations to help update and standardize breast cancer support information from the patient point of view. Then by acting as a neutral convener, PLP could request and receive the binders from all the region’s healthcare providers to help standardize and update the community resources across all the region’s cancer centers. The result is that any new breast cancer patient, regardless of where their access to care is, can receive consistent community-based information and resources.

Another result of this project showed the importance of the partnership of healthcare and human service agencies, especially in a post-pandemic world. As the pandemic continues to strain healthcare, community-based nonprofits have a unique role to help coordinate community resources and improve the quality of life for those affected by breast cancer.

Developing a Community Standard of Care for Individuals Diagnosed with Breast Cancer Across Oregon

Pink Lemonade Project/OHSU Community Partnership Program Grant: Developing a community standard of care for those diagnosed with breast cancer across Oregon.

The project’s main strength was that Pink Lemonade Project could draw upon on an existing coalition of local, community-based breast cancer organizations to help update and standardize breast cancer support information from the patient point of view. Then by acting as a neutral convener, PLP could request and receive the binders from all the region’s healthcare providers to help standardize and update the community resources across all the region’s cancer centers. The result is that any new breast cancer patient, regardless of where their access to care is, can receive consistent community-based information and resources.

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Pink Lemonade Project poster session

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People with metastatic breast cancer face barriers to finding information and support

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People with metastatic breast cancer face barriers to finding information and support

Background FORCE, a national nonprofit organization developed a health communication tool to help patients assess research relevance, key findings, and the quality of media reporting on cancer to support informed and shared health decision-making. People with metastatic breast cancer (mBC) are a priority population. Methods The organization conducted a survey about awareness of and access to breast cancer information and supportive services for people living with metastatic breast cancer. The organization promoted the survey through e-mail and social media, and a network of partner organizations that serve the metastatic breast cancer community. The survey invited respondents to volunteer to participate in focus groups and a follow-up survey in order to support efforts to serve this priority population. Results and Conclusions While interest in clinical trials was high, many users reported that they do not know how to find an appropriate clinical trial. A majority of the 335 respondents were interested in information about clinical trials, treatment side effects, research findings, long-term health issues, diet/exercise, fatigue, and emotional health. Three quarters of the respondents indicated that they had never participated in a clinical trial, 67% indicated they would be interested in participating in the future, and about 40% indicated they did not know how to find a
clinical trial recruiting people with metastatic breast cancer. Approximately one-third of participants were unable to obtain referrals to services they sought. Other barriers to services included lack of insurance coverage, lack of availability, and the COVID-19 public health emergency. Focus group responses indicate that women with mBC find the health communication tool to be useful, and appropriate in language, images, and tone. Results indicate that women with mBC are interested in finding information about clinical trials and other topics related to treatment side effects and quality of life. FORCE and partners are incorporating these results into tailored online resources to meet the needs of the mBC community.
Development of a patient advocate training at UNC’s Lineberger Comprehensive Cancer Center

Introduction: Patient advocates are survivors, caregivers, or people affected by cancer who represent the patient experience and bring a nonscientific viewpoint to the research process. Based on a previous assessment of engagement related needs of researchers and patient advocates at UNC’s Lineberger Comprehensive Cancer Center (LCCC), the need for a comprehensive training for patient advocates was identified to better facilitate collaboration in cancer research, including learning more about the role of patient advocates to prepare them for meaningful interactions with researchers. Purpose: To provide an engaging, empowering training for patient advocates involved in (or interested in becoming involved in) research projects with faculty and staff of LCCC. LCCC is committed to offering trainings that better equip researchers and patient advocates to meaningfully work together. This training will be the first step towards that goal and introducing patient advocates to patient advocacy, LCCC’s programs and services, and working with researchers. Methods: Prior to designing the patient advocate training, we, the student team working with LCCC, created a Curriculum Adaptation
Plan and Diversity, Equity, and Inclusion (DEI) plan to include implementation steps along with questions to ask, items to consider, and examples organized by section. We then conducted three interviews with members of LCCC to collect qualitative data on existing, external patient advocate trainings and provide insight on best practices. Using our findings, we created a five-part training to better equip advocates for research partnership. We reviewed the training for health literacy and to ensure alignment with the Curriculum Adaptation and DEI plans. Lastly, we facilitated a one-hour focus group via Zoom with experienced patient advocates to receive feedback on the training. As a result, we integrated key changes into the final training to encourage participants that all comments and questions are welcome, add clear definitions of patient advocacy, and include an optional activity reviewing research abstracts. Results: We developed a training to engage patient advocates involved or interested in becoming involved in research projects at LCCC. Training objectives include understanding LCCC’s goals and the role of patient advocacy, building a sense of community and passion for advocacy, and gaining confidence in providing feedback on research materials. The training consists of a facilitator script and outline, PowerPoint slide deck, handouts, and an evaluation survey to be delivered in a two-hour hybrid synchronous format. Training content is organized into five parts: Welcome and Introductions, Purpose of Training and Introduction to LCCC, What is Patient Advocacy at LCCC?, Practice Giving Feedback, and Conclusion. The training is designed to be skills-based, consisting of group discussions, an interview with a current patient advocate-researcher pair, and the opportunity for participants to make suggestions on research materials. Recommendations: Based on our recommendations, LCCC will offer the training as onboarding for new patient advocates with the option for seasoned patient advocates to attend as a refresher. An individual with direct involvement with patient advocates and researchers will lead the training. To tailor to varying patient advocates’ experience and knowledge, more advanced research examples based on participants’ experience in advocacy should be included. LCCC will use this training and consider ways to provide iterations of the training in other languages and engage individuals from different cultural backgrounds disproportionately burdened by cancer and not commonly involved in patient advocacy. We propose a scale-up implementation at other institutions to adapt this patient advocate training.

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Emily K. Walton, MPH: No financial relationships to disclose
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Costs of breast cancer recurrence after initial treatment for high risk early breast cancer using SEER-Medicare linked data

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Background:
Despite the good prognosis with treatment for most patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) early breast cancer (EBC), ~20–30% of patients experience locoregional or distant disease recurrence. To assist in value assessments of novel therapies in the adjuvant setting, this study aimed to determine the costs of treated breast cancer recurrence following treated EBC.

Methods:
This retrospective study analyzed linked patient data from the US Surveillance Epidemiology and End Results (SEER) registry (2010-2014) and Medicare claims (2009 to 2019, which included data from Part A, B, and Prescription Drug Events [Part D]). Data were analyzed for patients aged ≥65 years with HR+, HER2-, node-positive EBC at high risk of recurrence (consistent with monarchE trial high risk criteria). Treated recurrences were defined based on
treatment events/procedure codes, including surgery, radiation and systemic therapy, after a 90-day gap following the last treatment for initial EBC. Recurrences were classified based on Medicare claim diagnosis codes or SEER registry data. Extra cost was defined as cost attributable to treated recurrence. Cumulative extra costs were estimated by calculating cost differences between patients with treated vs non/untreated recurrence. Cumulative extra costs were analyzed over the first 6 years following first treated recurrence, a duration which ensured adequate sample size. Costs were inflated to 2021-US$.

Results:
We identified 3081 eligible patients (mean age at diagnosis 74.5±7.1 years, 97.4% female, 87.8% White). We identified 964 patients with treated recurrence (distant=432, locoregional=128, contralateral=9, unclassified=347) and 2117 patients with non/untreated recurrence. Six-year cumulative extra costs were higher for patients with distant recurrences ($168,656) than for patients with locoregional recurrences ($96,465) (Table 1).

Conclusions:
Cost of recurrence in patients with high risk EBC is considerable, particularly in patients with distant recurrences. Most patients who recurred in this population experienced distant recurrence. Delaying or preventing recurrence may reduce long term costs in these high risk EBC patients.

Table 1: Mean cumulative extra costs attributable to treated recurrence

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A cost-consequence analysis of pertuzumab in the neoadjuvant treatment of high-risk HER2+ Early-Stage Breast Cancer (EBC): health-economic considerations for drug availability in Italy

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Introduction: Neoadjuvant pertuzumab+trastuzumab+chemotherapy (TPC) combo is a well established treatment for HER2+ high-risk (EBC) as recommended by International and National guidelines. However, notwithstanding EMA approval, in some European countries (i.e. Italy and France) pertuzumab drug-access is prevented by the NHS decision not to reimburse the drug in a value-driven sustainability balance. This study aims to estimate the cost and consequences of TPC vs. the same combo w/o pertuzumab (TC) in the neoadjuvant treatment of high-risk HER2+ EBC to better understand the value of TPC regimen.

Methods: With a Markov model, we simulated the costs and consequences associated to TPC or TC neoadjuvant treatments, using 5 years time horizon and Italian Lombardy region Health System point of view. The model includes nine health states: Neoadjuvant treatment; Surgery; Invasive disease-free Survival (IDFS) with pathological complete response (pCR), IDFS with residual disease (RD), non-metastatic recurrence, remission, first-line treatment and subsequent-lines for metastatic cancer, and death. Transition probabilities and utilities were
derived from relevant clinical trials and literature. For each neoadjuvant treatment, the model estimates: direct (drug, administration, hospitalization, disease management), indirect (patients’ loss of productivity), total costs and different outcomes, as cumulative incidence of metastatic recurrence, days of work lost, days with activity impairment, IDFS life years, and quality adjusted life years (QALY). Costs and outcomes were estimated per 100-treated patients. An alternative scenario analysis with a 10-year time horizon and a deterministic sensitivity analysis was performed to assess the impact of model time horizon and parameters value.

Results: The estimated costs and outcomes for TPC and TC are reported in Table 1. TPC produces a total direct cost reduction of €75,630 per 100-treated patients, a small increase of TPC neoadjuvant treatment costs (+4.8%) is offset by the lower cost of metastatic treatment and management (-20.4%). Considering also the indirect costs, TPC is associated to a cost reduction of €124,956 per 100-treated patients. The cost saving is associated to a reduction of 5-year cumulative incidence metastatic recurrence (8.32% vs 10.42%, -20.14%), a reduction of days of work loss (-548 days) and days with activity impairment (-283 days) and a 10.5 QALY gained per 100-treated patients. Using a 10-year time horizon, the value of TPC compared to TC increases. Probabilities of pCR with TPC and TC were the parameter with the higher impact on model results.

Conclusion: Use of TC instead of TPC in high-risk HER2+ EBC derives a marginal savings (4.8%) according to the first year of our cost-consequence analysis. However, this negligible savings comes with the need for a heavily and long-lasting adjuvant cytotoxic therapy escalation because of a lower clinical activity of TC vs TPC. Moreover, according to medium-term cost-consequence analysis (5 years) the early negligible savings is overwhelmed by the subsequent increase in costs for the patients’ management, because of the lower clinical efficacy of TC vs. TPC. In Italy, the lack of pertuzumab in the neoadjuvant setting of high-risk HER2+ eBC is questionable; our results support the opportunity to reconsider the pertuzumab availability in Italy and reduce inequalities within Europe.

Cost and consequences of neoadjuvant treatments for high-risk HER2-Positive Early-Stage Breast Cancer: trastuzumab+pertuzumab+chemotherapy (TPC) vs trastuzumab+chemotherapy (TC)

**Table 1.tif**

IDFS, Invasive disease-free Survival; QALY, quality adjusted life years.

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boards) (Terminated, June 30, 2022), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, June 30, 2022); Novartis: Consulting Fees (e.g., advisory boards) (Terminated, June 30, 2022), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, June 30, 2022); Pfizer: Consulting Fees (e.g., advisory boards) (Terminated, June 30, 2022), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, June 30, 2022); Roche: Consulting Fees (e.g., advisory boards) (Terminated, June 30, 2022), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, June 30, 2022)

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Introduction Advances in genetic testing have contributed to improvements in our approach to early detection, prevention, and treatment of breast cancer. All populations, however, have not equally benefited from the scientific advances. Cancer genetic testing can directly impact the health and wellbeing of entire families. Uptake of cancer genetic testing continues to be significantly lower among Black patients with unequal access, fear, and medical mistrust all contributing to this disparity. Objective: To address the racial disparity in genetic testing uptake we are developing a short patient-centered video intervention to inform, educate, and
encourage Black women and men to consider genetic testing when recommended by a provider. Methods To begin, we created a 15-minute video using data from a recently completed video-based qualitative interview study that included 47 people who have a known genetic or inherited cancer risk. We reviewed coded transcripts of participants’ study videos, with a prioritization of the perspectives of the Black participants about learning about their cancer risk due to a hereditary predisposition, their decision making around genetic testing, and testing experiences. From this review, we created a montage video of short segments from 9 patients (4 of whom were Black). Next, we conducted qualitative stakeholder interviews with 10 Black patients who had undergone genetic testing for cancer within the last year and 10 oncologists and genetic counselors involved in genetic testing (mix of Black and non-Black providers). All participants were made aware that our goal is to develop a video intervention. Interviews were conducted via zoom, with interviewees being shown the montage in segments, followed by questions about why people choose to test (or not), barriers to and concerns around testing. We also asked for thoughts about what information might be important to improve chances of uptake of genetic testing for Black patients. Participants were also asked about whether patient-centered videos were an appropriate intervention strategy, and if so, the preferred voices and messages to be included. Results Initial analysis of the qualitative interviews shows strong support for an intervention focused on patient-centered videos, indicating possible acceptability and clinical utility of this approach. Relatability and representation were mentioned as key, though there was not agreement as to whether all patients need to be Black in an intervention targeting a Black audience. Patients described appreciating seeing other patients discuss genetic testing as a mechanism to reduce risk by facilitating early detection. Patients also felt that describing possible benefits for children and future generations could be a powerful message, and noted that given the widespread fear of cancer, the authenticity of the patients’ perspectives could provide important reassurance. In contrast, patient discussions of their specific problems with insurance and other barriers to testing were identified as possibly problematic for this approach, without explicit identification of solutions. Both providers and patients identified a need for factual information about inherited cancer risk, and the processes and implications of genetic testing alongside experiential content. Patients may not be best placed to deliver such information as it is usually outside of their expertise. Conclusions This developmental work suggests the potential impact of incorporating the patient voice into interventions to increase uptake of cancer genetic testing. Based on this work, we are planning to interview more patients to develop a video-based intervention that will combine information around inherited risk, testing, finances and implications of testing and patients’ perspectives that will then be evaluated in a randomized clinical trial.

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Title: Barriers to enrolling in observational trials for patients with stage IV breast cancer.
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Background and Purpose
Increasing research data support the existence of barriers and discrepancies to oncology interventional clinical trial enrollment rate based on patients' social-economic status. However, few studies examined if such discrepancy exists in observational trials. We hypothesize the enrollment discrepancy remains the same in specimen collection only protocols, and several factors including health literacy and religious belief contribute to such discrepancy.
Methods
Data was collected from March 1st, 2022, to July 7th, 2022, as part of an ongoing pilot study examining circulating tumor DNA (ctDNA) from patients diagnosed with stage IV metastatic breast cancer starting a new line of therapy treatment (BCM protocol number H-48751). This study was selected as specimen collected is part of normally scheduled standard of care clinical labs and beyond informed consent does not require any additional patient commitment for participation. This study was performed across both county and private practice sites: 1) Smith Clinic-Harris Health System 2) Baylor Saint Luke’s Medical center (BSLMC); respectively.

Correlations for independent variables potentially affecting enrollment were assessed to estimate the association between patient participation and socio-economic factors like religious affiliation and level of formal education received. Free-form text responses were collected from patients who declined study participation.

Results
Fourteen eligible candidates were asked to participate in the observational trial to determine whether serial changes in ctDNA ratio correlate with the results of first monitoring patients via imaging at three months. Out of 14 patients approached, 5 patients (36%) declined. Interestingly, all five patients who declined were from Smith Clinic- Harris Health System, while all BSLMC patients agreed to enroll. Based on the free-text response of why patients declined the ctDNA study, we identified a total of 4 different categories: Language barriers, low health literacy, religious objection, and disinterest in research. Using these four categories, we continue to collect data to improve our understanding of barriers in observational trial enrollment.

Conclusion
Low literacy and other socioeconomic factors serve as barriers to enrollment in observational trials for patients who suffer from stage IV breast cancers. In our preliminary data, we also noted that these barriers are only relevant for patients who are treated at the county hospital. An investigation to recognize low literacy and religious affiliation as barriers to poor trial accrual is ongoing.

Reasons to declining participation in observational trial.

<table>
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<th>Reason</th>
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<td>Language barrier</td>
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</tr>
<tr>
<td>Low health literacy</td>
<td>40</td>
</tr>
<tr>
<td>Religious objection</td>
<td>20</td>
</tr>
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<td>Disinterest</td>
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Huma Javaid, n/a: No financial relationships to disclose
Geographical variation of social deprivation, cardiovascular and other comorbidities in 226,516 patients with early breast cancer in England: results from a National Registry Dataset Analysis

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Background In England, as for many countries, there are geographical variations in treatment uptake and outcomes for patients with early breast cancer (EBC). It is important such inequalities are addressed. The co-existence of cardiovascular disease (CVD) in patients with early breast cancer (EBC) may complicate treatment choices, lead to deviations from standard of care, and be associated with worse cancer and CVD outcomes. Social deprivation is also associated with increased incidence of co-morbidities, reduced cancer treatment rates, and worse cancer survival. If there are regional differences in rates of CVD/ co-morbidities and social deprivation these may explain observed differences in treatment uptake and cancer outcomes in EBC. Therefore, in this analysis we evaluated rates of CVD and social deprivation in a large population of patients with EBC in 20 English Cancer Alliances. Methods Cancer registry data as part of The Virtual Cardio-Oncology Research Initiative (VICORI) were used to identify patients diagnosed with stage I-III breast cancer diagnosed between 2013 - 2018 in England. National data (hospital records and national cardiovascular audit databases) were used to describe CVD prevalence (CVDp), Index of Multiple Deprivation (IMD), and Charlson Comorbidity Index (CCI). Patient, disease, tumour, and treatment characteristics were allocated into Cancer Alliance tertiles according to CVDp (minimum (< 33.3rd percentile); middle (33.3rd – 66.6th percentile); maximum (>66.6th percentile)) with approximately equal patient numbers in each group. The disease burden was depicted in bar charts and regional variation as heat maps of England. The percentage of patients in the most deprived quintile of income domain of the IMD were plotted. Funnel plots were used to investigate variations in regional CVD rates based on a logistic regression model. Results Data from 226,516 patients with stage I-IIIA breast cancer with a mean age of 62.5 (+/- 13.7) were included in the analysis. 78,833 patients were assigned to the minimum (37.0%; 95% CI 36.7 – 37.2), 74,443 to the middle (35.5%; 95% CI 35.3 – 35.7), and 73,240 to the maximum (34.7%; 95% CI 34.5 – 34.9) tertile. Geographical variation between Cancer Alliances was demonstrated for CVDp (6% - 9.5%), IMD (2%- 30%), and CCI ≥ 4 (8.2% - 9.5%). Variation of CVDp revealed a South/North gradient between Cancer Alliances towards higher percentage, with centrifugal tendency from London. These findings were consistent with a similar pattern seen for variation in IMD quintiles with higher prevalence of most socioeconomic deprived patients located in cancer alliances in the North compared to the South of England. Regional variation was less obvious for CCI. After adjusting for age, TNM stage, IMD, and CCI, differences in the standardised CVD ratio persisted for some cancer alliances suggesting that other factors than those adjusted for are likely accountable for the higher CVDp seen in some Cancer Alliances. An adjusted ordinal logistic regression model demonstrated that older age (aged >75), white ethnicity, and social deprivation were associated with a higher risk of CVDp (p< 0.001). Conclusions This study highlights significant geographical variation of social deprivation, CVDp, and other comorbidities in early breast cancer patients in England which may contribute to the variability in treatment received and breast cancer survival in different regions within the country.

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Mark de Belder, MA, FRCP, MD: AstraZeneca: Executive Steering Committee, DAPA MI Trial (Ongoing)

Michael D Peake, FRCP, OBE: AstraZeneca: Writing and speaking fees (Ongoing); MSD: Writing and speaking fees (Ongoing)

Alistair Ring, MA, FRCP, MD(Res): AstraZeneca: Advisory board and speaker fees (Ongoing); Daiichi-Sankyo: Advisory board and speaker fees (Ongoing); Lilly: Advisory board and speaker fees (Ongoing); MSD: Advisory board and speaker fees (Ongoing); Novartis: Advisory board and speaker fees (Ongoing); Pfizer: Advisory board and speaker fees (Ongoing); Roche: Advisory board and speaker fees (Ongoing); Seagen: Advisory board and speaker fees (Ongoing)
Introduction: Social support (SS) is predictive of symptom distress among patients with breast cancer (BC) during the treatment and post-treatment phases. There is evidence of racial and economic disparities in SS seen among patients with cancer. Little is known about how race and income influence SS among patients with BC.

Objectives: 1) To describe SS in women with early-stage BC prior to or at their first chemotherapy treatment (i.e., baseline); 2) To examine how SS varies by race, income level, ability to meet basic financial needs at baseline; and 3) To examine the association between SS and symptom distress at baseline.

Methods: This secondary analysis employed a descriptive, correlational, comparative design.
with data from the baseline time point of SEMOARS: The Symptom Experience, Management and Outcomes According to Race and Social Determinants of Health (R01-MD012245), a multi-site, repeated, multi-method study comparing the symptom experience and management in Black and White women with early-stage BC. Inclusion criteria were female, Black or White race, age at least 18 years and prescribed chemotherapy for BC stages 1–3. Measures included self-reported race; income level measured by annual income (low: < $29,999; medium: $30,000 to $69,999, high: ≥ $70,000) and affordability of basic needs (single item: yes or no). The Interpersonal Support Evaluation List includes four subscales (possible range 0-30), assessing the perceived availability of support (emotional, tangible, self-esteem, and belonging). The Symptom Distress Scale measures the current experiences of 11 symptoms and their severity (possible range: item:1-5; total score:13-65). Descriptive, comparative, correlational, and regression analyses were used.

Results: Participants (N=248; mean age 52.9±12.3 years) were 58.9% White and 41.1%, Black, 54% married/partnered, 57.3% employed, 70.8% had some college education, and 98% insured. Half of the sample (50.5%) reported high income, 30.3% reported medium income, and 19.2% low income. One-fifth (18.5%) reported an inability to afford basic needs. Income and race are moderately correlated, with Black patients more likely to have low income (39.5% vs. 7.6) and less likely to have high income (22.4% vs. 66.7%) (Cramer's V=.472; p<.001). On average, patients reported moderately high levels of SS (emotional=26±5; tangible=25±6; self-esteem=23±4; belonging=25±5). Compared to White patients, Black patients reported lower levels of SS: emotional (24.4 vs. 27.0; p<.001), tangible (24.3 vs. 25.8; p=.02), and belonging (24.3 vs. 25.6; p=.02). Using one-way analysis of variance with multiple comparisons there were significant differences in SS by income level, where patients with low income had lower SS levels (all subscales) when compared with patients of high income (all p<.001) and lower tangible SS when compared with medium income (p=.005). Patients with a medium income had lower emotional and tangible SS when compared with those having high income (p=.003; .022; respectively). Inability to afford basic needs was associated with lower SS (all subscales; p<.01). For all SS subscales lower SS was associated with worse symptom distress (r=-.213;p=.004 to r=-.265; p<.001). Adjusting for race and income (high vs. low and medium; low vs. medium and high), lower scores for each SS subscale, except belonging, were predictive of higher symptom distress scores (all p<.05).

Discussion: For this cohort, Black race, low income, and inability to afford basic needs were associated with lower levels of baseline SS. Regardless of race and income, poor baseline emotional, tangible, and self-esteem SS were significantly correlated with increased symptom distress.

Future Directions: SS is a predictive marker of symptom distress as patients begin BC chemotherapy. Interventions to increase SS in Black and/or low-income women with BC at the patient, clinic, and community level are needed.

Coefficients of associations for individual social support subscales with symptoms distress adjusting for race and income level
### Coefficients of associations for individual social support subscales with symptoms distress adjusting for race and income level

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<th>p</th>
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<th>Adjusted R²</th>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>0.031</td>
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<tr>
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<td>1.25 - 7.046</td>
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<td>-0.55 - 0.04</td>
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<td>Belonging and Symptoms Distress</td>
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<td>-0.41 - 0.05</td>
<td>0.125</td>
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Notes: n=175; SS: social support; race was categorized as (0= Black; 1= White); income level was categorized as (0=medium and high; 1=low: reference)

Disclosure(s):

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Background: Providers and patients alike are unaware of the racial disparities that exist in triple-negative breast cancer (TNBC), which occurs at twice the rate in women of the African Diaspora (WAD) compared to White American women. WAD tend to be diagnosed at a more advanced stage, use under-resourced health care settings or encounter bias in their care, and experience higher rates of TNBC-related mortality. An historically difficult-to-treat breast cancer subtype, the TNBC landscape is changing with an influx of clinical data and newly approved treatments. An educational initiative was designed to heighten awareness of new therapies, including antibody drug conjugates, empower patients in their care, and to align on addressing disparities in TNBC care. Methods: Two, 1-hour online, interactive, video-based programs were designed for patients and providers. The patient/caregiver program was hosted on CancerCoachLive in April, 2022 and the provider program on OMedLive in May, 2022 and remains on-demand until May 2023. With a focus on addressing disparities in care, 78% of patients/caregivers attending the patient program were of African descent. The initiative was conducted in collaboration with TOUCH, the Black Breast Cancer Alliance and the National Breast Cancer Foundation. Four real-world patient accounts of TNBC navigation and management were embedded in the patient program; and represented women of Caucasian, African, and Native American ethnicity. While practice and knowledge gaps among HCPs, and knowledge gaps of patients were assessed, we report on the analysis of ‘tethered’, behavioral, practice pattern, and perception questions assessed across the patient and provider programs. Results: As of June 2022, 200 providers and 29,389 patients/caregivers participated in the ongoing activities. Post education, participants in the provider program anticipated the education would positively impact practice behavior (86%) while patients/caregivers reported greater confidence in discussions with their treatment team (92%). Pre- and post-evaluation of strategies addressing disparities revealed improvements in ‘ensuring access to care through integration of care coordinators or social worker as part of the healthcare team.’ Provider assessment of barriers to enrollment in clinical trials uncovered the top barrier as ‘lack of trials at my institution’ (33%) and the top barrier to integration of new therapies as ‘lack of knowledge regarding evidence-based strategies’ (44%). Misalignments in patient-provider perceptions were observed. ‘Patient lack of interest’ was a provider-identified barrier to clinical trials, yet 60% of patients/caregivers reported that they were ‘very likely’ to participate in a clinical trial if eligible. Similarly, differences were seen in the ranking of topics of highest interest regarding treatment decisions. Lastly, patient- vs provider-identified care challenges were not aligned. Themes from the real-world patient accounts provided greater context for the misalignments observed. Conclusions: Assessment and alignment of patient-provider care perceptions has potential to impact clinical practice behaviors, patient/caregiver communication and confidence,
and treatment/clinical trial knowledge for effective TNBC management. This educational partnership facilitated assessment of attitudes, perceptions, and barriers to care that can further guide how disparities in care for patients with TNBC are addressed. This ‘tethered’ approach to education was successful in empowering patients in shared decision-making, initializing changes in clinical practice, and gaining patient-provider insights in TNBC management. This activity was supported by an educational grant from Gilead Sciences, Inc.

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Reasons for Reduced Willingness to Participate in Clinical Trials During the COVID-19 Pandemic: The Translational Breast Cancer Research Consortium (TBCRC) 057 Survey

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Background:
Historically, less than 10% of adult patients with cancer enroll in clinical trials, however, enrollment dropped further at the onset of the COVID-19 pandemic. Barriers to trial participation during the pandemic have not been reported. As part of the TBCRC 057 survey on the impact of the pandemic on willingness to participate in breast cancer trials, we assessed reasons for reluctance to participate in trials during the pandemic.

Methods:
US residents who self-reported a breast cancer diagnosis were eligible to complete the online survey 8/6/21-9/30/21. Respondents indicated whether they were current trial participants and, if not, their willingness to consider participating in a trial during the pandemic using a 5-point scale (0-not at all willing to 4-definitely willing). Respondents who were not current trial participants and who were not "definitely willing" to consider participation during the pandemic were characterized as "reluctant" and asked to select reasons for their reluctance from a checklist. Pandemic-related anxiety was assessed on an 11-point scale (0-no anxiety to 10-worst anxiety possible). Respondents indicated how the option to conduct trial activities online would affect their decision to participate in a trial (much less likely, somewhat less likely, would not affect my decision, somewhat more likely, or much more likely). In exploratory analyses, we evaluated whether pandemic-related anxiety and favorable reactions towards opportunities to conduct trial activities online were associated with reluctance to consider trial participation during the pandemic due to fear of SARS-CoV-2 exposure. Means were compared with two sample t-tests and proportions with Fisher’s exact tests.

Results:
Of 385 survey respondents, 185 (48%) were characterized as reluctant to consider trial participation during the pandemic. Among these 185, median age was 55 (range 25-80), 85.7% were non-Hispanic White, 48.1% had metastatic disease and 44.2% received care at academic centers. Reasons for reluctance to consider trial participation during the pandemic cited by ≥15% of the 185 reluctant respondents are shown in the Table. Respondents who selected fear of exposure to SARS-CoV-2 as a reason for their reluctance to consider participating in a trial during the pandemic had higher mean pandemic-related anxiety (7.0 vs 5.2, p< 0.001). These respondents were more likely to indicate telemedicine doctor visits (p=0.01), virtual consents (p=0.001) and online study questionnaires (p=0.001) would make them somewhat or much more likely to participate in trials than respondents who did not select fear of exposure to SARS-CoV-2 as a reason for their reluctance.
Conclusions:
Reasons for reluctance of patients with breast cancer to consider participation in clinical trials during the pandemic are multifactorial. Although concerns about safety and efficacy remain prominent, fear of exposure to SARS-CoV-2 drives unwillingness to participate in >25% of reluctant patients. Trial accrual may benefit from incorporation of electronic activities when possible.

Table

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<th>Reason</th>
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<th>(%)</th>
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<tr>
<td>Worry about not getting best treatment</td>
<td>88</td>
<td>(47.6)</td>
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<tr>
<td>Worry about side effects</td>
<td>82</td>
<td>(44.3)</td>
</tr>
<tr>
<td>Worry about delaying cancer treatment</td>
<td>58</td>
<td>(31.4)</td>
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<tr>
<td>Fear of exposure to SARS-CoV-2</td>
<td>51</td>
<td>(27.6)</td>
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<tr>
<td>Financial concerns</td>
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<td>(26.5)</td>
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<td>Health insurance concerns</td>
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<td>(24.3)</td>
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<tr>
<td>Do not want to spend time away from home/family</td>
<td>32</td>
<td>(17.3)</td>
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<td>Too overwhelmed</td>
<td>32</td>
<td>(17.3)</td>
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Self-identified race and Area Deprivation Index in patients with invasive lobular carcinoma of the breast: associations with tumor characteristics and event free survival

Objectives: Investigators have shown a relationship between race/ethnicity and survival in invasive lobular carcinoma (ILC), the second most common type of breast cancer. While non-white patients with ILC were shown to have worse outcomes, there are no data evaluating the impact of socioeconomic factors. Herein we evaluated the relationship between self-reported race and socioeconomic factors with tumor features and outcomes in early-stage patients with ILC. Methods: We used chi-squared tests, t-tests, the Kruskal-Wallis test, multivariate Cox proportional hazards models, and tests for trend in Stata 16.1 to evaluate race, area deprivation index (ADI), and event-free survival (EFS) in a single institution cohort of patients with stage I-III ILC. Race was self-reported and categorized as black, white, or other. ADI was ascertained from a publicly available database using measures of income, education level, employment, and housing quality to provide information about neighborhood adversity. ADI was evaluated in quintiles, with quintile 1 signifying the least resource deprived neighborhoods, and quintile 5 signifying the most resource deprived. Tumor receptor subtype was defined by estrogen receptor (ER), progesterone receptor (PR), and HER2 status. Body mass index (BMI) of 18.5-24.9 kg/m² was categorized as normal, 25-29.9 kg/m² as overweight, and ≥ 30 kg/m² as obese. Results: Of 823 patients in our institutional database, self-reported race/ethnicity data
were available for 808, with 28 (3.5%) identifying as black, 638 (79.0%) as white, and 142 (17.6%) as other. ADI data were available for 816 patients, with 174 (21.3%) in quintile 1, 210 (25.7%) in quintile 2, 110 (13.5%) in quintile 3, 163 (20.0%) in quintile 4, and 159 (19.5%) in quintile 5. Tumor receptor subtype differed by ADI, with patients in the highest ADI category (most resource-deprived) being most likely to have ER positive, PR positive, and HER2 negative tumors (81.8% in ADI category 5 versus 69.0% in ADI category 1, p=0.001). Those in higher ADI categories were also more likely to have lymphovascular invasion (9.2% in ADI category 5 versus 4.3% in ADI category 1, p=0.008), and were less likely to present with stage I disease (55.5% in ADI category 5 versus 67.9% in ADI category 1, p=0.002). BMI was not associated with tumor characteristics, but was significantly associated with ADI, with a significant trend towards higher BMI in areas of higher ADI (p<0.001). Among patients who self-identified as black, age at diagnosis was significantly higher compared to those identifying as white or other (mean age 65.8, 59.9, and 58.0 years respectively, p=0.0074). There were no differences in tumor receptor subtype, grade, presence of LVI, or stage by self-identified race. Black-identifying patients were significantly less likely to have the lowest ADI category (0% versus 22.6% and 20.4% in white and other categories respectively, p=0.016), and were significantly more likely to have elevated BMI (79.2% overweight/obese versus 47% of white and 41.5% of other patients, p=0.003). On univariate analysis, self-identified black race, elevated ADI, and overweight/obesity were each associated with significantly worse EFS. However, in a multivariate model containing all three predictors, only overweight/obesity remained significantly associated with worse EFS (hazard ratio 1.6, 95% confidence interval 1.1-2.3, p=0.022). Conclusions: Although prior investigators identified a relationship between non-white race and worse outcomes in patients with ILC, our data show complex relationships between many factors that impact breast cancer outcomes. The relationship between race and EFS was mitigated by ADI and obesity, suggesting that race is not an independent predictor of outcome in patients with ILC.

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Rita Mukhtar, M.D.: No financial relationships to disclose
Introduction: On January 1, 2021, the Centers for Medicare and Medicaid Services (CMS) implemented the Hospital Price Transparency Final Rule to promote price competition and improve hospital care affordability. Hospitals in the US are required to disclose, among other items, the cash prices and the payer-specific negotiated prices for CMS-specified, high-volume common services. We investigated the compliance rate and descriptive costs for breast cancer services in the central New Jersey region. Methods: We collected CMS-specified hospital services representing 4 unique Current Procedural Terminology (CPT)/diagnosis related group codes (screening mammography, US guided biopsy, mastectomy, partial lumpectomy). Cash prices and payer-specific negotiated prices for these services were obtained from Turquoise Health, a data service company that specializes in collecting pricing information from hospitals. We collected the median cash price, the proportion of hospitals for which the cash price was lower than its median commercial negotiated price, interquartile ranges (IQR) for cash prices across all services by practice type, and the correlation between cash price of service and neighborhood poverty level. Results: 106 hospitals in a 50-mile radius from central New Jersey were reviewed, representing 22 academic and 84 community clinics. Of these, only 4 hospitals disclosed both their cash price and commercially negotiated price for all services. Overall, there was a correlation for mammography cash price and neighborhood level of poverty ($r = -0.34, p = 0.026$). No correlations were noted for the other services. Cash prices varied substantially across hospitals, as evidenced by large IQR for US-guided biopsy ($S = 1877.19 (1647.05 – 5388.2)$), mastectomy $S = 6417.00 (4847.34 – 48166.69), and lumpectomy $S = 3820.00 (3021.76 – 17041.84$) in academic centers. When compared to community hospitals, academic institutions were more likely to set their cash prices below negotiated insurance prices. Discussion: Of the 106 hospitals investigated, only 4 disclosed both their cash price and commercially negotiated price. As evidenced by the negative correlation between the cash median cash price of screening mammography and neighborhood level of poverty, hospitals encourage entry into the health system. Unfortunately, downstream costs for diagnosis and treatment are unpredictable and present major challenges in preventing financial toxicity and assuring health equity. Because of its descriptive nature, this study was unable to identify factors or outcomes
associated with the cash price variation. Uninsured or underinsured patients who choose to take the cash price offered by hospitals remain extremely vulnerable.

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Ramy Sedhom, MD: No financial relationships to disclose
Hyperglycemia in Hispanic MBC patients treated with alpelisib: single institution retrospective study

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Background: PIK3CA mutations are found in up to 40% of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) metastatic breast cancers (MBC). Alpelisib is an orally bioavailable PIK3CA inhibitor approved in combination with fulvestrant based on the SOLAR-1 study. However, uptake has been limited due to toxicity concerns, most commonly hyperglycemia (grade ≥3 was 37% in SOLAR-1 and 28% in the BYLieve study, which evaluated alpelisib after progression on a CDK 4/6 inhibitor). Patients with uncontrolled type 2 diabetes (T2DM) were excluded from both studies [defined as fasting plasma glucose (FPG) level >140 mg per deciliter, or a glycosylated hemoglobin (HgbA1C) level of >6.4%]. Of note, both trials enrolled a majority of non-Hispanic White (NHW) patients. Disparities regarding prevalence of diabetes has been reported among Hispanics (H). The Centers for Disease Control and Prevention reports that H are more likely to have T2DM than NHW (approximately 17% vs 8% respectively). Our study aims to characterize the incidence and management of hyperglycemia in H MBC patients treated with alpelisib. Methods: A retrospective chart review was performed to include patients with HR+ HER2- MBC with a documented PIK3CA mutation treated with alpelisib in combination with fulvestrant at Miami Cancer Institute from 2019-2022. Patients were identified using pharmacy records and the COTA real-world database (RWD, an analytics platform enabling investigation of longitudinal RWD). Cases were excluded where the start date was unclear, or treatment was given for a diagnosis other than breast cancer. Based on available data in the medical record, patients were categorized as H or NH. Descriptive statistics were used to describe variables in both groups of patients. Results: Of 46 patients
identified, 34 were included in the final analysis (17 H and 17 NH). The median age was 63 y (range 32-87). The most common PIK3CA mutation identified was H1047R (41.2% of H and 23.5% of NH; p > 0.05). Starting body mass index (BMI) was higher in H compared to NH (29.9 vs 24.8; p < 0.05). Starting FPG was the same for both groups (115 mg/dL), and within the first two weeks on treatment the highest FPG was higher in H vs NH (250 mg/dL vs 157 mg/dL; p > 0.05). H also had the highest peak glucose when compared to NH (333.8 mg/dL vs 217.8 mg/dL; p < 0.05). Furthermore, by the end of treatment H had a higher FBG than NH (247.4 mg/dL vs 118.0 mg/dL; p < 0.05). Overall, any grade hyperglycemia occurred in 70.6% (82.4% H, 58.8% NH; p > 0.05, with high rates of grade 3/4 hyperglycemia in both groups (53% H 41% NH; p > 0.05). A higher percentage of H patients required more than one anti-hyperglycemic medication as compared to NH (41% vs 12%; p > 0.05). Hispanics time on treatment was shorter compared to NH (151 vs 240 days; p > 0.05). Disease progression was the most frequent reason for treatment discontinuation in both groups 52.9%. However, more H patients discontinued alpelisib due to hyperglycemia (23.5% vs 5.9%; p > 0.31). Conclusions: Despite starting treatment with similar FPG levels, H had a higher peak plasma glucose level compared to NH. Although not statistically significant, likely due to a small sample size, the rates of hyperglycemia within two weeks of treatment was higher in H than NH. Furthermore, H required the use of more antiglycemic medications and had higher discontinuation rates. Therefore, there is a heightened need to increase education and awareness of glucose monitoring in H during treatment with alpelisib. Further prospective studies are warranted to better define the optimal management of hyperglycemia in H patients.

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7:00 AM - 8:15 AM

**P6-08-12**

**Toward Comprehensive Cancer Prevention for Women Experiencing Homelessness: Demonstrating the Need for Onsite Mammography, Education, Navigation, and Cross Cancer Screenings**

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**Background:** Persons experiencing homelessness (PEH) rarely receive regular preventative health care or consistent cancer screenings. Late stage detection of cancer and barriers to care are prevalent among PEH. Novel programs such as onsite mobile mammography services represents an approach to improve breast cancer disparities among women experiencing homelessness (WEH) and allows for understanding of barriers to cancer screening amongst WEH and to develop best practices. Objectives: During onsite mobile mammography events at shelters for WEH, develop best practices for improving breast cancer screening utilization while
developing approaches to increase use of other cancer screenings. Methods: In 2022, the Cleveland Clinic performed onsite mobile mammography screening events at area shelters and day centers. All seven screening events included onsite mammography, breast health education, and patient navigation. After WEH completed the education session, they completed the mammogram. Subsequently, at two events, patients had an opportunity for further consultation with an advanced practice provider (APP) including discussing additional screening tests (ex. colorectal, lung, cervical cancer) beyond mammograms with referrals as needed. Consultations also discussed approaches to reduce cancer risks with further education, referrals for dental care, and assistance securing a primary care provider (PCP).

Results: At the events that included consultations, 30 patients received mammograms and 80% (n=24) of patients chose to speak with the APP. Patients seeking consultation were 21-73 years old and identified as Black/African American (n=5), White (n=16), and other (n=3). Topics of discussion included mammograms (n=24, 100%), smoking cessation referral and/or lung cancer screening (n=16, 67%), colorectal cancer screening (n=11, 46%), and cervical cancer/HPV screening (n=11, 46%). Additionally, 46% of patients (n=11) were assisted with securing a PCP and 8% of patients (n=2) were referred for dental services.

Discussion: Our preliminary data demonstrate that most WEH undergoing onsite mammography screening are willing to engage in consultation to discuss additional cancer screenings with many patients eligible for additional cancer screenings. Additionally, this approach provided access to PCPs. Three best practices for cross cancer screenings include: 1) Onsite mobile mammography is an appropriate entry point for addressing breast health and also cancer screening broadly. 2) An onsite approach allows for education beyond cancer screening to provide access to primary care and other wrap around services. 3) Clinicians provide credibility and trust when they attend onsite mobile mammography events. Conclusion: Beyond breast cancer screening, WEH benefit from onsite mobile mammography, which can serve as a gateway to cross cancer screenings and access to primary care. Addressing disparities in this population should include wrap around services such as smoking cessation and connection to a PCP. Future research should examine best practices for following up with patients and completing navigation through cross cancer screenings.

Disclosure(s):

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Background The pandemic has accelerated the introduction of more flexible and cost-effective treatment forms. The efficacy of trastuzumab in the intravenous (IV) and SC forms is similar both in early and advanced HER2-positive breast cancer (BC) patients. Compared to IV administration, SC enables reduction of treatment costs and time, and saves equipment and human resources. SC formulation is more convenient for both patients and healthcare providers and may be implemented as a home-based therapy. Recently, systemic anticancer treatment (including chemotherapy) has been increasingly performed at home, improving patient comfort and reducing the burden on the healthcare system. Poland has already implemented home-based treatment with some biologic compounds; however, they have not included trastuzumab in BC patients. Objectives This RWE analysis aims to evaluate the organizational and therapeutic procedures related to the home-based treatment with SC trastuzumab and the attitudes of patients and healthcare providers to this approach. Material and methods The study
enrolled early HER2(+) BC patients treated with trastuzumab during the COVID-19 pandemic. Monitoring and treatment duration were consistent with SmPC and reimbursement regulations in Poland. The first 3-6 doses of SC trastuzumab (alone or in combination with CHT) were administered at a cancer center in outpatient and inpatient settings. Subsequent doses were administered at home by 3 qualified breast nurses. Post-injection follow-up was used for educational purposes. Data were analyzed with descriptive statistics. The study was reviewed and approved by the local Bioethics Committee. Results The analysis included 20 patients treated in two comprehensive cancer centers in Poland with a median age of 59 years (range, 36-72 years). Seven patients (35%) were professionally active. The average distance from the place of residence to the cancer center was 24 km (range, 2-65 km). A total of 232 doses were administered (mean 11.6 doses per patient; range 6-14), 133 doses at home and 99 at the cancer center. The overall tolerance of trastuzumab was good and consistent with the known safety profile described in Summary of Product Characteristics. Only 1 patient (5%) discontinued treatment prematurely due to decreased LVEF; another 19 patients completed treatment as planned. For 19 patients (95%), the benefits of SC treatment included time savings, the ability to continue working, and avoiding crowded places and infection risk. 2 patients (10%) considered the nurse's visit privacy disturbing, while 18 (90%) would recommend home-based drug administration. The average duration of a nurse's stay at home was 60 minutes (range 30 to 130 minutes). No logistical or technical problems were reported, except for occasional patient lateness. Nurses positively assessed the treatment provided in the nursing office, which was a source of additional knowledge, and experience. The overall impression of home-based therapy was positive for both patients and nurses. The limitation of the study is the declarative nature of the data. Conclusions Home-based treatment with SC trastuzumab should be pursued due to its safety, ease of organization, positive perception by patients and nurses, and reducing healthcare system resources. It can be particularly valuable for disabled patients who have difficulty reaching the hospital and professionally active patients. Specialized, trained nurses can self-sufficiently carry out part of the prolonged trastuzumab treatment, reducing physician involvement.

Disclosure(s):
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Background: Although the survival rates for breast cancer have improved, there is still a disparity gap between Hispanic women and non-Hispanic women. Hispanic women in the US are vulnerable to cancer inequalities due to a plethora of barriers including disproportionate poverty, lack of health insurance, and citizenship status. A Surveillance, Epidemiology, and End Results analysis found that Hispanic women had lower rates of both early-stage breast cancer and receipts of radiation therapy (RT) after breast-conserving surgery than White women. For patients without private or government health insurance, charity and county indigent programs have variable levels of coverage, and some patients cannot access radiation services. The aim of this study is to identify disparities in breast cancer treatment for patients referred to the Travis County indigent cancer treatment program.

Methods: We analyzed new referrals to the Ascension Seton Breast Clinic from April 2020 to January 2022. Demographics, disease stage, funding and treatments were extracted from medical records. We compared funding status at the time of referral vs time of surgery. We also analyzed the type of surgery elected and if RT was indicated and received. Results: We found that out of 242 referrals, 116 were diagnosed with a new malignancy. Of the 116, a total of 76 underwent breast surgery and RT was considered in 64 of these patients. 61% received RT. Of the remaining 25 patients, 16 patients elected simple mastectomies and 9 did not have funding to cover radiation (income was not low enough to qualify for RT benefit under the health district). Of the 9 women who did not have funding about 78% identified as Hispanic or Latino. 4 opted for simple mastectomies thus no longer needing RT, 3 received modified radical mastectomies without RT, 1 accessed charity funding for RT and 1 had lumpectomy without radiation and had recurrence of her breast cancer. Overall, the rate of breast conserving surgery was 43%. Discussion: The safety net system for patients in the US without access to private or government funding for healthcare is inherently limited. Costs of radiation treatment for cancer can be prohibitive for charity and indigent programs, but patients are forced to choose between mastectomy or risk a higher rate of recurrence. This data will be used to advocate for health district funding for this patient population.

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- **Maria De Los Leon-Camarena, MD**: No financial relationships to disclose
- **Neha Reddy, MD**: No financial relationships to disclose
- **Kimberly Ellison, DNP**: No financial relationships to disclose
- **Boone Goodgame, MD**: No financial relationships to disclose
Introduction: In patients (pts) with ER+/HER2- mBC, insights into the foremost concerns regarding their mBC treatment goals and QOL are often assumed by providers but are vastly understudied. The objectives of this survey were to better comprehend treatment goals and QOL concerns in pts with ER+/HER2- mBC. Methods: The 42-question, online EQUALS (ESR1 QUAlity of Life Survey) survey was sent to US subjects in June 2022 from 1) the Cure Media Group (n=6,625) by email, 2) private Facebook groups of pts with mBC and 3) members of a BC clinic. Subjects were eligible if they had ER+/HER2- mBC. A $10 gift card was obtained at survey completion. Survey answers were summarized descriptively. Results: 213 pts completed the survey. Respondents had a mean age of 57 y (range, 31–83 y), and were mostly white (91%), living in an urban/suburban setting (75%), with a higher education degree (71%) and household income ≥$75k (53%). Mean year of mBC diagnosis was 2018 (range, 1995–2022). Most common first-line mBC treatments were aromatase inhibitor (AI) + CDK4/6 inhibitor (CDK4/6i; 44%), AI alone (18%), or fulvestrant + CDK4/6i (16%); 54% had received chemotherapy in the metastatic setting. Pts most frequently received information about new mBC treatments from other people living with mBC (42%), followed by physicians (34%), social media (31%), or medical journals/conferences (28%). Two-thirds of pts (64%) reported good/very good QOL, with 12% reporting poor/very poor QOL. Common side effects mostly/moderately impacting QOL were: fatigue (74%), joint pain (64%), vaginal atrophy/dryness (56%), and vasomotor symptoms (47%). Most (84%) were comfortable/very
comfortable discussing side effects with their medical team (MT). Worry about disease progression occurred often: everyday (38%), a few times a week (21%) or month (18%), or only before scans (15%). Upon progression, pts worried more about efficacy of new treatment (76%) and having additional options (70%) than they did about side effects (33%). Pts' current treatment goals were: control cancer growth/spread (93%), prolong life (82%), maintain QOL (81%), tolerate side effects (61%), and relieve suffering/pain (57%); similar to their goals at diagnosis. Almost two-thirds of MTs addressed these goals at the beginning of treatment (63%) and continued annually (60%). Most pts (70%) were very concerned that their mBC diagnosis impacted their family although 81% felt supported at home. Since diagnosis, major/moderate life impacts were: side effects (82%), mental health/stress (78%), QOL (71%), inability to engage in activities (62%), and finances (61%). Most pts (64%) thought their mBC or treatment impacted their intimate/sexual relationship negatively and half (50%) worried about sexual intimacy. Only 44% of pts were comfortable discussing intimacy/sexual side effects with their MT. More pts were comfortable/very comfortable discussing sexual side effects with their MT if their oncologists were female (64%) vs male (51%), BC (73%) vs general (45%), or academic (70%) vs community hospital (52%) or office-based practice (49%). Most (92%) were concerned that their treatments may have a negative impact on their bones. Conclusion: In this survey of pts with ER+/HER2- mBC, >70% received information about new mBC treatments from other pts or social media vs physicians. Pts' primary concerns were disease control and treatment options, although treatment side effects had the most impact on QOL. Mental health/stress, intimacy and relationships, and bone health were also impacted. Respondents to online surveys in mBC may portray non-representative populations lacking diversity and attempts to diversify future research are much needed, and further efforts are ongoing to address this knowledge gap.

Disclosure(s):
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Elizabeth Attias, ScD: Sermonix Pharmaceuticals: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing)
Knowledge of tumor/blood genomic testing (NGS) and ESR1 mutations in a survey of patients with ER+/HER2- metastatic breast cancer (mBC)

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Introduction: In patients (pts) with ER+/HER2- mBC, acquired ESR1 mutations after endocrine therapy can lead to treatment resistance, metastasis, and poor prognosis. The objective of this survey was to understand the knowledge of NGS in pts with mBC.

Methods: The 42-question, online EQUALS (ESR1 QAulity of Life Survey) survey was sent to US subjects in June 2022 from 1) the Cure Media Group (n=6,625) by email, 2) private Facebook groups of pts with mBC and 3) members of a BC clinic. Eligible pts were those with ER+/HER2- mBC. At survey completion, respondents received a $10 gift card. Survey answers were summarized descriptively.

Results: Of 236 pts who responded to the survey, 213 completed. Participants had a mean age of 57 y (range, 31–83 y), mean mBC diagnosis year of 2018 (range, 1995–2022), and were mostly white (91%), living in an urban/suburban setting (75%), with mean household income of ≥$75k (53%), and higher education degree (71%). First-line mBC treatments were aromatase inhibitor (AI) + CDK4/6 inhibitor (CDK4/6i; 44%), AI alone (18%), fulvestrant + CDK4/6i (16%), chemotherapy (12%), selective estrogen receptor modulator (SERM; 4%) or other/clinical trial (7%). Second-line therapies were none (31%), AI + CDK4/6i (28%), fulvestrant + CDK4/6i (18%), or AI alone (12%). Of the 54% (114/213) who received chemotherapy in the metastatic setting, 34% (39/114) had received ≥3 lines of chemotherapy. Pt’s oncologist gender (female 56%) and type (general [52%], breast cancer only [48%]) or setting (office [22%], community [35%], academic [43%]) of oncology practice were well balanced.
Most pts’ oncologists (63%) had discussed tumor NGS by a blood test or tumor biopsy with them, but only 29% of them had explained liquid biopsy (assessment of circulating tumor DNA from a blood draw). Regardless, pts knew a lot/moderate amount about NGS (65%), less so of liquid biopsies (44%). NGS awareness by location was different with more suburban pts (73%) knowing a lot/moderate amount than urban (63%) or rural (59%) pts, and by income (> $50k [68%], $35k to < $50k [61%], <$35k [52%]), but not by age (< 50 y [71%]; 50-60 y [62%]; ≥60 y [69%]).

When asked if they knew what an ESR1 mutation was, about a third each knew a fair amount, a little bit, or did not know much; only 24% of pts thought they had been tested for an ESR1 mutation. ESR1 awareness (Table) differed by location, with more urban pts (40%) knowing a lot/moderate amount about ESR1 mutations vs rural (30%) or suburban (26%) pts, by income (> $50k [32%], $35k to < $50k [28%], <$35k [14%]) and by oncologist setting (academic [39%] vs office [23%] or community [24%]), but not by age. Slightly more pts had an ESR1 test in urban (26%) vs rural (20%) settings, and with higher (29%) vs lower (10%) incomes, but similar by age. Overall, most pts believed that ESR1 testing results could affect their treatment options/decisions (92%), were comfortable asking about NGS (94%), and would prefer a blood test over a tumor biopsy for more targeted mBC treatments (88%).

Conclusion: In this survey of ER+/HER2- pts living with mBC, most had some knowledge of NGS but knowledge of ESR1 mutations was lower. Discordance between physician discussion of NGS and liquid biopsies was observed. Awareness of NGS and ESR1 mutations analyzed by demographics data suggests socioeconomic disparities in pt education and knowledge. Further education on NGS and ESR1 mutations is needed as NGS testing is becoming an important aspect of mBC treatment.

Table. Awareness of ESR1 mutations based on demographics

<table>
<thead>
<tr>
<th>Region</th>
<th>n (%)</th>
<th>Do you know what an ESR1 mutation is?</th>
<th>Have you been tested for an ESR1 mutation?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>55</td>
<td>19 (35%)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Suburban</td>
<td>100</td>
<td>39 (39%)</td>
<td>39 (39%)</td>
</tr>
<tr>
<td>Rural</td>
<td>54</td>
<td>21 (39%)</td>
<td>15 (28%)</td>
</tr>
<tr>
<td>NGS awareness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% to &gt;100%</td>
<td>40</td>
<td>15 (38%)</td>
<td>15 (38%)</td>
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<tr>
<td>100% to &gt;150%</td>
<td>28</td>
<td>8 (29%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>&gt;150% to &gt;200%</td>
<td>28</td>
<td>8 (29%)</td>
<td>8 (29%)</td>
</tr>
<tr>
<td>&gt;200% to &gt;250%</td>
<td>27</td>
<td>10 (37%)</td>
<td>10 (37%)</td>
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<tr>
<td>&gt;250% to &gt;300%</td>
<td>16</td>
<td>6 (38%)</td>
<td>6 (38%)</td>
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<tr>
<td>&gt;300% to &gt;350%</td>
<td>15</td>
<td>5 (42%)</td>
<td>5 (42%)</td>
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<tr>
<td>&gt;350% to &gt;400%</td>
<td>13</td>
<td>4 (47%)</td>
<td>4 (47%)</td>
</tr>
<tr>
<td>Oncologist setting</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Community hospital</td>
<td>74</td>
<td>29 (39%)</td>
<td>29 (39%)</td>
</tr>
<tr>
<td>Academic hospital</td>
<td>75</td>
<td>29 (39%)</td>
<td>29 (39%)</td>
</tr>
</tbody>
</table>

*Never heard of it or heard of it but don’t know what it is.

Disclosure(s):
Jane Meisel, MD: AstraZeneca: Consulting Fees (e.g., advisory boards) (Terminated, October 1, 2021), Contracted Research (Terminated, October 1, 2021); Clovis Oncology: Consulting Fees (e.g., advisory boards) (Terminated, July 20, 2020); Genentech: Consulting Fees (e.g., advisory boards) (Terminated, September 29, 2021); Glaxo SmithKline: Consulting Fees (e.g., advisory boards) (Terminated, December 19, 2020); Novartis: Consulting Fees (e.g., advisory boards) (Terminated, March 10, 2022); Pfizer: Consulting Fees (e.g., advisory boards) (Terminated, June 4, 2022), Contracted Research (Terminated, June 4, 2022); Puma: Consulting Fees (e.g., advisory boards) (Terminated, August 11, 2020); Sanofi Genzyme: Consulting Fees (e.g., advisory boards) (Terminated, July 16, 2021); SeaGen: Consulting Fees (e.g., advisory boards) (Terminated, March 10, 2022), Contracted Research (Terminated, March 10, 2022)

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Examining recollections of Black women with breast cancer who participated in clinical trials: A grounded practical theory study of patient-provider communication

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Precious Okoruwa

Introduction: The presence of strong barriers to research participation for Black and Brown women is indisputable. However, existing evidence clearly supports the possibility of equal levels of participation among members of minoritized populations in past breast cancer clinical trials, demonstrating that while these participation barriers do undoubtedly exist, they are not always insurmountable. A main implication of this current study is that researchers should take greater strides to remove the onus of recruitment responsibility from racialized population members, and instead leave it with the providers, investigators, and health care teams who hold enough power to make change. Purpose: This project takes a grounded practical theory (GPT) approach to engage with Black women who have been diagnosed with breast cancer and have participated in a breast cancer clinical trial and explores their recollections of conversations with their providers. GPT focuses on reconstructing particular communication practices, highlighting both the important procedural role of communication in practice and its ability to present intricate complications that echo society’s norms and values. The aim of this work is to investigate and analyze those patient-provider conversations to try to illuminate how providers can better engage these women in ways that will positively influence their perceptions of breast cancer clinical trial participation. Methods: The current study was part of a larger project examining the recruitment of Black women to breast cancer clinical trials. Fourteen women (N=14) from six different states in the U.S., all of whom self-identified as Black, Black American, or African American, agreed to be interviewed as part of a larger study. All participants had participated or were currently participating in a breast cancer clinical trial. The interviews yielded a wealth of interesting and potentially important additional data about Black female breast cancer patients and their communication experiences with their providers. Employing grounded practical theory as a framework helped increase insight into the patient-provider communication needs of Black women who have participated in a breast cancer clinical trial. Results: Findings were summarized into four categories: 1) the participants held differing perspectives and personal impressions toward their providers; 2) the women reflect on their individual breast cancer journeys through richly described incidences, describing searching for, and finding trials on their own, or being guided by healthcare providers who suggested a clinical trial for them; 3) each participant’s shared details of their unique communication relationship with medical and research providers; and 4) the cultural aspects of participants’ patient-provider communication, focusing primarily on their expressions of faith. These findings have important implications for health communication scholars, healthcare providers, and breast cancer clinical trial research principal investigators and team members. Conclusion: As opposed to the conclusion that one may draw from most published explanations of poor minority accrual to clinical trials, which appear to put the blame on the minoritized
population members themselves, the current work outlines the actions and non-actions of many providers, and suggests that adjusting to approaches that demonstrate more encouragement and acceptance of their patients might result in better clinical trial participation outcomes from these group members.

Disclosure(s):
**Katherine E. Ridley-Merriweather, MA:** No financial relationships to disclose
Oncologist-reported Barriers and Facilitators to enrolling patients in optimization trials that test less intense cancer treatment

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Background: As outcomes improve in early-stage breast cancer, clinical trials are undergoing a paradigm shift from intensification trials (more therapy) to improve survival to optimization trials, which assess the potential for using less toxic therapy while preserving survival outcomes. However, little is known about physician perspectives in community and academic settings about possible barriers and facilitators that could impact accrual to optimization clinical trials and about the generalizability of future findings. Methods: We conducted a qualitative study with semi-structured interviews of medical oncologists from different academic and community practices to assess their perspectives on optimization trials. Interviews were audio-recorded and transcribed. Three independent coders utilized a content analysis approach to analyze transcripts using NVivo. Major themes and exemplary quotes were extracted. Results: Forty-six physicians were approached from 3/31/21-11/5/21; 39 oncologists from different oncology practices across 17 states completed interviews, 7 either declined or did not respond to email requests. Physician characteristics were balanced: men vs. women (49% vs 51%) and community oncologist vs. academic oncologist (49% vs 51%); and time practicing as medical oncologist (31% 0-9 years; 33% 10-19 years; 36% 20+ years). All 39 physicians reported that they would enroll patients in optimization clinical trials. Oncologists reported the need for treatment optimization, with one oncologist noting “historically, we've given way too much treatment to patients.” Oncologists highlighted specific reasons to consider optimization trials. They included quality of life improvement by reducing toxicity; reduction in financial toxicity; fertility preservation; ability to avoid chemotherapy; minimization of overtreatment in patients with comorbid conditions; personalized treatment; opportunities to test novel therapies; and leveraging the availability of targeted therapies. At the same time, there was hesitancy amongst some oncologists with this approach, “All my life I've worked to try to improve things and so I am not totally philosophically comfortable with the notion that I'm going to be happy with a result that says, we haven't improved it but we can get by with less.” In addition, oncologists also identified accrual barriers, like tumor-specific biology, individual (host) factors (e.g. disease characteristics, patient demographics, patient psychological state, patient preferences), prognostic markers of risk, access to therapies, provider experience, and system constraints. They voiced recommendations regarding preliminary data, trial design, and tools to support communication about and enrollment in optimization trials. Conclusions: While optimization clinical trials are generally accepted to be beneficial by oncologists, barriers impact their acceptance. Scientifically robust design and education to overcome barriers are needed to support future enrollment on trials tailoring therapy based on risk and potential benefit to allow true personalization of treatment.

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Using Mixed Methods to Examine Clinician and Patient Use of Terminology to Describe Trastuzumab Biosimilars

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Although the uptake of trastuzumab biosimilars to treat HER2-positive breast cancer is growing, knowledge gaps remain for both, patients and clinicians. In a mixed-methods study, inconsistencies in terminology used to describe trastuzumab biosimilars. We analyzed open-ended questions from surveys (n = 143 breast cancer patients, n = 33 medical oncologists) and interviews (n = 8 patients, n = 4 oncologist, nurse, pharmacists) indentifying terminology as an a priori (top-down) category for qualitative thematic analysis. We specifically looked for examples of inconsistent or incorrect use of terminology in the interviews. Findings suggest that 1) terminology used to refer to trastuzumab biosimilars is variable across patients and some is not representative of the formal definition (e.g. generic, generic-like, interchangeable, Herceptin, generic Herceptin (as per how their oncologist refers to biosimilars) and 2) clinicians discussed the challenges of talking about biosimilars in a manner that is both understandable to patients and accurate. Specifically, one pharmacist highlighted concerns around this complexity and suggested that it should be part of clinician education to use the correct terminology, rather than using the term generic. A medical oncologist said that “Explaining biosimilars to a patient can be challenging” as part of their survey response. Lack of consistent terminology for trastuzumab biosimilars is a potential barrier to effective patient-clinician communication on this topic and may perpetuate lack of comprehension on the part of patients. Further, the intentional use (to make information more digestible to patients) of incorrect terminology by clinicians has the potential to negatively impact the patient-clinician relationship in cases where patients identify conflicting information on their own. The adoption of terminology that is consistent across clinicians and patient-facing resources on the introduction and description of trastuzumab biosimilars, may serve to facilitate common grounding among all roles.

Disclosure(s):
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Immunotherapy has dramatically impacted cancer therapy, but it has been challenging to apply immunotherapy to estrogen receptor (ER) positive breast cancer and many other solid tumors that do not display neoantigens. One way to target these tumors is to induce necrosis, which robustly activates immune cells, inducing immunogenic cell death. However, anticancer therapy-induced necrosis was primarily characterized by morphological changes, and the molecular drivers of necrosis were largely obscure. To probe necrosis, we used our necrosis-inducing anticancer agents, the small molecules BHPI and second-generation ErSO, which kill cancer cells by hyperactivating the anticipatory unfolded protein response (a-UPR). In orthotopic mouse xenografts, ErSO induces complete regression without recurrence of large, therapy-resistant primary ER positive breast tumors, of most lung, bone, and liver metastases, near complete regression of challenging breast cancer brain metastases and robust responses in PDX and patient derived organoids (PDOs) models. ErSO also induces complete or near complete regression in mouse xenograft models of ER positive ovarian and endometrial cancer. Using genome wide CRISPR-Cas9 screens with negative selection against our necrosis-inducing a-UPR hyperactivators, BHPI and ErSO, we identified the calcium-activated, ATP-
inhibited, plasma membrane sodium channel, Transient Receptor Potential Melastatin Member 4 (TRPM4) as critical for anticancer therapy induced necrosis. TRPM4 knockout in multiple models abolished ErSO-induced ATP depletion, sustained UPR activation, cell swelling, necrotic cell death and increased migration of immune cells. Notably, knockout of TRPM4 completely abolished the ability of ErSO to induce regression of ER positive breast tumors in mice. Supporting a broad role for the TRPM4 pathway in anticancer therapy induced necrosis, rapid cancer cell death induced by four necrosis-inducing cancer therapies unrelated to ErSO, that range from FDA-approved to preclinical, is strongly reversed by TRPM4 knockout. ErSO treatment induces migration of macrophage into regressing tumors. Medium from cancer cells killed by necrosis-inducing ErSO, but not by an apoptosis inducer, dramatically increases macrophage migration and activation, as shown by induction of pro-inflammatory cytokines. This work identifies a protein that plays a pivotal role in the action of diverse anticancer therapies inducing immunogenic necrosis. Since increasing levels of TRPM4 increase sensitivity of breast cancer cells to killing by ErSO, TRPM4 is a novel biomarker whose levels can be used to identify patients most likely to benefit from ErSO and other necrosis-inducing cancer therapies.

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Self-assembled nano drugs of pyrotinib and indocyanine green based on photothermal photodynamic therapy

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Background: Photothermal and photodynamic therapy is a new tumor treatment strategy, which can kill tumor cells and reduce the damage to surrounding normal tissues, but the lack of targeting limits its efficacy. In this study, the targeted photothermal and photodynamic nanodrug P/ICG was synthesized by self-assembly of the targeted drug pyrotinib and photosensitizer indocyanine green (ICG), and its application in the photothermal and photodynamic therapy of HER2 positive breast cancer was explored.

Method: In this study, the nano drug P/ICG was self-assembly synthesized of pyrotinib and ICG, and its physical parameters and stability were tested. We used 808nm near-infrared light and infrared thermal imager to verify the photothermal effect of nano drugs. Then we used DCFH-DA probe to detect the level of ROS in cells by laser confocal and flow cytometry to verify the photodynamic effect of the nano drug, and verified the antitumor effect of P/ICG combined with near-infrared light irradiation in vitro.

We established a PDX mouse breast cancer model and verified the efficacy and safety of P/ICG in the treatment of HER2-positive breast cancer in vitro. Finally, the effect of P/ICG on ferroptosis was verified by MDA, CCK8 and WB experiments.

Result: We mixed pyrotinib and ICG in a certain proportion, and purified them by high-speed centrifugation and ultrafiltration to synthesize nano drug P/ICG. P/ICG has good stability and can be effectively ingested by HER2-positive breast cancer cells. Subsequently, we proved through in vitro and in vivo experiments that P/ICG combined with near-infrared light irradiation can significantly inhibit the growth of tumor cells and improve the survival rate of mice. At the same time, P/ICG combined with near-infrared light irradiation increased the phosphorylation of Nrf2 protein, increased the level of free KEAP1 protein, and decreased the levels of SLC7A11, GPX4 and FTH1 protein, significantly increased the lipid peroxidation of tumor cells, and promoted the ferroptosis of tumor cells.

Conclusion: Pyrotinib and ICG self-assembled nano drug P/ICG can significantly promote the ferroptosis of HER2-positive breast cancer cells and inhibit the growth of cancer cells, which can be used as a new strategy for the treatment of HER2-positive breast cancer.

Key words: pyrotinib; HER2-positive breast cancer; Photothermal therapy; photodynamic therapy

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Jun Deng, n/a: No financial relationships to disclose
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Datopotamab Deruxtecan (Dato-DXd) in Advanced Triple-Negative Breast Cancer (TNBC): Updated Results From the Phase 1 TROPION-PanTumor01 Study

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Background: Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 mAb covalently linked to a highly potent topoisomerase I (Topo I) inhibitor payload via a stable, tumor selective, tetrapeptide-based cleavable linker. Dato-DXd has previously shown encouraging activity in heavily pretreated patients (pts) with metastatic TNBC (Krop, SABCS 2021). Here we report updated results from the TROPION-PanTumor01 study in pts with advanced/metastatic TNBC. Methods: TROPION-PanTumor01 (NCT03401385) is a phase 1, multicenter, open-label, 2-part dose-escalation/expansion study evaluating Dato-DXd in previously treated pts with solid tumors. Based on previous clinical and exposure-response results from pts with NSCLC, Dato-DXd 6 mg/kg IV Q3W is being evaluated in pts with advanced TNBC that relapsed/progressed on standard therapies; 2 pts received 8 mg/kg prior to selection of 6 mg/kg. The primary objectives were safety and tolerability. Tumor responses, including objective response rate (ORR; complete response [CR] + partial response [PR]) and disease control rate (DCR; CR + PR + stable disease [SD]), were assessed per RECIST v1.1 by blinded independent central review. Results: As of April 29, 2022, 44 pts received Dato-DXd (median follow-up, 16.6 mo [range, 13-22]) at the time of data cutoff. The primary cause of treatment discontinuation was disease progression (86%; PD or clinical progression), and 4 pts are still receiving therapy. Median age was 53 y (range, 32-82); 32% had de novo metastatic disease. Pts were heavily pretreated with a median of 3 (range, 1-10) prior regimens in the metastatic setting. Prior treatments included taxanes (91%), anthracyclines (75%), capecitabine (61%), platinum (52%), immunotherapy (43%), Topo I inhibitor–based ADC therapy (32%), and PARPi (18%). Treatment-emergent adverse events (TEAEs; all cause) occurred in 100% (any grade) and 50% (grade ≥3) of pts, respectively. Most common TEAEs (any grade, grade ≥3) were stomatitis (73%, 11%), nausea (66%, 2%), vomiting (39%, 5%), fatigue (34%, 7%), and alopecia (36%, 0%). One pt had grade 3 decreased neutrophil count; no cases of interstitial lung disease (ILD) or grade ≥3 diarrhea were observed. Serious TEAEs were reported in 9 pts (20%); no deaths associated with adverse events (AEs) were observed. Dose reductions occurred in 8 pts (18%) due to stomatitis (n=3), fatigue (n=2), dry eye (n=1), retinal exudates (n=1), and dysgeusia (n=1); 12 pts (27%) delayed treatment due to stomatitis (n=5), dry eye (n=1), keratitis (n=1), blurred vision (n=1), fatigue (n=1), bronchitis (n=1), skin infection (n=1), musculoskeletal chest pain (n=1), dysgeusia (n=1), chronic obstructive pulmonary disease (n=1), and dyspnea (n=1; >1 AE per pt). One pt (2%) discontinued treatment due to grade 1 pneumonitis (which was centrally adjudicated as not ILD). ORR in all pts was 32% (1 CR, 13 PRs), DCR was 80% (35/44), and clinical benefit rate (CR + PR + SD ≥6 mo) was 34% (15/44). Median duration of response was not yet reached; median progression-free survival (mPFS) was 4.3 mo (95% CI, 3.0-7.3), and
median overall survival (mOS) was 12.9 mo (95% CI, 10.1-14.7). In the subset of pts without prior Topo I inhibitor–based ADC therapy and with measurable disease at baseline, ORR was 44% (12/27). Among all pts without prior Topo I inhibitor–based ADC therapy (n=30), mPFS was 7.3 mo (95% CI, 3.0-NE), and mOS was 14.3 mo (95% CI, 10.5-NE). Conclusions: Dato-DXd continues to demonstrate encouraging and durable antitumor activity, along with a manageable safety profile, in heavily pretreated pts with metastatic TNBC. Based on these findings, the phase 3 randomized TROPION-Breast02 (NCT05374512) trial comparing Dato-DXd vs chemotherapy as 1L therapy for pts with metastatic TNBC is currently underway.

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Background: Homologous recombination deficiency (HRD) is highly prevalent in triple-negative breast cancer (TNBC) and predictive of response to PARP inhibition in the primary setting (Eikesdal et al, Ann Oncol, 2021). However, the prevalence of HRD across breast cancer subtypes has not been established. Methods: Pretreatment tumor biopsies from 201 patients (32 TNBC and 169 non-TNBC) with primary breast cancer in the phase II PETREMAC trial (ClinicalTrials #NCT02624973) were examined. These samples underwent targeted cancer gene panel sequencing and BRCA1 promoter methylation analysis to assess HRD status.
defined by homologous recombination repair (HRR) gene mutations and/or BRCA1 promoter methylation. HRR genes included BRCA1, BRCA2, BRIP1, BARD1, and PALB2 by strict definition (HRR-S), and additionally ABL1, ATM, ATR, ATRX, BLM, CDK12, CHEK1, EMSY, ERCC4, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, MEN1, MRE11, NBN, PTEN, and SETD2 by wider definition (HRR-W). HRD strict (HRD-S) was defined as biallelic gene inactivation by HRR-S mutations or BRCA1 methylation. Finally, tumors underwent PAM50 gene expression subtyping and evaluation of functional HRD by RAD51 nuclear foci analysis, for which a low score has been associated with HRD. Results: HRD-S was present in 13% of the breast cancers (total: n= 27/201; TNBC: 15/32; 47%; non-TNBC: 12/169; 7%), whereas HRD-W (HRR-W or BRCA1 methylation) was observed in 29% (total: n=58/201; TNBC: 19/32; 59%; non-TNBC: 39/169; 23%). Among 190 tumors analyzed for PAM50 intrinsic subtype, HRD-S was detected in 3/60 and 4/48 (5% and 8%) of tumors classified as luminal A and B, respectively, 1/35 (3%) of HER2-enriched, 4/21 (19%) of normal-like, and 12/26 (46%) of basal-like tumors. Out of 58 non-TNBC biopsies examined by RAD51 staining, four (7%) were classified as HRD-S and all these were scored as RAD51 low. The remaining 54 non-TNBC samples were homologous recombination proficient, and none of these exhibited functional HRD by RAD51 low scores. All four HRD-S/RAD51 low tumors were hormone receptor-positive, HER2 negative, and belonged to the luminal A (n=1), luminal B (n=2 ), and basal-like (n=1) subtypes, with HRD caused by germline BRCA1 (gBRCA1), gBRCA2, somatic BRCA1 mutations and BRCA1 methylation, respectively. Conclusion: The prevalence of HRD across all breast cancer subtypes suggests that HRD analysis and therapy targeting such DNA repair defects should be tested in future clinical trials.

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Mutations in the RNA Splicing Factor SF3B1 drive endocrine therapy resistance and confer a targetable replication stress response defect through PARP inhibition.

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Background:
Heterozygous hotspot mutations in the RNA splicing factor SF3B1, occur in 3% of unselected breast cancers and are associated with oestrogen receptor (ER+) breast cancer (BC) where they are enriched in metastatic disease and are associated with a poor clinical outcome. SF3B1 mutations drive distinct signatures of alternative splicing through cryptic 3’ splice site selection leading to global transcriptomic and proteomic changes. The functional consequences of the mis-splicing events and resultant genetic vulnerabilities are poorly understood and precision medicine approaches that exploit these characteristics are not clinically available (Table 1).

Methods:
To understand the role of SF3B1 mutations in ER+ BC, we generated a series of SF3B1 mutant (SF3B1MUT) isogenic cell lines which were characterised using RNA-sequencing and high content mass-spectrometry proteomic profiling. SF3B1 interactome analysis was also performed using immunoprecipitation of SF3B1 followed by mass-spectrometry. The molecular consequences of aberrant splicing were investigated using a targeted screening approach of 280 genes predicted to be alternatively spliced in SF3B1MUT BC, while high-throughput drug screens were used to identify novel therapeutic options for patients with SF3B1MUT breast cancer using isogenic cells. Hits were validated in vitro and in vivo using cell line and patient derived xenografts.

Results:
Transcriptomic and proteomic profiling of SF3B1MUT cells identified global alternative 3’ splice site selection and subsequent proteomic changes induced by the mutations. Investigation of the SF3B1K700E interactome identified an enrichment of SF3B1K700E binding with ER+, aberrant splicing of ER target genes, global rewiring of ER+ chromatin binding and resistance to endocrine therapy. Silencing of the aberrantly spliced candidate genes PPIH, TRIM37, HIGD1A, BRD9, and PHKG2 significantly enhanced the growth of the SF3B1 mutant cells, suggestive of a dose dependent tumour suppressive effect.

Through synthetic-lethal drug screens we found that SF3B1MUT cells are selectively sensitive to PARP inhibitors. SF3B1MUT cells display a defective response to PARPi induced replication stress. Mechanistically, this occurs via defective ATR signalling in SF3B1MUT cells, which upon PARPi exposure leads to increased replication origin firing and loss of pChk1 (S317) induction. The resultant replication stress leads to failure to resolve DNA replication intermediates via the endonuclease MUS81 and cell cycle stalling at the G2/M checkpoint. These defects can be further targeted by ATM, CDK7 or FACT inhibition, when used in combination with PARPi treatment. This SF3B1MUT selective PARPi sensitivity is preserved across multiple cell lines and patient derived tumour models. In vivo, PARPi produce profound anti-tumour effects in multiple SF3B1MUT cancer models and eliminate distant metastases.

Conclusions:
Our integrative analysis reveals mechanistic insight into the role of SF3B1 mutations in endocrine therapy response in ER+ breast cancers, where altered SF3B1 induces ER-transcriptional re-programming. We further identified a robust synthetic-lethal relationship of mutant SF3B1 with PARP inhibition that is caused by a defective response to PARPi induced replication stress. Furthermore, we identified several potential selective combination strategies together with PARPi that are selective for SF3B1MUT cells. Together, these data provide the pre-clinical and mechanistic rationale for assessing already-approved PARPi in a biomarker-
defined subset of advanced ER+ BC.

Table 1
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Identified potential therapies for SF3B1 mutant cancers from this study and the literature

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**Rachael Natrajan, PhD:** Pfizer: Academic research grant with Breast Cancer Now (Ongoing)
A preoperative window-of-opportunity study of imlunestrant in estrogen receptor-positive, HER2-negative early breast cancer: Results from the EMBER-2 study.

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Background: Imlunestrant is a novel, orally bioavailable selective estrogen receptor degrader (SERD) with pure antagonistic properties that result in sustained inhibition of estrogen receptor (ER)-dependent gene transcription and cell growth. In a phase 1 study, imlunestrant monotherapy showed favourable safety, pharmacokinetics (PK) and preliminary efficacy in heavily pre-treated ER-positive (ER+) advanced breast cancer patients (Jhaveri ASCO 2022). Here, we present pharmacodynamic (PD) data from the preoperative window of opportunity (WOO) study (EMBER-2, NCT04647487), evaluating the biological activity of imlunestrant
monotherapy in ER+, HER2-negative (HER2-) early breast cancer (EBC).
Methods: Post-menopausal women with stage I–III operable ER+ (>50%) or Allred score >5, HER2- untreated EBC ≥1 cm in diameter were randomized 1:1 to imlunestrant 400 mg once daily (QD) or imlunestrant 800 mg QD for 15 days (treatment window of -2 to +7 days) up to the surgery date. Pre- and on-treatment tumor samples were compared for changes in PD biomarkers. Primary study objective was change in ER expression (measured by IHC and quantified by H-score). Secondary objectives were change in progesterone receptor (PR) expression (measured by IHC and quantified by H-score) and Ki-67 (measured by IHC and expressed by percentage positive scoring) along with evaluation of safety and tolerability.
Results: From Apr 28, 2021, to Mar 11, 2022, 58 patients were enrolled of which 54 were biomarker-evaluable for ER expression (400 mg: n = 28; 800 mg: n = 26). Patient demographics and tumor characteristics for all enrolled patients were similar across cohorts, with a median age of 64 years (50-83), 72% invasive ductal carcinoma (IDC), 28% invasive lobular carcinoma (ILC), 59% stage I, 36% stage II and 5% stage III disease. 91% of the patients had a compliance rate higher than 80%. Among biomarker evaluable patients, relative reduction in PD biomarkers after a median of 15 days (range 13 to 23 days) of treatment are presented in Table 1. There was no significant difference in PD biomarker modulation noted between the two imlunestrant doses (400 mg vs 800 mg) or based on tumor histology (IDC, ILC). Imlunestrant was well tolerated. There were no discontinuations due to adverse events (AEs). Treatment-related AEs (TRAEs) were mainly grade 1, most commonly: fatigue (10%), diarrhea (9%), hot flushes (7%), and nausea (5%). There were no TRAEs of diarrhea and nausea observed at the 400 mg dose. No grade 3 or higher TRAEs were reported.
Conclusion: Imlunestrant demonstrated evidence of target engagement along with consistent biological activity across all evaluated dose levels and was well tolerated in an EBC population, further supporting continued adjuvant development in the ongoing EMBER-4 study. Additional biomarker analyses for the EMBER-2 study are also planned.

Table 1. Relative reduction in PD biomarkers from Baseline to Day 15
<table>
<thead>
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<th>400 mg cohort</th>
<th>800 mg cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER (N=54)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n (%)</td>
<td>28 (52)</td>
<td>26 (48)</td>
<td>54 (100)</td>
</tr>
<tr>
<td>Geometric mean percent change <em>(90% CI)</em></td>
<td>-81 (-91, -61)</td>
<td>-70 (-78, -59)</td>
<td>-76 (-84, -65)</td>
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<tr>
<td>Geometric mean ratio <em>(90% CI)</em></td>
<td>2 (1, 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR (N=52)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>26 (50)</td>
<td>26 (50)</td>
<td>52 (100)</td>
</tr>
<tr>
<td>Geometric mean percent change <em>(90% CI)</em></td>
<td>-76 (-80, -38)</td>
<td>-72 (-81, -59)</td>
<td>-71 (-78, -63)</td>
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<tr>
<td>Geometric mean ratio <em>(90% CI)</em></td>
<td>1 (1, 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ki67 (N=42)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>22 (52)</td>
<td>20 (48)</td>
<td>42 (100)</td>
</tr>
<tr>
<td>Geometric mean percent change <em>(90% CI)</em></td>
<td>-71 (-80, -57)</td>
<td>-72 (-81, -59)</td>
<td>-71 (-78, -63)</td>
</tr>
<tr>
<td>Geometric mean ratio <em>(90% CI)</em></td>
<td>1 (1, 2)</td>
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Ki67 among patients with baseline Ki67 ≥ 5% (N = 39)

<table>
<thead>
<tr>
<th></th>
<th>400 mg cohort</th>
<th>800 mg cohort</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>22 (50)</td>
<td>17 (44)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Geometric mean percent change <em>(90% CI)</em></td>
<td>-71 (-80, -57)</td>
<td>-78 (-84, -70)</td>
<td>-74 (-80, -67)</td>
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<tr>
<td>Geometric mean ratio <em>(90% CI)</em></td>
<td>1 (1, 1)</td>
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</tbody>
</table>

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**Patrick Neven, MD, PhD:** AstraZeneca: Consulting Fees (e.g., advisory boards) (Ongoing); Hoffmann-La Roche: Consulting Fees (e.g., advisory boards) (Ongoing); Lilly: Consulting Fees (e.g., advisory boards) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing); Radius Health: Consulting Fees (e.g., advisory boards) (Ongoing); Sanofi: Contracted Research (Ongoing); Teva: Consulting Fees (e.g., advisory boards) (Ongoing)

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CDK2 inhibition with BLU-222 in combination with ribociclib demonstrates robust antitumor activity in pre-clinical models of CDK4/6 inhibitor-naïve and -resistant HR+/HER2- breast cancer

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Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are standard of care in combination with endocrine therapy in advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer. Despite improved progression-free and overall survival, almost all patients develop CDK4/6 inhibitor resistance and experience disease progression on treatment. Aberrant activation of CDK2/cyclin E is a key resistance mechanism by which tumors can evade CDK4/6 blockade. Therefore, patients with HR+/HER2- breast cancer could benefit from treatment with a selective CDK2 inhibitor in combination with CDK4/6 inhibitors both in the resistant and first-line (1L) settings. BLU-222 is a novel, potent, and selective small-molecule inhibitor of CDK2 with favorable pharmacokinetic properties when administered orally, currently in early-stage clinical development. In pre-clinical studies using the MCF-7 xenograft model of HR+ CDK4/6-responsive breast cancer, treatment with BLU-222 combined with the CDK4/6 inhibitor ribociclib led to pronounced and durable tumor regression superior to ribociclib alone. In a derived palbociclib resistant MCF-7 xenograft model, ribociclib had no anti-tumor activity while BLU-222 led to a strong and durable anti-tumor response (83% tumor growth inhibition [TGI]) that was further improved when given in combination with ribociclib (110% TGI). To further explore the mechanism of aberrant CDK2 activation in CDK4/6 resistant, HR+ breast cancer, we engineered isogenic T47D cell lines to overexpress cyclin E1 (CCNE1) with or without p16, an endogenous inhibitor of CDK4/6 activity. In in vitro proliferation assays, co-expression of CCNE1 and p16 sensitized T47D cells to BLU-222 by approximately 10-fold compared to the parental control (110 nM vs 1078 nM, respectively). CDK4/6 inhibition with ribociclib had no anti-proliferative effect in the CCNE1 overexpressing cell lines regardless of p16 expression status. In vivo, treatment of the empty vector control T47D xenografts with ribociclib led to tumor stasis, while ribociclib in combination with BLU-222 led to tumor regression. T47D xenografts overexpressing both CCNE1 and p16 were resistant to ribociclib however CDK2 inhibition with BLU-222 single-agent treatment led to tumor regression. Finally, the activity of BLU-222 was evaluated in a patient-derived xenograft (PDX) model of CDK4/6 inhibitor-resistant HR+/HER2- breast cancer where the patient had progressed on 1L palbociclib/fulvestrant and 2L abemaciclib/fulvestrant therapy. In this PDX model, BLU-222 in combination with ribociclib led to tumor stasis, even in the absence of fulvestrant. In conclusion, these data support CDK2/cyclin E activation as a key vulnerability in CDK4/6 resistant, HR+/HER2- breast cancer and provide a rationale for the study of BLU-222 in patients with disease progression following CDK4/6 inhibitor treatment. Additionally, the improved durability of response when BLU-222 is combined with CDK4/6 inhibitors in the CDK4/6-naïve setting
supports the combination of these agents as 1L treatment. BLU-222 is currently under investigation in VELA (NCT05252416), a phase 1/2, first-in-human trial for patients with cyclin E aberrant cancers and HR+/HER2- breast cancer.

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Background Inflammatory breast cancer (IBC) and triple-negative breast cancer (TNBC) are aggressive breast cancer subtypes with poor clinical outcomes due to the lack of well-validated and actionable targets and the onset of chemo-resistant metastasis. TNBC and IBC account for 15-20% and 2-4% of all breast cancer diagnoses but result in 30% and 8%-10% of breast cancer-related deaths, respectively. MELK (maternal embryonic leucine zipper kinase) is a potential therapeutic target in both TNBC and triple-negative IBC (TN-IBC). We have shown that 1) MELK expression is higher in basal tumors (mostly TNBC) and in IBC than in non-IBC, 2) high MELK expression is an independent prognostic factor for poor overall survival.
(P=0.0002) and poor distant metastasis-free survival (P=0.008) in breast cancer, and 3) MELK knockout leads to significantly lower metastatic burden and prolonged survival in a xenograft model of TNBC (unpublished data). MELK inhibitor (MELKi) OTS167 is in clinical trials but it lacks specificity and cross-reacts with other essential kinases. It is critical to discover novel, selective inhibitors with good bioavailability that target MELK and minimize adverse effects. We have developed a second-generation small-molecule MELK inhibitor 30e that is a highly potent and slow-binding ATP-competitive inhibitor of MELK. 30e exhibits potent cellular inhibition of MELK (IC50< 10 nM), as assessed using a live cell NanoBRET assay, and is highly selective as assessed by live-cell KiNativ profiling experiments in MDA-MB-231 TNBC cells. Methods We screened a panel of TNBC and IBC cell lines for MELK expression by western blot and qPCR analysis. We assessed the effects of MELK inhibition with the 30e on migration and invasion. The role of MELK in regulating cancer stem cell phenotypes was assessed using the mammosphere assay and flow cytometry (CD44+/CD24-/low surface marker). MELK's protumorigenic role was determined in vitro using a soft agar assay, and the anti-tumor activity of 30e was assessed in vivo using a TN-IBC orthotopic xenograft mouse model. Results We found that TNBC had high mRNA levels of MELK (62%) compared to non-TNBC cell lines (25%), which correlated with MELK protein levels. 30e inhibited cell viability in TNBC and IBC cells in a dose-dependent manner and with IC50s ranging from 0.45 to 1.76 μM (P≤0.05). However, no significant effect was observed when normal MCF-10A breast cells were treated with 30e (IC50>20 μM). 30e also significantly reduced colony formation ability. Further, we observed that 30e reduced mammosphere formation efficiency and the CD44+/CD24-/low subpopulation in both TNBC and IBC cells in a dose-dependent manner (P≤0.05), suggesting the potential of 30e to inhibit the stem cell population in vitro. The soft agar assay also showed a significant decrease in colony formation in the TNBC and IBC cells after treatment with 30e, an indirect indicator of in vivo tumorigenicity. To assess the efficacy of 30e treatment on tumor growth, we evaluated this inhibitor as a single agent in a SUM-149 (TN-IBC) orthotopic mouse model. The mice were treated with intraperitoneal injections daily with 3 doses (2.5, 5, and 10 mg/kg) of 30e. Our data show that 30e suppressed tumor growth in a dose-dependent manner (P< 0.007). Conclusions and Future Directions Our data demonstrate that a novel, potent and specific MELK inhibitor inhibits tumor growth by suppressing the cancer stem cell phenotype. MELK is a promising target for aggressive cancers such as TNBC and IBC. We are evaluating how MELK inhibition modulates the tumor microenvironment, which is a critical component of breast cancer response to treatment. We performed a cytokine antibody array and are validating the top targets. Further, we will evaluate 30e in combination with standard-of-care treatment for toxicity and inhibition of metastasis.

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**Mutational landscape of breast cancer patients in ROME trial: preliminary results**

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BACKGROUND: The Rome Trial is a randomized phase II trial (NCT04591431). The aim is to evaluate efficacy and safety of a tailored treatment (TT) compared to standard of care (SoC) in patients with solid tumors. Here we report the preliminary results of the molecular alterations, microsatellite status (MS) and tumor mutational burden (TMB) in metastatic breast cancer (mBC) cohort. METHODS: MBC patients who received at least 1 and no more than 2 systemic treatments were enrolled. Tissue samples were collected within 6 months from the screening. Centralized Next Generation Sequencing (NGS) was performed on both tissue and liquid biopsy. Molecular alterations were evaluated by the Molecular Tumor Board (MTB) using COSMIC, ClinVar, OncoKB and VarSome datasets. Genes with at least 10% frequency of mutation, MS and TMB are reported. RESULTS: From Oct 2020 to June 2022, 980 pts with solid tumors were enrolled. Complete screening mutational data are available for sixty-two pts from the mBC cohort (63% HR+/HER2-, 35% triple negative, 2% HR-/HER2+). NGS was available both on tissue and liquid biopsy in 48 (77%) pts, 14 had only liquid biopsy available due to tissue test failure. 328 genes resulted altered with a median of 7 alteration per pts (0-31). Some pathways were frequently altered: PIK3CA/AKT/MTOR (60%), TP53 (60%), Cell cycle/cycline (35%), FGFR/FGFR (26%), BRCA1/2 (17%). The most frequent altered genes were: TP53 (61%), PIK3CA (50%), ESR1 (27%), CCND1 (27%), FGF19 (24%), FGF3 (24%), FGF4 (22%), MYC (22%), FGFR1 (21%), PTEN (21%), EMTY (16%), RB1 (14%), RAD21 (14%), TET2 (13%), BRCA2 (11%), GATA3 (11%), KRAS (10%). No pts with MSI status were reported. Eight (13%) had a high TMB (>10) and the overall median TMB was 5.5 (0-24). Median TMB was similar in tissue and liquid samples (5 and 5.3 mut/mb, p = 0.8). Actionable mutations were detected in 34 pts (54%). Twenty-eight (45%) pts were assigned to a specific TT after the MTB discussion: ipatasertib (16), pemigatinib (5), lapatinib plus trastuzumab, TDM1 and everolimus (1). MTB requested a germline test for 6 pts: 4 were confirmed (66%; 2 BRCA, 1 PALB2, 1 BRIP1). CONCLUSIONS: The extensive NGS analysis performed in the ROME trial shown that several pathways are commonly mutated in mBC, with target drug potentially available. About 15% of pts had a high TMB but MSI is confirmed as a rare event in breast cancer. Germline mutations have been identified in patients with no prior indication for germline testing.

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Genetic alterations in breast cancer associated with MDM2 dependency and sensitivity to the MDM2 inhibitor milademetan

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Background: Murine double minute 2 (MDM2), a potent negative regulator of p53, promotes tumorigenesis if dysregulated. MDM2 dysregulation occurs via different mechanisms, including MDM2 gene amplification, MDM2 overexpression, and loss of cyclin-dependent kinase inhibitor 2A (CDKN2A), which encodes the MDM2 regulator p14ARF. Combined inactivation of MDM2 and GATA3 in hormone receptor-positive (HR+) breast cancer is lethal to the cell. Pharmacologic inhibition of MDM2 is a rational therapeutic strategy for MDM2-dependent, TP53 wildtype (WT) tumors, including tumors with MDM2 amplification or CDKN2A loss, and GATA3-mutant HR+ breast cancers. We determined the frequency and associated characteristics of genetic alterations of MDM2-dependent breast cancers, and evaluated sensitivity of these tumors to the small-molecule MDM2 inhibitor milademetan (RAIN-32).

Methods: Genomic data were obtained from three datasets: METABRIC; TCGA PanCancer Atlas, GDC v23.0 (April 2020); AACR Genie, v11. Among TP53 WT breast cancer samples from each dataset, the frequency of GATA3 frameshift mutations, MDM2 amplification (copy number [CN] ≥12), and CDKN2A homozygous loss was determined individually and as co-alterations. The antitumoral activity of milademetan was evaluated in a GATA3-mutant, TP53 WT HR+ breast cancer cell line (MCF7 GATA3 G336fs*17), a breast xenograft model (MCF7 GATA3 G335fs), and ex vivo in MDM2-amplified patient-derived breast cancer organoids (CTG-2810, ER+/PR+/HER2−, MDM2 CN 8).

Results: Genetic alteration frequencies in TP53 WT breast cancers by dataset are shown in the Table. GATA3 frameshift mutations (7.3–11.7%), MDM2 amplification (0.3–1.1%), and CDKN2A loss (0.2–1.2%) occurred across breast tumors, but were found with highest frequencies in HR+ tumors. Co-alteration frequencies in TP53 WT breast cancers across the aforementioned datasets were < 1%: GATA3 mutations/MDM2 CN ≥12 (0.2–0.3%); GATA3 mutations/CDKN2A loss (0.1–0.2%); MDM2 CN ≥12/CDKN2A loss (0%). Mean MDM2
expression (log2 (TPM+1)) in HR+ breast cancers (TCGA) were: GATA3 mutations, 5.12; CDKN2A loss, 5.88; MDM2 CN ≥12, 8.13, TP53 WT without these alterations, 4.78; mutant TP53, 4.35. A GATA3-mutant ER+ breast cancer cell line was sensitive to milademetan in vitro (IC50 126 nM). Milademetan 100 mg/kg displayed antitumor activity in GATA3-mutant HR+ breast cancer xenograft and PDX models (p< 0.05 vs. vehicle). Milademetan also displayed activity in MDM2-amplified HR+ breast cancer organoids (IC50 0.2 μM). In a phase I study (NCT01877382), a patient with heavily pretreated MDM2-amplified breast cancer (MDM2 CN 16.8) had tumor shrinkage (18.2%) and PFS of 7.3 months with milademetan (orally 260 mg 3/14 days).

Conclusions: The frequency of genetic alterations potentially targetable by MDM2 inhibition among TP53 WT breast cancers (i.e., GATA3 mutations, MDM2 amplification, and CDKN2A loss) is greatest in the HR+ subset, and these genetic biomarkers are associated with higher MDM2 expression. Preclinical data show that the MDM2 inhibitor milademetan has antitumor activity in GATA3-mutant and MDM2-amplified HR+ breast cancers, and support the clinical evaluation of milademetan in these tumors. Two clinical trials of milademetan – MANTRA-2 (Phase 2 basket study in solid tumors with TP53 WT and MDM2 CN ≥12; NCT05012397) and MANTRA-4 (Phase 1 study of milademetan + atezolizumab in solid tumors with CDKN2A loss) – are enrolling patients or in planning.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>TPS3 WT samples, N</th>
<th>Frequency of alterations in TPS3 WT samples, %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>GATA3 fs mutations</td>
<td>MDM2 CN ≥12</td>
</tr>
<tr>
<td>METABRIC</td>
<td>1246</td>
<td>7.3</td>
</tr>
<tr>
<td>HER2-/HR+</td>
<td>1107</td>
<td>7.6</td>
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<tr>
<td>HER2+</td>
<td>74</td>
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<tr>
<td>HR+</td>
<td>50</td>
<td>0.4</td>
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<tr>
<td>HR-</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>TNBC</td>
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<td>TCGA PanCancer Atlas</td>
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<td>11.2</td>
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<tr>
<td>HER2-/HR+</td>
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<td>HER2+</td>
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</tr>
<tr>
<td>HR+</td>
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<tr>
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<tr>
<td>TNBC</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>AACR Genie*</td>
<td>3590–7578</td>
<td>8.9</td>
</tr>
</tbody>
</table>

CN, copy number; fs, frameshift; HR, hormone receptor; TNBC, triple-negative breast cancer.

*No hormone receptor or molecular subgroup data available.

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Engineered neoantigen-specific T cell receptors to treat metastatic breast cancer

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T cell receptor engineered T cell (TCR T) therapy has emerged as a promising therapeutic modality for solid cancer following recent trials demonstrating the safety and efficacy of TCR T therapies against some types of metastatic solid cancers. However, the broader application of TCR T towards many solid tumors, including metastatic breast cancer (MBC), has been limited by several factors, chiefly among them the current scarcity of tumor selective target antigens. Neoantigens, which are expressed exclusively in cancer cells, are currently underrepresented in TCR T development, being targeted in only about 7% of trials conducted to date, and thus represent a relatively untapped source of potentially safe and effective novel targets. Driver
mutations in AKT1, ESR1, PIK3CA, and TP53 are common in patients with MBC, and could serve as ideal neoantigen targets for TCR T therapies. We hypothesized that we could generate MBC driver mutation-specific T cells from which we could isolate and clone neoantigen-specific TCRs to generate TCR T products for MBC. We identified 13 driver missense mutations that are among the most frequent in patients with MBC, which included AKT1 (E17K), ESR1 (K303R, Y537S, D538G), PIK3CA (E542K, E545K, H1047L, H1047R), and TP53 (R175H, R248Q, R248W, R273C, R273H), then designed peptide libraries consisting of 15-mer overlapping peptides that contain these mutations. To determine if these neopeptides could elicit T cell responses, we isolated T cells from 15 healthy donors and 11 MBC patients who expressed at least one of the targeted mutations and performed successive stimulations with neopeptide pulsed dendritic cells, then screened the resulting T cell lines for neoantigen specificity using an IFN-γ ELISpot assay. We observed neopeptide T cell responses in 8/16 lines generated from healthy donors and 7/11 lines generated from MBC patients, which were collectively directed against 11/13 of the targeted driver mutations. To isolate neoantigen-specific TCRs from one of these lines, we performed IFN-γ capture, limiting dilution, and 5' RACE, and isolated an HLA-B*35 restricted TP53 R248W-specific TCR. Gene transfer of this TCR conferred edited T cells with potent activity towards the TP53 R248W and not the TP53 WT peptide as assessed by ELISpot (1036 vs 46 SFU/1x10^5 cells, respectively) and chromium release cytotoxicity assay targeting peptide pulsed autologous PHA blasts (37.5% vs 0% lysis at E:T 40:1, respectively). To increase the throughput of TCR discovery, we next used a single cell RNA sequencing based TCR discovery approach whereby we stimulated T cells from one of the generated lines with ESR1 WT or neopeptide and identified responsive T cell clones through upregulation of IFN-γ and/or TNF-α. This strategy has so far enabled us to identify and validate two ESR1 mutant-specific TCRs. This includes an HLA-C*01 restricted TCR that confers both activity towards both ESR1 Y537S and D538G, but not WT peptide as determined by both ELISpot (2094, 3194, and 79 SFU, respectively) and chromium release cytotoxicity (31.3%, 77.8%, and 9.1% lysis, respectively), as well as an HLA-B*40 restricted TCR that confers high ESR1 Y537S specificity (5039 vs 138 SFU in response to ESR1 Y537S vs WT peptide, respectively). In summary, we have demonstrated responses of T cells derived from both healthy donors and MBC patients towards neopeptides derived from common MBC driver mutations. We have so far isolated neoantigen specific TCRs from two of the neoantigen-specific T cells lines, including TCRs specific towards TP53 R248W, ESR1 Y537S, dual ESR1 Y537S+D538G that are restricted to three different HLA alleles, and have successfully used these TCRs to generate TCR T products with high neoantigen activity. These results encourage further efforts to identify TCRs recognizing these MBC driver mutations, with our ultimate aim to translate neoantigen-targeted TCR T therapies to clinical trials of MBC.

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Discovering and Development of Next-Generation Estrogen Receptor Mutant Inhibitors using DNA-Encoded Chemical Library Screening

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Background: Activating somatic ESR1 mutations Y537S and D538G occur more frequently in endocrine therapy-resistant metastatic breast cancer, which is associated with an aggressive phenotype and poor survival in breast cancer patients. These gain of function mutant receptors are constitutively active and allow resistance to first-line endocrine therapies. Therefore, the development of next-generation small molecule drugs targeting mutant estrogen receptor (ER) is an important priority. Here, we searched the small molecule inhibitors for Y537S and D538D ER mutants using DNA-encoded chemical library screening. Methods: Wild type (WT) and mutant ER ligand binding domain (LBD) proteins were expressed in E. coli. The soluble proteins were purified by Ni-NTA chromatography followed by anion exchange and size exclusion chromatography. Homogeneous time-resolved fluorescence (HTRF) and fluorescent polarization (FP) assays were performed in these purified proteins. We employed a DNA-encoded chemical library affinity selection using our in-house collection of 6 billion compounds. Hit compounds were resynthesized and validated in biochemical assays. Finally, we have performed functional studies in CRISPR-Cas9 knock-in of Y537S and D538G mutant MCF-7 breast cancer cells. Results: We have successfully purified microgram amounts of ERα LBD of WT, Y537S, and D538G proteins. To test whether the purified WT and mutant proteins are active, HTRF and FP assays were performed in the presence of estradiol and 4OH tamoxifen. Steroid receptor coactivator 3 (SRC3) peptide binding to the WT ER protein occurred only in the presence of estradiol. However, Y537S and D538G proteins are recruited by the SRC3 peptide in the absence of estradiol, indicating that these mutants are constitutively active and bind to SRC3. Furthermore, an in vitro biochemical FP assay was also established for WT and mutants in the presence of estradiol and 4OH tamoxifen. The screen of our multibillion small molecule collection of DNA-encoded chemical libraries identified several hits in WT and mutant ER. To confirm the selection output, we synthesized off-DNA compounds and validated these in biochemical and cell-based studies. We have identified that the compounds, CDD-1272 and CDD-1274, are active in HTRF and FP assays. Furthermore, these
compounds inhibit WT and mutant cell growth in the presence of estradiol. More importantly, CDD-1274 degrades ER mutant and cyclin D1 proteins. In addition, CDD-1274 induced p21 protein expression in WT and mutant cells. Conclusions: We have identified potent novel ER mutant binders by using our DNA-encoded chemical library platform. Our compounds are active in biochemical and ER mutant cell lines, suggesting these molecules are potential chemical probes to explore in in vivo models of breast cancer. Support: NIH/NCI R03 CA259664 and CPRIT RP220524 to MP.

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Yong Wang, Ph.D: No financial relationships to disclose
Damian W. Young, Ph.D: No financial relationships to disclose
Suzanne A. Fuqua, Ph.D.: No financial relationships to disclose
Martin M. Matzuk, M.D., Ph.D.: No financial relationships to disclose
An update to a Phase I trial of CFI-402257, an oral TTK inhibitor, in patients with advanced solid tumors with HER2-negative breast cancer expansion cohorts

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Background: TTK (also known as MPS1), a dual-specificity serine-threonine kinase, is critical for the spindle assembly checkpoint, chromosome alignment, and error correction in mitosis. Inhibition of TTK causes premature mitotic exit with unattached chromosomes, to result in chromosomal missegregation, aneuploidy, and cell death. CFI-402257 is a potent and highly selective inhibitor of TTK. Robust suppression of tumor growth was achieved upon oral dosing of single agent CFI-402257 in ER+/HER2- cell line and patient derived xenograft models. CFI-402257 demonstrated enhanced cytotoxicity in CDK4/6 inhibitor resistant ER+ breast cancer cell line models compared to parental cell lines, including those with RB1 loss. CFI-402257 has previously exhibited monotherapy and combination efficacy with a tolerable safety profile in ER+/Her2- Breast cancer patients in an ongoing clinical study which is updated here. Methods: This is an ongoing phase I, multi-center, dose escalation study (3+3 design) to determine the safety, tolerability, and maximum tolerated dose of CFI-402257 and to evaluate anti-tumor activity at the recommended phase 2 dose (RP2D). CFI-402257 was dosed once daily on a continuous schedule in 28-day cycles at a starting dose of 5 mg. Dose escalation included
patients (pts) with advanced solid tumors. Dose expansion at the RP2D included pts with advanced solid tumors (Cohort A), advanced Her2-negative (ER+ or TNBC) with 1-4 prior lines of chemotherapy for metastatic disease (Cohort B), and ER+/Her2- breast cancer in combination with Fulvestrant (500 mg IM Day 1, 15 and 29 and then every 28 days) who have had prior treatment with an aromatase inhibitor in combination with a CDK4/6 inhibitor (≥ 3 months) and ≤1 prior chemotherapy for metastatic disease (Cohort C). Results: At data cutoff of May 2, 2022, 87 pts were enrolled. 86 pts (66 pts receiving monotherapy and 20 patients receiving combination therapy received ≥1 dose of study therapy and were analyzed for safety. One pt was not dosed due to elevated liver enzymes prior to first dose. The median age for mono was 61 years (range, 35-81) and for combo was 54 (range, 31-70). The median number of prior regimens mono and combo was 5 (range, 0-17; and 1-9, respectively). Tumor types in mono were breast cancer (27 pts), ovarian cancer (7 pts), GI cancer (3 pts), pancreatic cancer (3 pts), and other (30 pts). 20 breast cancer pts were enrolled in the combo. To date, 11 dose levels have been studied (range: 5 to 294 mg) in mono. There were 4 dose limiting toxicities (neutropenia >7days at 168mg/day, febrile neutropenia at 210mg/day, and neutropenia and colitis at 294mg/day, all grade 3). The RP2D of 168 mg was established. 3 pts in mono (biliary obstruction, febrile neutropenia, and pancytopenia) and 0 pts in combo discontinued study due to adverse events (AEs). Treatment emergent adverse events (TEAE’s) occurring in ≥30% of pts were fatigue (31 pts; 47%), nausea (30 pts; 46%), decreased appetite (22 pts; 33%), and diarrhea (21 pts; 32%) in mono; and nausea (11 pts; 55%) and diarrhea (7 pts; 35%) in combo. 35% of mono and 39% of combo AEs were considered related to CFI-402257 by the investigators. Grade ≥3 AEs and serious AEs were reported in 25 pts (38%) and 17 pts (26%), respectively in mono; and 5 pts (25%) and 3 pts (15%) in combo. The investigator assessed best overall response rate (partial response [PR] or better within the efficacy population) of 6% (PR; hepatocellular carcinoma n=1, breast cancer n=2 from n=47) in mono and 18% (PR; n=2 breast cancer) in combo (n=11), with additional patients still to be assessed. Conclusion: CFI-402257 is well tolerated as mono and combination with fulvestrant. Efficacy signals are emerging with pts in the combo cohort demonstrating anti-tumor activity. Additional efficacy will be updated at the time of the presentation.

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Lysosomal acid lipase (LIPA) as a novel therapeutic vulnerability for treating TNBC

Background: TNBCs have the highest mortality rate among all BC subtypes. There is thus an urgent and unmet need for effective targeted therapies in TNBC. Recently we, identified a novel agent ERX-41 that showed good efficacy in treating TNBC in preclinical mouse models, however, its molecular action remain unknown. In this study, we identified LIPA as novel molecular target of ERX-41. Methods: We have used CRISPR knockout pooled library and multiple TNBC models for identifying molecular target of ERX-41. Mechanistic studies were performed using LIPA mutants, RNA-seq, Turbo-ID mapping, Mass spectrometry, Immunoprecipitation, and Western blotting. The in vivo efficacy of ERX-41 was examined using four different patient-derived xenograft (PDX) models. We evaluated LIPA protein expression in TNBC using tissue microarray (TMA). Results: To identify the molecular target of ERX-41, we performed an unbiased CRISPR–Cas9 knockout (KO) screen in MDA-MB-231 cells and the results identified LIPA as a top hit. KO of LIPA alone (which encodes lysosomal acid lipase (LAL) abrogated cytotoxic response to ERX-41. Cellular thermal shift assays confirmed that ERX-41 binds to LAL. In silico modelling and mutational studies confirmed that ERX-41 interacts with LAL through residues in its LXXLL domain and that ERX-41 ability to induce ER stress and cell death in TNBC is independent of the lipase activity of LAL. Unbiased RNA-seq studies with and without ERX-41 in parental and LIPA KO SUM-159 cells revealed induction of genes involved in ER stress and UPR response by ERX-41 in parental SUM-159 cells but not in cells with LIPA KO. Ultrastructural studies using live-cell confocal microscopy show that LIPA KO abrogated ER morphological changes at 2 and 4 h after ERX-41 treatment. Further, subcellular localization studies showed LIPA localizes to endoplasmic reticulum (ER). Unbiased proteomic approaches (TurboID and DIA mass spec) identified a core set of proteins that were both LAL binders and affected by ERX-41 treatment. GO analyses of LAL binding proteins
confirmed their involvement in protein folding. Tumor micro array (TMA) analyses confirmed that >80% of primary TNBC tumors had significant and detectable LAL protein expression in contrast, normal breast tissue had lower LAL expression. ERX-41 (10 mg/kg body weight) decreased growth of four distinct TNBC patient-derived xenografts (PDXs) in vivo. Conclusions: Our results identified a new molecular target (LAL) for ERX-41 and novel mechanism of action (disruption of protein folding and induction of ER stress) that may have utility in treating patients with TNBC.

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Targeting MARCKS in inflammatory breast cancer increased paclitaxel sensitivity

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Background. Because of its high metastatic potential, inflammatory breast cancer (IBC) is the most lethal and aggressive form of breast cancer. We previously demonstrated that Myristoylated Alanine-Rich C Kinase Substrate (MARCKS) protein overexpression was associated with shorter metastasis-free survival (MFS) in IBC patients, but not in non-IBC (nIBC) patients. However, the mechanism of action of MARCKS and its particular association to poorer outcome in IBC compared to nIBC are poorly understood. Methods. We evaluated in vitro the inhibitory effect of MPS (MARCKS phosphorylation site domain), a peptide targeting MARCKS phosphorylation site domain (PSD) in single and in combination with paclitaxel treatment, on cell proliferation and cell motility in two cell lines of different phenotype (SUM149 for IBC and MDA-MB-231 for nIBC), as well as its distinct molecular mechanisms of action. We also assessed the clinical relevance of the protein expression of MARCKS and phosphatase and tensin homolog (PTEN) in a large series of IBC vs. nIBC patients. Results. In vitro, the treatment with MPS peptide impaired cell proliferation, migration, and invasion in SUM149 compared to MDA-MB-231 cells. More important, MARCKS inhibition increased paclitaxel sensitivity when using combination therapy in SUM149 cells compared to MDA-MB-231 cells. Interestingly, we could partially explain this specific inhibitory effect in IBC cells using western blot: MARCKS inhibition in single and in combination induced up and downregulation of the PTEN/AKT signaling pathway respectively in IBC compared to nIBC cells. Importantly, a negative correlation of MARCKS and PTEN was only found in the clinical IBC samples (180 patients) compared to nIBC samples (355 patients). More importantly, the group of patients with negative MARCKS and positive PTEN protein expression was associated to better 5-year MFS only in IBC patients. Conclusion. These results indicate two major findings: first, the important prognostic value of the negative correlation of MARCKS and PTEN expression in IBC patients, and second the specific role of MARCKS in regulating different downstream pathways and increasing the paclitaxel response in combination treatment in IBC compared to non-IBC. They suggest a potential IBC-specific targetable biomarker, the inhibition of which might impair disease aggressiveness and perhaps enhance patients’ survival.

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WITHDRAWN
Pharmacological Strategies to Target Circadian Clock Genes in TNBC

Yuanzhong Pan, Priya Jayachandran, Evanthia T. Roussos Torres, Steve A. Kay

Background: Triple-negative breast cancer (TNBC) remains the most aggressive form of breast cancer and more targeted treatment options remain challenging. Our recent analysis of clinical data showed that circadian clock genes (including positive regulators BMAL1 and CLOCK, and negative regulators CRYs, PERs, and REV-ERBs) play important roles in breast cancer, and most prominently in TNBC. We have also shown in other cancer types that cells with a mesenchymal signature and stem-cell like state rely on BMAL1/CLOCK activity to support proliferation. BMAL1 and CLOCK are transcription factors that have remained “undruggable” to date. Alternatively, our lab developed small molecule compounds that target the negative regulators CRY, REV-ERB and CK2. We are therefore prompted to study if the clock genes can serve as a therapeutic target in TNBC using our small molecules that target clock regulators in TNBC. In addition, BMAL1 and CLOCK require ubiquitin E3 ligases and proteasomes for their transcriptional function, thus we hypothesize proteosome inhibitors may provide synergy to improve response to our novel clock-based therapeutics. Methods: We first used shRNA-mediated gene knockdown (KD) to disrupt the core circadian clock regulator BMAL1 and CLOCK in a panel of TNBC cell lines across different molecular subtypes (MDA-MB-231, MDA-MB-157 and MDA-MB-436, MDA-MB-453, HCC70, HCC1143, BT549, Hs578T). After KD, cell proliferation was quantified using CellTiter-Glo. We then tested our small molecule compounds SHP656—that stabilizes CRY, SR29065 and derivatives—that agonizes REV-ERB, and GO289—an inhibitor of CK2 that stabilizes PER. Based on our knowledge of the clock regulators, we tested drug synergy between SHP1705 and proteasome inhibitors MG132 and Carfilzomib across a range of concentrations. RNA-seq of cells treated with either single drug or drug combination were performed to study the mechanism of the synergistic effect. Results: A subset of the tested TNBC cell lines showed significantly impaired proliferation after BMAL1 or CLOCK KD. All cells in the mesenchymal-like molecular subtype responded to BMAL1/CLOCK KD, which is consistent with our previous data in other cancer types. It also confirmed BMAL1 and CLOCK have the potential to serve as therapeutic targets for mesenchymal-like TNBC. We then tested
the clock compounds in our TNBC panel. We found SR29065 and GO289 both inhibit cancer cell proliferation at a clinically relevant EC50. Combination of our novel small molecule SHP1705 with the proteosome inhibitor MG132 and carfilzomib, demonstrated significant synergistic effects in vitro. In order to understand the mechanism of the synergistic effect between clock compounds and proteasome inhibitors, we performed RNA-seq on single drug and combo-treated cells. Differential expression analysis revealed that over two-thousand genes are specifically changed in the combo group. GO analysis showed that these genes are enriched in MYC target genes. Because MYC is also, like BMAL1 and CLOCK, a E-box binding transcription factor, this result implies that the mechanism driving synergy may be due to a disruption of E-box-dependent transcription. Conclusions: Here we showed that the core circadian clock regulator BMAL1 and CLOCK are potential therapeutic targets in mesenchymal-like TNBCs. Using REV-ERB agonists and CK2 inhibitors to target BMAL1/CLOCK transcription activity, we can achieve compound EC50s in single-micromolar range. In vivo experiments in murine models of TNBC are underway to determine the efficacy of single agent and combination therapy with proteosome inhibitors. Given the recently established safety of CRY stabilizers there is great potential for translation of these findings to clinical trials in patients with TNBC.

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Developing novel lysyl oxidase (LOX) inhibitors to overcome chemotherapy resistance in triple negative breast cancer

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Triple negative breast cancer (TNBC) is the most aggressive breast cancer subtype. It accounts for ~15% of all breast cancer patients yet is responsible for 30% of breast cancer deaths. TNBC is treated primarily with conventional chemotherapy; however, resistance to therapy is common, leading to high mortality rates. Importantly, the benefit of current therapeutic strategies used in chemoresistant TNBC, i.e., immunotherapy and antibody-drug conjugates, is confined to only a fraction of patients, and survival benefit is limited. Therefore, there is an urgent need to identify novel and effective treatment strategies to overcome chemoresistance. Recently, we identified hypoxia-induced ECM re-modeler, lysyl oxidase (LOX), a member of LOX family, as a key mediator of chemoresistance in TNBC. However, currently available LOX inhibitors are either non-selective and/or show toxicity. Here, we performed a high-throughput cell-based LOX activity screen (HTS) with more than 5,000 molecules selected from a diversified compound library and identified the bi-thiazole derivatives as novel potent LOX inhibitors. Our structure activity relationship (SAR) analysis resulted in two lead compounds 6403, a relatively LOX-specific inhibitor, and 6415, a more LOX/LOXL2 inhibitor. Both compounds reduced collagen cross-linking (canonical function of LOX) and led to chemosensitization in TNBC cell lines and in chemoresistant TNBC PDX organoids. In addition, 6403 and 6415 reduced the TGF-beta induced fibrosis and inhibited migration capacity of the breast cancer cell lines. Importantly, 6403 showed excellent pharmacokinetic profile and did not lead to any observable toxicity in mice. Notably, 6403 overcame doxorubicin resistance in LOX-expressing 4T1 syngeneic model with no apparent toxicity. Furthermore, our novel LOX and LOX/LOXL2 dual inhibitors show superior inhibition of LOX activity compared to the recently developed and clinically tested LOX family or LOXL2/LOXL3 inhibitors. Overall, we identified novel potent LOX inhibitors with no observable toxicity for further preclinical development and future clinical testing to overcome chemoresistance in TNBC.
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Drug repositioning can overcome both substantial costs and the long process of new drug discovery and development in cancer treatment. Some FDA-approved drugs have been found to have the potential to be repositioned as anti-cancer drugs. However, the progress is slow due to only a handful of strategies employed to identify drugs with repositioning potential. In this study, we evaluated GPCR-targeting drugs by high throughput screening (HTS) for their repositioning potential in triple-negative breast cancer (TNBC) and drug-resistant human epidermal growth factor receptor-2-positive (HER2+) breast cancer (BC), due to the dire need to discover novel targets and drugs in these subtypes. We assessed the efficacy and potency of drugs/compounds targeting different GPCRs for the growth rate inhibition in the following models: two TNBC cell lines (MDA-MB-231 and MDA-MB-468) and two HER2+ BC cell lines.
(BT474 and SKBR3), sensitive or resistant to lapatinib + trastuzumab, an effective combination of anti-HER2 therapies. We identified 7 drugs/compounds as potential hits, out of which 4 were FDA-approved drugs. We focused on beta-adrenergic receptor-targeting nebivolol as a candidate, primarily because of the potential role of these receptors in BC and its excellent long-term safety profile. The effects of nebivolol were validated in an independent assay in all the cell line models. The effects of nebivolol were independent of its activation of β3 receptors and nitric oxide (NO) production. Nebivolol reduced invasion and migration potentials which may suggest its inhibitory role in metastasis. Analysis of the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset found a reduced but not statistically significant risk of all-cause mortality in the nebivolol group. In-depth future analyses including detailed in vivo studies and real-world data analysis with more patients are needed to investigate further the potential of nebivolol as a repositioned therapy for BC.

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Scaffold attachment factor B1 modulates cholesterol pathways in triple-negative breast cancer

Historically known as a tumor suppressor by estrogen receptor (ER) co-repression in breast cancer (BC), the matrix binding protein Scaffold Attachment Factor B1 (SAFB) binds scaffold or matrix attachment region DNA elements (S/MAR DNA) in eukaryotic DNA. SAFB1 plays a role in cellular stress response, DNA repair, differentiation, and apoptosis. SAFB loss in ER-independent BC and pancreatic cancer (PC) patients resulted in poor survival rates, hinting at the role of SAFB1 as a tumor suppressor. To understand the tumor suppressive mechanism of SAFB1, we performed shRNA-mediated knockdown (KD) of SAFB in PC cell lines and triple-negative breast cancer (TNBC) cells, an aggressive subgroup of BC. Analysis of onco-properties showed an increase in clonogenicity potential and cell proliferation in SAFB KDs in both PDACs and TNBCs cells. Further, RNA-Seq analysis of SAFB KDs in the TNBC cell line revealed activation of the mevalonate (MVA) pathway and the resulting cholesterol biosynthesis as the key metabolic change. Both pancreatic ductal adenocarcinoma (PDACs) and TNBC exhibited higher levels of MVA pathway gene expression upon loss of SAFB. Sterol regulatory element binding proteins (SREBP) 1 and 2 dictate cholesterol biosynthesis, and SREBP2 promotes tumor properties via the MVA pathway. Molecular and metabolic analysis of SAFB KD TNBC showed an increase in lipid droplets and SREBP2 maturation. Using Chromatin Immunoprecipitation and quantitative real-time PCR (ChIP-qPCR) in TNBC we demonstrate the direct binding of SAFB to the SREBP2 promoter region. In addition, byproducts of the MVA pathway have been shown to activate YAP/TAZ-dependent tissue homeostasis and tumorigenesis. We also observed increased YAP1 mRNA levels and decreased YAP1 (Ser127) phosphorylation with SAFB loss in TNBC, explaining the aggressive tumorigenicity gained with SAFB loss. Our study thus far suggests SAFB has overt control over the SREBP2-MVA-YAP1 pathway, and loss of SAFB results in an enhanced tumor phenotype.

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Mitochondria-Nuclear Crosstalk Regulates the WNT Pathway in Triple-Negative Breast Cancer

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Compared to hormone receptor (HR) positive breast cancer (BC), basal or triple-negative BC (TNBC) suffers a poor prognosis caused by a limited understanding of its driver signaling pathways. We used the transmitochondrial cybrid approach to understand the metabolic reprogramming and mitochondria-nuclear crosstalk in metastatic TNBC. In cybrids, mitochondria from cancer and benign cells are compared under a commonly defined nuclear background. Using cybrid-based discovery and its validation in cell lines, patient-derived xenografts, and clinical data, we have previously reported the activation of fatty acid oxidation (FAO) in metastatic TNBC. Recently, we developed a unique gene (DEG) signature by integrating gene expression data from cybrids with different omnibus databases such as TCGA and METABRIC. Our DEG could effectively distinguish the PAM50 subtypes of BC. Further analyses nominated negative regulation of the canonical WNT signaling pathway as one of the major pathways altered by mitochondrial character. The WNT pathway is known to regulate cell signaling, metabolism, epithelial-mesenchymal transition (EMT), and cancer stemness. Cybrids with benign mitochondria showed transcriptional activation of negative WNT regulators, including DKK1, SOST, DAB2, and CAV1. Citrate is a key metabolite from the tricarboxylic acid cycle (TCA cycle) and is an intermediate of many other metabolic pathways. Analysis of TNBC cybrids, cell lines, and BC tissues suggest that in TNBC, citrate levels are increased with the activation of CPT1A, the rate-limiting enzyme of FAO. We confirmed the reduction of the beta-catenin protein in TNBC cells after pharmacological and genetic inhibition of CPT1A and mitochondrial citrate transporter (SLC25A1). We further analyzed the gene set enrichment analysis (GSEA) using gene expression data developed from short and long-term CPT1A inhibited TNBC cells and observed that the FAO alters polycomb repressive complex 2 (PRC2) activity. PRC2 is a critical modulator of the H3K27 methylation pattern as well as pathways related to cancer stemness, including WNT/beta-catenin and Hedgehog (SHH) pathways. These results suggest that the mitochondrial FAO transcriptionally inhibits WNT antagonist genes through repressive histone modification and consequently activates the canonical WNT pathway and cancer stemness. Overall, our current observations provide new insights into the regulation WNT pathway by mitochondria-nuclear crosstalk in TNBC.
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Lipid-rich environment induces epigenetic reprogramming in non-transformed breast epithelial cells enhancing a mammary cell plasticity

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Introduction. The identification of women specifically at risk for estrogen receptor negative breast cancer (ER- BC) and the targeted treatment of this disease are significantly unmet clinical needs. We analyzed the gene expression profiles of epithelial cells from the contralateral unaffected breasts (CUBs) of BC patients and identified a lipid metabolism gene signature enriched in the CUBs of women with ER- BC (PMID: 28263391). Subsequently, we observed that exposure of non-transformed breast epithelial cells to lipids results in significant changes in gene expression and histone posttranslational modifications; and increased flux through multiple metabolic reactions, including those of serine and methionine (PMID: 35508495). Interestingly, the upregulated genes are involved in neural development, axon guidance, neural crest pathways and stemness. Neural genes are highly expressed in Triple Negative Breast Cancers (TNBCs) especially in the C2 cluster. Given that mammary stem/progenitor cells have distinct metabolic properties compared to other mammary cell subsets, we hypothesized that upon lipid exposure, stem-like cells have a survival advantage, and that lipid induces epigenetic reprogramming into neural-like cells which may foster a malignant transformation. Methods. To interrogate potential mechanisms linking lipids and epigenetic reprogramming, we performed CUT&RUN for H3K4me3 and H3K27me3 in non-transformed, estrogen and progesterone receptor negative MCF-10A cells cells exposed to vehicle or octanoic acid (OA) for 24 hrs. Peaks were called using MACS2 and differential peaks identified with DiffBind. Differentially expressed genes affected by OA (PMID: 28263391) were compared with target genes from the CUT&RUN. To determine the contribution in OA exposed cells of serine and methionine metabolism to S-adenosyl methionine (SAM), 13C-glucose tracing was performed. The Aldefluour assay was used to identify stem-like (ALDH+) cells in lipid-exposed MCF-10A cells. To determine if lipid-exposed cells adopt a neural-like phenotype, MCF-10A cells were grown on Poly-D-Lysine/Laminin (PDL/LM) coated plates. Results. A total of 661 differential peaks were identified for H3K4me3 (FDR < 0.05) encompassing TNBC C2 markers (NRTN, CHRM3) and genes involved in neuron differentiation, axonogenesis (NGFR, NGF, FOXA2), neural crest migration (NTRK2, MMP2) and EMT (DLL4, MMP15). Approximately 73% of H3K4me3 OA-associated peaks encompass regulatory regions of genes...
that experienced a significant increase in gene expression with OA exposure (FDR < 0.01), including NGFR (log2 FC = 11.7), FOXA2 (log2 FC = 11.6), NGF (log2 FC = 8). Twelve H3K27me3 peaks were significantly enriched in vehicle (FDR < 0.05) and associated with increased gene expression in OA, among them were the stem cell markers LGR6 (log2 FC = 1.9) and PLAG1 (log2 FC = 2.8). 13C stable isotope tracing revealed that in presence of OA, glucose contributes to increased fractional abundance of the SAM M+1 isotopologue (adj p = 0.003) indicating that carbons derived from the serine synthesis pathway are used for remethylation of homocysteine to methionine. Vehicle treated cells growing on PDL/LM plates assumed an epithelial phenotype while OA-treated cells adopted a neurite-like phenotype. Upon OA treatment the percentage of ALDH+ cells increased by a minimum of 10%.

Conclusions. The increase of fractional abundance of SAM and the upregulation of neural genes regulated by H3K4me3 as well as the enrichment of ALDH+ cells and the development of a neural-like phenotype in a rich lipid environment, suggests that lipid exposure affects the production of SAM, which results in epigenetic fostered plasticity, leading to reprogramming/selecting cells with a multi-potential embryonic or stem-like state and/or differentiation to a neural/neural crest-like state.

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Novel roles of Inosine Monophosphate Dehydrogenase 2 (IMPDH2) in TNBC doxorubicin resistance

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Triple negative breast cancer (TNBC) is one of the major subtypes of breast cancer, being associated with the lowest survival rate after metastasis occurs. TNBC patients face limited therapeutic options, relying mostly on a combination of chemotherapies (anthracycline, taxanes and cyclophosphamide). However, around 40% of patients treated with chemotherapy relapse due to onset of chemoresistance, contributing to the dismal survival of this aggressive subtype. Therefore, understanding the molecular mechanisms underlying chemoresistance is critical to identify better therapeutic target options. Guanosine triphosphate (GTP) is important for several biological processes, including cell proliferation. We and others have shown that inosine 5’-monophosphate dehydrogenase 2 (IMPDH2), the rate limiting enzyme in the de novo synthesis of GTP, is important in migration and invasion of cancer, including TNBC, however the role it plays in chemoresistance remains to be elucidated. Our preliminary data revealed that IMPDH2 expression levels modulate doxorubicin sensitivity in different TNBC cell lines. Moreover, we have generated MDA-MB-231 cells that are resistant to doxorubicin (referred to as DoxoR), and revealed IMPDH2 to be upregulated in DoxoR cells, at both protein and mRNA levels as well as having higher activity. Consistently, DoxoR cells have ~50% more GTP than their naïve counterpart and, interestingly, are twice more sensitive to treatment with Ribavirin, a well-tolerated FDA approved IMPDH inhibitor, suggesting that Ribavirin could be repurposed for the treatment of chemoresistant TNBC. As expected, RNA sequencing of DoxoR cells revealed increased stemness properties when compared to naïve cells, which we confirmed experimentally in tumor sphere formation assays. Importantly, knockdown of IMPDH2 reverted the ability of DoxoR cells to form bigger tumor spheres, as well as reduced the IC50 of doxorubicin to that of naïve cells. Therefore, our data suggests that increased IMPDH2 and GTP levels in resistant setting could be a potential new vulnerability to be leveraged therapeutically to suppress and/or prevent the growth of chemoresistant lesions.

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Breast cancer (BC) is the most commonly diagnosed cancer and second leading cause of cancer-related deaths in women in the United States, with more than 70% of the cases are hormone receptor positive (HR+) disease. Endocrine based therapies (ET) are successfully used, however, 30-50% will acquire ET resistance leading to tumor progression. Since the mechanism of acquired resistance remains unknown for ~60% of patients, identifying novel mechanisms of resistance is essential. We recently reported that carnitine palmitoyltransferase 1A (CPT1A), the rate limiting enzyme in fatty acid oxidation, is overexpressed in aggressive HR+ tumors, including ET resistant patients. We propose that CPT1A level and activity changes the tumor microenvironment to enhance tumorigenesis and contribute to ET resistance. To determine the mechanism by which CPT1A is promoting cell proliferation, tumor microenvironment, cellular signaling and ET resistance, we used a series of in vitro studies incorporating a panel of either endogenously or experimentally derived CPT1A-low and CPT1A-high controls, HR+ breast cancer cell lines as well as their ET resistant counterparts. We determined that CPT1A is upregulated in cell lines that acquire ET resistance. Our analyses demonstrated that levels of CPT1A can affect tumor formation ability in both CPT1A-high and adjacent CPT1A-low tumor cells with concurrent changes in both intra- and inter-cellular signaling which may be essential to promote tumor progression and mediate therapeutic response. This represents a promising step in understanding the mechanisms that promote tumorigenesis and ET resistance in HR+ breast cancer.

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Capecitabine, eribulin and paclitaxel differentially impact the metabolite pool in metastatic breast cancer patients

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Introduction: Metabolic reprogramming is recognized as a hallmark of malignancy. Cancer growth, and progression has been associated with lipid and amino acid absorption by cancer cells. However, the differential impact of chemotherapeutic agents on energy balance and metabolism while on-treatment and at the time of clinical progression, in breast cancer patients, is largely unknown. We hypothesize that increases in lipid and other related metabolites, like amino acids, throughout chemotherapy treatment are therapy-specific, and associated with disease progression. Methods: Serum samples from 15 metastatic breast cancer patients (hormone-receptor positive and triple negative breast cancer), receiving different chemotherapy regimens (n=5 paclitaxel, n=5 eribulin, n=5 capecitabine), were collected at multiple time points (baseline, 3-week on-treatment and disease progression). Samples were prepared for metabolomics and analyzed via mass spectrometry using the MxP Quant 500 kit (Biocrates Life Sciences AG, Innsbruck, Austria). Data was processed using MetIDQ software (Biocrates Life Sciences AG). Limma was used to identify differential metabolites during treatment and at the time of disease progression as compared to metabolites at baseline. Results: With capecitabine treatment, there was a differential impact on many lipid metabolites, including ceramides, with an initial decrease on treatment: Cer(d18:2/18:1)(-1.95 log-fold change (logFC)); and arachidonic acid, (-1.32 logFC) (p < 0.05 for both). However, at the time of disease progression, there was a 1.8 to 2 log-fold increase in Cer (d18:0/20:0); Cer (d18:1/22:0); Cer (d18:2/22:0); Cer (d18:1/23:0); 1.7 log-fold increase in diacylglycerol (DG (16:0_20:0)) along with 1.6 log-fold increase in amino acid methionine (p < 0.05 for all). Conversely, in the eribulin group, while on treatment, there was a 1.2 to 1.3 log-fold increase in triglycerides (TG), i.e., TG(16:1_36:2); TG(16:0_36:2); TG(18:1_33:1); TG(16:1_36:1); TG(20:4_34:1) and 1.5 log-fold increase in amino acid kynurenine; while there was a 1.3 to 1.4 log-fold decrease in fatty acids (FA), such as FA(20:2); FA(18:2); FA(18:1) (p < 0.05 for all). At the time of disease progression, there was a 1.2 to 1.3 log-fold decrease in lipids like cholesteryl esters (CE) and phosphatidylcholines (PC), e.g. CE (18:2); CE (18:3); PC aa 36:3; PC aa 36:2 (p < 0.05 for all). Similarly, in the paclitaxel group, with treatment, there was a 1.2 to 1.8 log-fold increase in CE(22:0); Hex2Cer(d18:1/26:1) and
DG(18:3_20:2) (p < 0.05 for all), while, at the time of disease progression, there was a 2 log
d fold decrease in PC like lyso PC a C20:3; and lyso PC a C16:1, as well as 2 to 2.5 log-fold
decrease in amino acids like glutamine, and sarcosine (p < 0.05 for all). Conclusion: Lipid and
amino acid pool while on treatment and at disease progression were differentially impacted by
the three classes of chemotherapies, some of which to the same functional extent. Although a
decrease in lipid metabolites was observed while on capecitabine (prodrug of 5-fluorouracil)
treatment, an increase in both lipid metabolites and amino acids was observed at disease
progression. With both paclitaxel and eribulin treatment, which are microtubule inhibitors, a
decrease in lipid metabolites and amino acids was observed at disease progression. An
understanding of differential metabolic reprogramming with different chemotherapeutic agents
may provide novel points of therapeutic intervention for anti-cancer treatment, such as
combination of chemotherapy with inhibitors of ceramide metabolism or amino acid inhibitors
and contribute towards efficacious personalized medicine.

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Hormone receptor (HR+) breast cancer (BC) is responsible for more than 80% BC cases and more than 60% BC-related deaths in the US. The incidence and severity of BC are influenced by a variety of modifiable risk factors, including (but not limited to) nutritional behaviors and obesity. Specifically, women with a body mass index (BMI) > 25 Kg/m² exhibit an approx. 1.4-fold increase in the risk of developing postmenopausal HR+ BC as compared to women with BMI < 25 Kg/m². Along similar lines, women with type 2 diabetes (T2D) – one of many consequences of obesity – are at 1.23-fold increased risk to develop postmenopausal HR+ BC as compared to women without T2D. Moreover, a BMI > 30 Kg/m² has been associated with decreased progression-free survival and overall survival (OS) in women with HR+ BC. Thus, a high number of postmenopausal HR+ BC cases and BC-related deaths could be effectively avoided by modifying dietary habits, both in prophylactic and therapeutic settings.

Mechanistically, obesity provokes numerous alterations that have been linked to accrued postmenopausal HR+ carcinogenesis, encompassing (1) increased circulating levels of glucose and insulin – reflecting insulin resistance (IR) coupled to T2D, (2) increased levels of estrogen, produced locally and systematically by adipocytes, and (3) chronic inflammation of the breast adipose tissue (AT). However, the relative contribution of IR vs. other obesity-associated alterations to BC development and sensitivity to treatment has not been elucidated. At least in part, this reflects the two most common approaches employed to cause obesity in preclinical studies: the use of high-fat diets (HFDs) and/or mice genetically predisposed to develop obesity (e.g., ob/ob mice), neither of which is suitable to uncouple IR from all other metabolic, hormonal, and inflammatory effects of obesity. Here, we combined a unique model of HR+HER2- carcinogenesis that recapitulates key immunobiological features of human HR+ BC.
(notably, a cold tumor microenvironment coupled to a scarce sensitivity to immunotherapy, and exquisite sensitivity to CDK4/6 inhibitors), as established in mice by medroxyprogesterone acetate (M) pellets combined with 7,12-dimethylbenz[a]anthracene (D) oral administration, with a novel model of pure IR originating from the AT-specific deletion of RAB10, member RAS oncogene family (Rab10), a transducer of insulin signaling in adipocytes. Importantly, these mice are neither hyperphagic nor overweight, have normal glucose level at baseline and do not exhibit inflammatory alterations in the AT, but nonetheless display IR. While a HFD shortens tumor-free survival (TFS) in immunocompetent mice subjected to M/D-driven oncogenesis, it does not alter the growth of detectable M/D-driven tumors. Conversely, IR as imposed by the loss of Rab10 in the AT failed to alter TFS but accelerated the growth of tumors, resulting in shortened OS. Moreover, the deletion of Rab10 from the mouse AT enabled the development of tumors displaying features of increased aggressiveness, including systematic loss of progesterone receptor (PR) expression. Finally, the growth of tumors emerging in the context of a Rab10 /- AT could be efficiently controlled by the systemic administration of metformin. In line with this notion, orthotopically injected mouse triple negative BC AT-3 cells grew faster in mice bearing an AT-specific deletion of Rab10 as compared to their wild-type littermates. In conclusion, IR as imposed by the loss of Rab10 in the mouse AT converts HR+ mammary carcinomas as driven by M/D into HR- lesions with increased aggressiveness. These findings have major implications for ethnic groups that are at high risk for T2D at BMIs that are considered normal for Caucasians, such as women of African American and Asian descent, especially in view of the fact that women from these ethnic groups are known to be at increased risk for aggressive triple-negative BC as compared to their Caucasian counterparts.

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Non-transformed breast epithelial cells show neural-like gene signature after lipid exposure

Introduction: The identification of women specifically at risk for estrogen receptor negative breast cancer (ER-BC) and the targeted treatment of this disease are significantly unmet clinical needs. To that end, we analyzed the gene expression profiles of epithelial cells from the contralateral unaffected breasts (CUBs) of BC patients and identified a lipid metabolism gene signature, which was enriched in the CUBs of women with ER-negative BC (PMID: 28263391). Subsequent experiment revealed that exposure of non-transformed breast epithelial cells to lipid results in significant changes gene expression, chromatin accessibility and histone posttranslational modifications (PMID: 35508495). Several of the upregulated genes are hallmarks of the various fates of vagal neural crest: Neural, neurogenic and mesenchymal lineages. We hypothesize that lipid exposure imparts a survival advantage of stem-like cells, that lipid-induced epigenetic changes lead to a neural crest-like transcription signature and that these genes are not expressed normally in the breast. Methods: MCF10A cells were exposed to vehicle or octanoic acid (OA) for 24 hours. Gene expression was assayed by RNA-seq and OA responsive genes were identified (PMID: 35508495). Single-cell RNA sequencing (scRNA-seq) data from 14 human reduction mammoplasties (RM) was obtained from a publicly accessible data set (PMID: 34031589). The scRNA data was clustered and identified by unsupervised clustering (Seurat, v3.4.1) using cell-type markers curated using Supplementary table 2 from (PMID: 34031589). The bulk RNA-seq data from the OA treated cells was deconvoluted to cell-lineages using Bisque. The most significant upregulated VNC neural/neuronal/mesenchymal genes from the gene expression analysis were then plotted on the lineage clusters using FeaturePlot to determine if these markers are found in the normal breast epithelium, or other cell lineages. The plots were then filtered and re-clustered to look at basal-luminal cell types only. We utilized a second resource, a web-application for snATAC-seq data from various stages of mouse mammary development developed by the Wahl lab (https://wahl-lab-salk.shinyapps.io/Mammary_snATAC/), to query these same genes. Results:
Deconvolution of the bulk RNA-sequencing data revealed a transition to a pericyte transcription program following exposure to OA. Nerve growth factor (NGF) was found to be expressed in pericytes while nerve growth factor receptor (NGFR) was found within the basal epithelial cell lineage. Genes overexpressed in the VNC neural cluster and overexpressed in the OA-exposed MCF10 cells, PPP1R1C (2.39x, adj p=1.6E-5), FOXD3 (6.7x, adj p=6.7E-10), DIO3 (5.9x, adj p=3.9E-6) and MOXD3 (4.2x, adj p=1.5E-23) all evidence little to no expression in the normal breast but are observed in murine fetal mammary stem cells. Schwann cell precursor (SCP) markers, CDH19 and ROPN1, significantly upregulated in OA treated cells: 5.4x and 1.6x, respectively, exhibited low expression in luminal progenitors but in the mouse were observed in the mammary stroma. CDH19, a gene exclusive to SCPs, is expressed in stroma following murine birth. PRRX1, a key regulator of the VNC mesenchymal cell fate cluster, is 9.3-fold (p adj=4.9E-49) overexpressed in the OA treated cells, expressed strongly in pericytes and stroma and to a lesser extent in basal epithelial cells of the normal human breast and stroma of the murine mammary gland. Conclusions: Treatment of non-transformed mammary epithelial cells with lipid, specifically OA, shows significant upregulation of multiple VNC genes associated with both neural and mesenchymal fate. scRNA-seq from RM patients reveals that many of these same markers are either found in non-epithelial cell clusters or are found with low expression in luminal mammary lineages (both progenitors and mature).

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Effects of a 12 Week Breast Cancer Exercise Program on the Mitochondrial Derived Peptide MOTS-c

Background:
Breast cancer survivors have an increased risk for comorbid conditions such as cardiovascular disease, diabetes, and hypertension. In addition, cancer related treatments negatively affect bone health, muscular strength, and quality of life. Exercise is an effective strategy to combat cancer related symptoms (fatigue, anxiety) and common comorbid conditions.

MOTS-c is a Mitochondrial Derived Peptide (MDP) that has a number of beneficial effects on metabolism, insulin sensitivity, and exercise capacity. Previously published preclinical studies have shown that MOTS-c treatment improves physical performance in young, middle-age, and old mice. In humans, it has been implicated to promote metabolic homeostasis, stimulate glucose utilization, fat-oxidation, reduce inflammation, and protect against both cardiovascular and metabolic disease.

We implemented a 12-week exercise program in breast cancer survivors. We evaluated changes in baseline and post12-week MOTS-c levels and corresponding body composition.
changes.
Methods:
We evaluated 25 participant paired samples at baseline and post 12-weeks of exercise. Participants engaged in a 12-week exercise program, 3 times a week for 90 minutes/session. At baseline and post 12-weeks, participants underwent a DXA scan, body composition analysis, and a blood draw. The blood samples were analyzed using an in-house ELISA and compared to various clinical and body composition metrics.

Results:
The median age was lowest for the high responders (56.7 years) compared to moderate responders (57 years) and reduced MOTS-c (61.5 years). We found 3 distinct groups: reduced MOTS-c with exercise (n=8), increased MOTS-c moderate responders (0-10 pg/ml; n=2), and increased MOTS-c high responders (>10 pg/ml; n=15). MOTS-c had an inverse relationship with almost all tested metrics including: age, weight, BMI, waist to hip ratio, body composition—visceral (fat area, fat mass, fat volume), subcutaneous fat mass, whole body (body lean, body mass, body percent fat, bone mineral content (BMC), and bone mineral density (BMD). Although the majority of the metrics improved and had inverse relationships for MOTS-c, the reduced MOTS-c group had increased BMC and BMD. Interestingly, despite a higher MOTS-c value, there was an increase in visceral fat as well as an increase in whole body fat across all groups. Of the 25 participants, 22 were Asian, two were Caucasian, and one was Native Hawaiian/Pacific Islander. Given the small number of participants, there does not appear to be any correlation between MOTS-c and ethnicity in our study.

Summary:
We found significant changes in MOTS-c according to clinical and body composition metrics after a 12-week exercise program. The findings in this study support previous findings on MOTS-c metrics including MOTS-c levels decreasing with age. However, there are few clinical trials evaluating MOTS-c in cancer survivors. MOTS-c is a potential biomarker related to exercise in cancer survivors. Our study was predominantly conducted in Asian women where there is limited data. This emphasizes the need for more clinical trials to be conducted with racially/ethnically diverse populations to better understand MOTS-c's role in our varied cancer populations.

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Investigating the role of mitochondrial protein translation in the metabolic adaptation of chemoresistant triple negative breast cancer

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BACKGROUND: Nearly 50% of patients with triple negative breast cancer (TNBC) treated with neoadjuvant chemotherapy (NACT) retain residual tumors resulting in high rates of metastatic relapse and poor overall survival. Residual tumors surviving NACT (Adriamycin plus cyclophosphamide; AC) were found to undergo a metabolic transition to heightened mitochondrial oxidative phosphorylation (oxphos; PMID: 30996079). Pharmacologic inhibition of mitochondrial electron transport chain (ETC) complex I with IACS-010759 (PMID: 29892070) had enhanced efficacy in residual, rather than treatment-naïve, tumors of orthotopic patient-derived xenograft (PDX) models. Our analyses of mitochondrial structure and function in human TNBC cell lines revealed differing adaptations in residual cells surviving treatment with conventional NACT agents. While DNA-damaging chemotherapies (e.g., Adriamycin, carboplatin) induced mitochondrial fusion and oxphos, taxanes (e.g., paclitaxel, docetaxel) induced mitochondrial fragmentation and reduced oxphos (Baek et al., Biorxiv Doi 10.1101/2022.02.25.481996). The mechanistic basis of these mitochondrial adaptations is not yet understood. The mitochondrial ETC consists of 92 proteins, 13 of which are encoded in the mitochondrial genome (mtDNA) and translated by the mitoribosome, while the remaining are encoded by the nuclear genome (nDNA), translated by the cytoribosome, and inserted into the inner mitochondrial membrane by accessory proteins, namely Oxidase (Cytochrome C) Assembly 1-Like (OXA1L). Disruption of OXA1L in mammalian cells has been shown to affect the levels and activity of ETC complexes I, III, IV, and V, and thus diminish oxphos. We aim to determine whether mitochondrial translation and OXA1L activity represent therapeutic vulnerabilities to overcome pro-survival metabolic adaptations in chemoresistant TNBC thereby augmenting treatment response. METHODS: We are evaluating the effects of conventional TNBC chemotherapies singly, and in standard combinations, on mitochondrial translation and ETC formation in human TNBC cells and PDX models (PIM001-P, WHIM14, BCM15116) using metabolomic and proteomic profiling. To perturb these processes genetically, we knocked down (KD) OXA1L with siRNA. We are complementing these studies pharmacologically using conventional antibiotics, such as tigecycline, as previous studies showed they inhibit mitochondrial translation in breast and other cancers (PMID: 25625193). These studies will reveal whether OXA1L and mitochondrial translation are required for metabolic adaption and chemotherapy resistance of residual TNBC cells. PDX preclinical trials based on our published residual tumor testing schema (PMID: 30996079), will reveal whether the sequential combination of NACT followed by tigecycline can effectively perturb residual tumor relapse. RESULTS: Proteomic profiling of longitudinally harvested PDX tumors demonstrates substantial disruption of mitochondria-and nuclear-encoded ETC components in residual vs. treatment-naïve tumors. Interestingly, these patterns are distinct between different chemotherapy treatments, with an increase of ETC components in carboplatin-treated residual tumors compared to a decrease in docetaxel-treated residual tumors. Western blot analyses of human cell lines show OXA1L KD perturbs levels of both nuclear-and mitochondria-encoded ETC components. Preliminary findings suggest OXA1L KD increases sensitivity to chemotherapies in human TNBC cell lines. Finally, tigecycline effectively inhibits TNBC cell growth. We next will evaluate whether residual cells not killed by conventional chemotherapies have enhanced tigecycline susceptibility. CONCLUSION: These data suggest targeting mitochondrial translation may be a promising approach to overcome pro-survival metabolic adaptations in residual TNBC cells not killed by conventional chemotherapies.

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Breast cancer stem cell marker, CD24 regulates metabolic reprogramming in triple negative breast cancer

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Breast cancer stem cell (BCSC) is a subset of cancer cells that can dictate the tumor initiation, metastatic progression, and therapeutic resistance in BC. The eradication of this unusual population is emerging as a new paradigm in cancer treatment. Molecularly, CD24 negativity in conjunction with high expression of CD44 is considered a hallmark for the BCSCs. While extensive studies have been performed to delineate the role of CD44 in BCSCs, the regulation of CD24 and its functional role have not been fully understood. In this study, we investigated the regulatory mechanisms responsible for low CD24 expression in BCSCs and their functional relevance in BCSCs. Analysis of DNA from tumor tissues and blood from BC patients as well as BCSCs sorted from BC cell lines suggest that CD24 is epigenetically regulated via DNMT-1/HDAC1-dependent increased methylation of CpG islands in the CD24 proximal promoter region. To understand the role of CD24 in triple-negative BC (TNBC), an aggressive subgroup of BC, we knocked down (CD24-KD) and overexpressed (CD24-OE) CD24 in metastatic TNBC cells. While CD24-KD resulted in increased proliferation and stemness, CD24-OE diminished the proliferative and stem-like potential. To further identify the signaling cascade underpinning these effects, we performed phospho-proteome analysis using Reverse Phase Protein Array (RPPA). Remarkably, we observed an enhanced activation of AMPK and NF-kB signaling cascades, and reduced PDGFRβ signaling upon depletion of CD24. As signaling cascades are intricately linked to cellular metabolism, we performed a metabolomic analysis of CD24-KD and CD24-OE cells. Our comprehensive analysis revealed heightened activation of mitochondrial fatty acid β-oxidation (FAO) in CD24-KD and increased glutamine metabolism in CD24-OE cells. In coherence with these findings, we observed significant regulation of genes related to fatty acid metabolism in the TNBC patient cohort expressing low levels of CD24. Consistently, the CD24-KD cells demonstrated increased sensitivity towards FAO inhibitors while CD24-OE cells were more sensitive to glutamine metabolism inhibitors. In vivo studies to further understand the translational significance of this metabolic axis is underway. Taken together, our study demonstrates, for the first time, that CD24 presents a novel metabolic vulnerability that can target BCSCs to gain a therapeutic advantage in the treatment of drug-resistant TNBC patients.
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WITHDRAWN
Ferroptosis Heterogeneity in Triple-Negative Breast Cancer Reveals an Innovative Immunotherapy Combination Strategy

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Treatment of triple-negative breast cancer (TNBC) remains challenging. Deciphering the orchestration of metabolic pathways in regulating ferroptosis will provide new insights into TNBC therapeutic strategies. Here, we integrated the multiomics data of our large TNBC cohort (n=465) to develop the ferroptosis atlas. We discovered that TNBCs had heterogeneous phenotypes in ferroptosis-related metabolites and metabolic pathways. The luminal androgen receptor (LAR) subtype of TNBC was characterized by the upregulation of oxidized phosphatidylethanolamines and glutathione metabolism (especially GPX4), which allowed the utilization of GPX4 inhibitors to induce ferroptosis. Furthermore, we verified that GPX4 inhibition not only induced tumor ferroptosis but also enhanced antitumor immunity. The combination of GPX4 inhibitors and anti-PD1 possessed greater therapeutic efficacy than monotherapy. Clinically, higher GPX4 expression correlated with lower cytolytic scores and worse prognosis in immunotherapy cohorts. Collectively, this study demonstrated the ferroptosis landscape of TNBC and revealed an innovative immunotherapy combination strategy for refractory LAR tumors.

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Mitochondrial structure and function adaptation in residual triple negative breast cancer cells surviving chemotherapy treatment

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Background: Neoadjuvant chemotherapy (NACT) used for triple-negative breast cancer (TNBC) eradicates tumors in only 45% of patients. TNBC patients with substantial residual cancer burden have poor metastasis-free and overall survival rates. Our previous studies demonstrated mitochondrial oxidative phosphorylation (OXPHOS) was elevated, suggesting a unique therapeutic dependency of residual tumor cells that survived after NACT. However, mechanisms underlying this enhanced reliance on OXPHOS are yet unknown. Mitochondria are morphologically plastic organelles that cycle between fission and fusion to maintain mitochondrial integrity and metabolic homeostasis. Methods: We modeled residual disease in human TNBC cells by treating with chemotherapeutic agents at the IC50 of cell killing, then evaluating surviving cells after 48 hours of treatment. We modeled residual TNBC in orthotopic patient-derived xenograft (PDX) model (PIM001p) by treating with standard front-line NACT (Adriamycin + cyclophosphamide; AC), then longitudinally harvesting tumors prior to treatment, residual, and upon regrowth. We analyzed mitochondrial morphology, mtDNA content and integrity, mitochondrial oxygen consumption rate, and metabolomic flux. We developed a U-Net based deep learning model that automatically detects and quantifies mitochondrial features in transmission electron micrographs. To test the functional dependency of mitochondrial structure in TNBC, we perturbed mitochondrial fusion genetically (by knocking down the fusion-driving protein Optic Atrophy 1, OPA1) and pharmacologically (using the first-in-class small molecule OPA1 inhibitor, MYLS22). Results: Pharmacologic or genetic disruption of mitochondrial fusion and fission resulted in decreased or increased OXPHOS rate, respectively, in TNBC cells, revealing for the first time that mitochondria morphology regulates OXPHOS in TNBC. Upon comparing mitochondrial effects of conventional chemotherapies, we found that DNA-damaging agents (adriamycin, carboplatin) increased mitochondrial elongation, mitochondrial content, flux of glucose through the TCA cycle, and OXPHOS, whereas taxanes (paclitaxel, docetaxel) instead decreased mitochondrial elongation and OXPHOS rate. Increased levels of the short protein isoform of OPA1 were observed in residual cells that were killed by DNA-damaging chemotherapy treatment. Treatment of cells with adriamycin followed by MYLS22 or given concurrently with MYLS22 drastically decreased cell growth. Conversely, cells treated with adriamycin, inducing fusion, followed by the DRP1 inhibitor Mdivi-1, further inducing fusion, were less sensitive to adriamycin than were vehicle-treated cells. Further, we observed heightened OXPHOS, OPA1 protein levels, and mitochondrial elongation in residual tumors of the PDX model following AC treatment. We found that sequential treatment first with AC, then inducing mitochondrial fusion and OXPHOS, followed by MYLS22 to inhibit OPA1 in residual tumors, was able to suppress mitochondrial fusion and OXPHOS and significantly inhibited residual tumor regrowth. Our deep-learning algorithm identified distinct changes in mitochondrial phenotypes in residual tumors of multiple PDX models. Treatment of non-chemotherapy-treated mice with the OPA1 inhibitor MYLS22 as a single agent had no effect on tumor growth, revealing that post-AC residual tumors have an enhanced dependency on mitochondrial fusion compared to treatment-naïve tumors. Taken together, our findings establish a functional role for mitochondrial structure in chemotherapeutic response and metabolic reprogramming, which may confer survival advantage to TNBC cells. These results suggest that pharmacologic perturbation of mitochondrial structure can overcome
chemoresistance in TNBC cells when administered rationally based on our understanding of chemotherapy-induced mitochondrial adaptations.

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Lipid accumulation in residual triple negative breast cancer cells surviving chemotherapy treatment

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Background: Triple negative breast cancer (TNBC) is an aggressive breast cancer subtype for which limited targeted therapies are available. Therefore, conventional chemotherapy remains the backbone of standard neoadjuvant treatment (NACT) for TNBC patients. Unfortunately, ~45% of patients will have substantial residual tumor burden post neoadjuvant chemotherapy, leading to poor prognoses (PMID: 28135148). Recently, it has been demonstrated that mitochondrial oxidative phosphorylation (oxphos) is upregulated and is a therapeutic vulnerability in chemoresistant TNBC (PMID: 30996079; Baek et al., BioRxiv doi.org/10.1101/2022.02.25.481996). However, mechanisms driving increased oxphos in chemoresistant TNBC are not understood. Upregulated fatty acid (FA) metabolism is a common adaptation in tumors, providing an energy source through fatty acid β-oxidation (FAO), and promoting lipid accumulation after fatty acid synthesis (FAS) when energy needs are met. Chemotherapy can induce oxidative stress through the generation of reactive oxygen species.
Cancer cells adapt to these damaging molecules by increasing de novo lipogenesis, resulting in the accumulation of lipid droplets (LDs) in the cytosol (PMID: 32782526, 20876798). We hypothesize that TNBC cells metabolically adapt to the stress of NACT by upregulating lipid metabolic pathways, providing highly energetic molecules that can be utilized to drive oxphos in chemoresistant TNBC. Methods: Using orthotopic patient-derived xenograft (PDX) models of TNBC (PIM001-P, PMID: 30996079, HCI-010, PMID: 22019887; WHIM14, PMID:24055055), we are measuring protein levels of fatty acid synthase (FASN) in vehicle tumors vs residual tumors surviving treatment with the standard front-line neoadjuvant chemotherapy regimens (Adriamycin plus cyclophosphamide (AC), docetaxel, carboplatin, or docetaxel+carboplatin) using immunohistochemistry (IHC). Vectra 3 microscopy (Akoya) is being used to quantify tumor cell-specific staining. We complemented our IHC analysis with reverse-phase protein array (RPPA). To assess LD accumulation in residual PDX tumors, we conducted transmission electron microscopy (TEM). To complement these PDX studies, we modeled the residual tumor metabolic state in cultured human TNBC cells. Following treatment with the IC50 of standard chemotherapeutic agents (AC, carboplatin, paclitaxel, docetaxel), we assessed oxphos by measuring oxygen consumption rate (OCR) using a Seahorse Bioanalyzer (Agilent). Further, we tested LD accumulation using LipidTOX staining. In ongoing studies, we are measuring incorporation of 13C palmitate into the tricarboxylic acid cycle (TCA) prior to and following chemotherapy treatments to assess if lipids fuel mitochondrial metabolism in residual TNBC cells. Results/Discussion: IHC in the PIM001-P PDX model after in vivo AC treatment revealed increased levels of FASN in post-AC residual tumors compared to the treatment-naive tumors. Further, key proteins involved in fatty acid synthesis, FASN and Acetyl-CoA carboxylase, were significantly increased in residual PIM001-P cells that survived AC compared to vehicle by RPPA. TEM analysis of the HCI-010 PDX revealed significantly more LDs in carboplatin-treated tumors compared to vehicle. This finding was supported by increased LDs observed in TNBC cell lines treated with NACT compared to vehicle in our LipidTOX analyses. Taken together, these data indicate that NACT induces increased expression of key lipid metabolism proteins and accumulation of cytosolic LDs. Our future experiments will reveal if chemoresistant TNBC cells preferentially utilize and incorporate lipids into the tricarboxylic acid cycle, in turn driving oxphos. These data have the potential to provide rationale for the incorporation of FAO/LD inhibitors in sequential combinations with conventional chemotherapies to more effectively kill TNBC cells that are chemo-refractory.

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Withaferin A induces metabolic crisis in breast cancer cell lines via decreasing c-myc expression: potential therapeutic implication

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Background: Breast cancer is the most diagnosed cancer and the leading cause of mortality among women in India and worldwide. Reprogrammed glucose metabolism is considered as the hallmark of the cancer with immense therapeutic relevance. Withaferin A (WA), a phytocompound isolated from the plant Withania somnifera, commonly known as Ashwagandha has the remarkable anticancer role. However, the mechanism of action of WA in breast cancer metabolism is still unelucidated. Breast cancer cells have metabolic vulnerability and high glucose dependency. Thus targeting glycolysis could be the better therapeutic approach. Chemotherapy and radiotherapy have the side effects, to overcome this natural products can be used to treat cancer. The potential of natural compounds in targeting metabolic vulnerabilities of cancer and highlighting prospective therapeutic benefits that can be determined by improving our understanding of this field. Aims and Objective: To explore the therapeutic effect of WA in breast cancer cell lines and to identify the role of WA in targeting Warburg effect via c-myc. Cancer cells exhibit upregulated Warburg effect, to fulfill the bioenergetics and biosynthetic demands of the rapidly growing cancer cells. Thus targeting the Warburg effect could be the better therapeutic approach. Materials and methods: Breast cancer cell lines (MBA-MB-231, MBA-MB-468, MBA-MB-453 and MCF-7) were procured from NCCS Pune and maintained in DMEM media supplemented with 10% FBS. SRB dye was used for cell viability as it binds to the protein of the cells. Further Colony formation assay (using crystal violet dye) was done to evaluate the effect of WA on colony formation. Metabolic assays (lactate production, glucose uptake and ATP generation) were performed using kits (Eton Bioscience). Transient silencing using si-RNA of c-myc was done with lipofectamine 3000.
Silencing of c-myc was done for Warburg effect and protein expression. RNA was isolated from breast cancer cells using Qaigen kit and RT-PCR was performed to evaluate the glycolytic gene expression before and after the treatment of the WA in breast cancer cell lines. To check the expression of glycolytic genes at protein level we had done the western blot. Protein isolation was done in RIPA lysis buffer and western blot was performed using primary antibodies of GLUT1, HK2, PKM2, c-myc. Statistical analysis was analyzed in graph pad prism. Breast cancer patient METABRIC data was analyzed and pathway deregulation score was calculated from Pathifier algorithm. Results: Withaferin A decreased the glucose uptake, lactate production and ATP production in different breast cancer cell lines. Further, WA induced suppression of key glycolytic enzymes via c-myc, decreased cell proliferation, biomass and colony formation ability of the breast cancer cells. Silencing of c-myc gene also showed the similar results to WA such as decrease in Warburg effect and reduction in glycolytic proteins expression. Through the LC-MS analysis WA decreases the key glycolytic metabolites and other pathway metabolites, induce metabolic catastrophe in breast cancer cells. Clinical relevance of our experiments was validated in dataset of ~2000 breast tumors (METABRIC) using Pathifier algorithm wherein we calculated deregulation score of glycolysis pathways in each of the tumor and normal sample. Importantly, higher deregulation of glycolysis was observed in breast tumor compared to normal tissues and found to be associated with poor prognosis. Conclusion: Our results highlight the anti-carcinogenic effect of Withaferin A in modulating breast cancer metabolism and the clinical significance of glycolysis in general. WA decreases the glucose metabolism and its flux through key metabolic pathways associated with the glycolytic intermediates. Therefore it could be argued that therapeutic targeting of breast cancer metabolism by WA may improve clinical outcome.

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Introduction. ALCAM (Activated Leukocyte Cell Adhesion Molecule), also known as CD166, is a cell adhesion molecule which belongs to the immunoglobulin superfamily and is widely expressed in various human tissues. It has been demonstrated that ALCAM plays an important role in the progression of malignant diseases and tumour metastasis in multiple cancer types including breast cancer. However, the molecular mechanism of ALCAM and cancer progression is currently unclear. The present study performed protein array analyses using ALCAM genetically manipulated cell models to select potential protein partners of ALCAM. The study focused on MET (Hepatocyte Growth Factor (HGF) Receptor), a prominent ALCAM interacting protein kinase and a protooncogene contributing to cancer progression and spread. Method. Human breast cancer cell lines MCF-7 and MDA-MB-231 were selected to create ALCAM knockdown cell models. A range of other breast cancer cell line with differing hormone receptor status were also used. Protein samples of transfected cells were used to perform Kinexus protein kinase microarray analysis. The protein interaction between ALCAM and other prospective protein kinases including MET was verified by the method of immunoprecipitation. Additionally, the ALCAM knockdown model was also assessed for the impact of ALCAM and HGF/MET on the biological functions by Electric Cell-substrate Impedance Sensing (ECIS). Results. MCF-7 and MDA MB-231 cells both were strongly expressed ALCAM. Cells models with ALCAM knocking down were successfully created by way of anti-ALCAM shRNA. We have shown on the protein kinase microarray analysis that the hepatocyte growth factor (HGF) receptor, MET was one of the kinases significantly affected following ALCAM knocking down. It was also found that the alteration of protein interaction between the MET protein kinase and ALCAM protein showed an opposite pattern between ER positive and ER negative ALCAM knocking down cells. This protein interaction was observed by immunoprecipitation in MDA-MB-361 and MDA-MB-231 cell lines, but not in MCF-7 cells. The biological analyses using the ECIS technologies showed that MET kinase inhibitors and exogenous recombinant HGF affected the ALCAM-mediated cell adhesion in different breast cancer subtypes. Conclusion. ALCAM is associated with HGF/MET signalling and the interaction between ALCAM and MET is different amongst subtypes of breast cancer which have different hormone receptor status.

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Estrogens are steroid hormones that play a key role in a wide range of physiological and pathological processes. Estrogen receptor-alpha, ERα, functions primarily as a nuclear transcription factor (TF) through ligand-dependent activation by 17β-estradiol (E2), the predominant naturally-occurring estrogen. This results in dimerization, DNA binding to cis-regulatory elements called enhancers, and gene regulatory function of ERα. In vivo, E2 production and action fluctuates during reproductive cycles and possibly even in a circadian manner. In tissues and cells, E2-regulated gene expression is dynamic, with rapid induction of enhancer formation and target gene expression (or repression), followed by enhancer “decommissioning” and cessation of the gene regulatory effects. The effects of sustained E2 production and signaling, fluctuations in E2 levels, and removal of E2 on estrogen-regulated gene expression are unknown. Classical experiments exploring the gene regulatory effects of E2 involve stimulation of cultured cells throughout the duration of the experiment with a continuous and typically high dose of hormone, with the cells harvested at the end of the stimulation period. While this has allowed us to understand the molecular underpinnings of signal-dependent transcription, it has not allowed analysis of physiological fluctuations in estrogen signaling involving periods of stimulation (i.e., the presence of hormone) and non-stimulation (i.e., the absence of hormone). In our studies, we are applying a combination of next generation sequencing techniques and fluorescence microscopy to investigate signal-dependent responses to fluctuating and short duration E2 exposures using ERα-positive MCF-7 human breast cancer cells after E2 treatment and removal. Our initial results suggest that different E2 target genes respond differently to low dose E2 treatment and E2 withdrawal. Moreover, for some E2 target genes, sustained E2 treatment may not be required for a complete E2 transcriptional response. With these studies, we hope to connect physiological aspects of E2 production, release, and action with the molecular mechanisms of E2-dependent gene expression - an aspect of our understanding of estrogen signaling that has been lacking.
Proinflammatory and estrogen signaling modulates the chemoresistance and metastasis of breast cancer cells through post-translational modifications of pioneering factor FOXA1

ER-positive breast cancers compose most breast cancers at the time of diagnosis and are primarily driven by mitogenic estrogen signaling. In ER-positive breast cancers, the pioneer transcription factor FOXA1 plays a critical role in the estrogen receptor (ER) function. It binds to condensed chromatin and promotes chromatin accessibility for subsequent ER binding upon estrogen stimulation. We have reported that TNFa-stimulated proinflammatory signaling relocates FOXA1 to a new set of latent enhancers, which initiates the binding of estrogen liganded ER and subsequent expression of a unique transcriptome with clinical significance. The redistribution of FOXA1 occurs within 40 mins of the TNFa treatment, which implies a rapid signaling cascade that arises from changes to either FOXA1’s post-translational modifications (PTMs) or its binding partners. To understand this genomic redistribution of FOXA1, we compared the post-translational modifications (PTMs) of FOXA1 from Vehicle, E2, TNFa, and E2+TNFa treated MCF-7 breast cancer cells. More than five acetylation and phosphorylation events have been identified around the DNA binding domain of FOXA1 by semi-quantitative and quantitative mass spectrometry approaches, and their abundance varies across
treatments. To study these PTMs of FOXA1, we used CRISPR/Cas9 to create specific knock-in mutations to mimic or prevent acetylation events in MCF-7 cells. Specifically, we engineered MCF-7 cell lines where K270 was mutated to glutamine (K270Q) to mimic acetylation. And for comparison, we also created cell lines where K270 was mutated to arginine (K270R) to prevent acetylation of FOXA1. Our data, including FOXA1 ChIP-seq and RNA-seq, revealed the genomic redistribution of FOXA1 with these PTMs, which subsequently alters gene expression programs and promotes cell growth, migration, or chemoresistance. These results were confirmed in other ER+ cell lines (such as T47D cells) providing evidence for the generalizability of our findings. Taken together, our data suggest that inflammatory signaling signaling can reshape the enhancer landscape of FOXA1 through post-translational modifications, resulting in changes to estrogen signaling that have profound effects on breast cancer biology.

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Background: Metastasis and therapeutic resistance are a major clinical challenge, responsible for the vast majority of cancer deaths. A subpopulation of tumor cells known to have intrinsic resistance to standard therapies and contribute to metastasis function as “cancer stem”, or tumor-initiating, cells (TICs). Enriched populations of TICs are typically identified by markers such as aldehyde dehydrogenase activity, the cell surface marker combination of CD44+/CD24-, or fluorescent reporters for signaling pathways that regulate TIC function such as STAT3. Despite their utility, TIC markers and reporters have limitations. Marker expression can be unstable and there is no established method to lineage trace long-lived TICs or to follow them as they undergo cell state changes.

Methods: To augment existing TIC reporters, we developed a two component TAM-inducible, Cre recombinase-dependent, STAT3 signaling-specific lentiviral LT system. The first component is a vector that labels cells with active STAT3 signaling (EGFP+), followed by a self-cleaving peptide and TAM-inducible Cre-recombinase (4M67-EGFP-P2A-CreERT2). The second component is a constitutively expressed dual-color switching Cre-dependent reporter vector (EFS-loxPdsRedloxP-mNeptune2). Addition of TAM drives color switching from dsRed to mNeptune2 via CreERT2 recombination in STAT3 signaling cells. Both lentiviral vectors were constructed using Gateway® Cloning. Sum159 cells were transduced with the LT system and reporter activity was validated both in vitro and in vivo using confocal microscopy and flow cytometry. Four LT cell populations (EGFP+/mNeptune2+, EGFP+/dsRed+, EGFP-/mNeptune2+, and EGFP-/dsRed+) were enriched using fluorescence activated cell sorting, then analyzed by single cell RNA sequencing (scRNA seq). Results: Our results confirm the STAT3 LT reporter identifies STAT3 signaling cells (EGFP+), which can be labelled (mNeptune2+) upon addition of TAM. We conducted a TAM dose response curve to identify the optimal TAM dose for complete and partial labeling of STAT3 signaling cells. scRNA seq uncovered gene expression patterns within the TIC compartment and revealed similarities and differences in gene expression between the TIC compartment and the remaining LT reporter populations. Conclusion: These data demonstrate our LT system is a powerful tool that can be applied to uncover the role of TICs in metastasis and therapeutic resistance, as well as identify genetic vulnerabilities to specifically target TICs.

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The role of endothelial-specific AXL and its associated signaling pathways in the tumor microenvironment

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Most breast cancer deaths result from the development of metastases. The complex tumor microenvironment provides signals that can instruct both breast cancer cells to invade and tumor blood vessels to be leaky, hence supporting metastasis. We identified the receptor tyrosine kinase (RTK) AXL to be essential for metastasis. Genetic ablation of Axl in mouse models of HER2+ breast cancer, either globally or specifically in mammary epithelial cells, blunts metastasis but not primary tumor growth. We found that Axl expressed in tumor cells contributes to the remodeling of the tumor microenvironment, including immune cell recruitment and abnormal blood vessels. Hence, AXL in epithelial cells promotes cell invasion and shapes a pro-metastatic microenvironment that would be poorly responding to treatments such as immunotherapy. While AXL is known to be expressed on endothelial cells, its endothelial function has yet to be clearly defined. This project aims to address the hypothesis that AXL expressed on endothelial cells promotes processes that lead to abnormal blood vessel formation to promote metastasis. To address this hypothesis, we first studied the specific intracellular interactions between two RTKs, AXL and the known pro-angiogenic receptor VEGFR. Our preliminary analyses indicates that GAS6 can not only induce the phosphorylation of the permeability marker eNOS on its own but can also potentiate the VEGF’s response. The index of linearity of the endothelial tight junctions upon GAS6 stimulation show increased permeability of the endothelial cells. To further characterize the signaling pathways controlled by these receptors, we plan to perform a phosphoproteomics screen. We will focus on studying the AXL+VEGFR phosphoproteome and define the signaling pathways that impact vascular permeability. The most interesting candidate(s) will be studied in the context of mouse tumor models. In parallel, we are generating a conditional deletion of Axl in endothelial cells by crossing Axlfx/fx mice with Pdgfb:iCreER animals. With this, we will study the specific endothelial effects of Axl in vivo, specifically with vessel permeability and retinal angiogenesis assays. Multiple anti-angiogenic therapies for cancer failed in the clinic highlighting the need for new strategies to target endothelial cells in cancer. This project will provide essential information on the role of endothelial specific AXL, in the context of the HER2 breast cancer, and of its downstream effectors. With more specific targets, anti-angiogenic therapies could decrease their off-target effects and increase their efficacy in the clinic. This project has the potential to uncover therapeutic targets that could reduce the metastatic burden in breast cancer patients, and therefore better the prognostic for the HER2 cancer subtype.

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Neratinib vs. Trastuzumab plus Ribociclib in ERBB2-positive breast cancer: Preclinical mechanistic efficacy study

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Background: Despite the wide-ranging clinical success of human epidermal growth factor receptor 2 (HER2)-directed therapies, many HER2-positive breast cancer patients eventually progress because of the development of primary or acquired resistance. PIK3CA is found often mutated in breast cancer (>30%, TCGA dataset) and responsible for HER2-directed treatment failure. Purpose: Inhibition of pan-tyrosine kinases of HER-receptors along with the blockade of estrogen receptor (ER) prevents the activation of downstream effectors and crosstalk between HER2 and ER, leading to tumor cell death. Similarly, the combined inhibition of HER2-receptor signaling with cell cycle arrest leads to efficient tumor cell apoptosis. Here, we evaluate the mechanistic efficacy and comparability of neratinib (N) (an irreversible pan-ERBB tyrosine kinase inhibitor) in combination with fulvestrant (F) against ribociclib (R) plus trastuzumab (T) in HER2-amplified breast cancer cells. Methods: HER2+ breast cancer cell lines with Rb- wild-type- BT474 (ER+), SKBR3 (ER-), and MDA-MB453 (ER-, PIK3CA mutated [H1047R]) were used for the study. Cells were treated with N+F (F added in ER+ cell line only) or R or T as a single-agent or combination and assessed for real-time proliferation, 3D ON-TOP assay, changes in mitochondrial potential, and apoptosis. Cells treated with R and/or T were additionally examined for cell cycle arrest and changes in CDK4 mRNA transcription. Baseline CCND1 mRNA transcripts were quantified by RT-qPCR. Immunohistochemistry was used to assess baseline BCL2 expression in HER2+ tumor microarrays (TMA). Western blot was used to evaluate the effects on key downstream signaling proteins in response to the above treatment or combination. Results: High CCND1 expression was found in HER2+ cell lines that show promise for CDK4/6 inhibition. High BCL2 expression was found in HER2+ TMA that confirmed the natural resistance to programmed cell death. BT474 and MDA-MB453 were highly sensitive to N (+F), and high growth inhibition was evident at lower doses (< 20 nM). SKBR3 was comparatively less sensitive to N monotherapy and required dosing >160 nM to induce marked cell death. BT474 and MDA-MB453 had pronounced cytostatic responses to R or T+R, while a moderate response was observed in SKBR3. Substantial reduction in CDK4 transcription was noted following R or R+T treatment in MDA-MB453/BT474 but not in SKBR3. Apoptosis assays confirmed enhanced cell death with the R+T combination in BT474 and MDA-MB453 but not in SKBR3. Inhibition of key downstream oncogenic signaling (p-AKT/p-S6RP/p-ERK) was more evident with N compared to R, T, or R+T combination. Attenuated p-Rb expression (Ser 780 & Ser 807/811) was detected in all cell lines from R administration,
indicating interruption in cell cycle progression. Conclusion: Mechanistically, N+F was superior to T+R in terms of inhibition of HER2 and its downstream signaling in the HER2+/ER+ BC model. N+F induced significantly more apoptosis and inhibited cell proliferation compared to T+R. Additionally, N monotherapy was highly effective in HER2-amplified/ER-negative breast cancer cells with PIK3CA mutation.

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WITHDRAWN
Identifying FOXA1 Binding Partners using Proximity Labeling

Approximately 75% of breast cancers are driven by the estrogen receptor alpha (ER), and despite the advent of endocrine therapy to block ER signaling pathways, a significant portion of women develop resistance to these drugs. The pioneer factor FOXA1 has been shown to facilitate nearly all DNA-binding events of ER in response to estrogen in ER+ breast cancer (ER+BC). Notably, up-regulation of FOXA1 is a hallmark of endocrine-resistant phenotypes and has been shown to reprogram enhancer elements, leading to an altered transcriptome. However, FOXA1 is a critical pioneer factor for multiple nuclear hormone receptors, aside from ER, and is implicated in regulation of important factors such as HER2 and the androgen receptor (AR). With the diverse array of breast cancer molecular subtypes displaying complex interplay between ER, HER2, AR, PR, and other hormone receptors, describing the complete ensemble of FOXA1 binding partners in various contexts, such as endocrine-resistant tumors, is of increasing importance. To define a comprehensive catalog of FOXA1 binding partners under basal conditions, we generated MCF-7 cell lines stably expressing constructs of FOXA1 fused at its N- or C-terminus to the biotin ligase miniTurbo. Using proximity labeling coupled with mass-spectrometry, we have comprehensively cataloged binding partners of FOXA1, including many expected proteins such as ER, AR, MLL3, YAP1, and GATA-3. Moreover, we have discovered more than 150 previously unidentified binding partners of FOXA1, which may exert profound effects on FOXA1 function. Importantly, high hazard ratios and significant dependencies are associated with several of these new binding partners, such as subunits of a previously described histone deacetylase (HDAC) complex containing genetic suppressor element 1 (GSE1) and lysine-specific histone demethylase 1A (KDM1A). Genomic approaches are currently underway to characterize where in the genome FOXA1 is interacting with these novel proteins and to guide future exploration into the physiological significance of these interactions. Integrating biochemical, molecular, and genomic approaches, we have potentially highlighted new mechanisms of FOXA1, which could have significant clinical impact in the future.

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Retinoic acid receptor (RAR) signalling plays a role in neratinib (NER) resistance in HER2+ breast cancer (BC) cell lines

Introduction: NER is a pan-HER tyrosine kinase inhibitor (TKI) approved for the treatment of HER2+ BC in the adjuvant setting following trastuzumab and in combination with capecitabine for advanced disease. Resistance to small molecule TKIs like NER can develop in the clinic. Pre-clinical studies have highlighted that retinoic acid can inhibit BC growth and modulate HER2 signalling pathways. The RAR family of nuclear transcription factors consists of RARα, RARβ and RARγ. The synthetic retinoic acid fenretinide (FN) acts as a pan-RAR agonist, while AGN194310 (AG) acts as a pan-RAR antagonist. In order to investigate the anti-proliferative potential of co-targeting RAR and HER2 pathways in sensitive and resistant BC cell line models, we examined the effect of FN and AG in combination with NER in two HER2+, estrogen receptor-negative, trastuzumab-resistant cell lines HCC1569 and HCC1954, and their NER-resistant (NR) sub-lines HCC1569-NR and HCC1954-NR. Methods: HCC1569 and HCC1954 cell lines were cultured in RPMI/10% FCS at 370C/5% CO2. NR cell lines were generated by continuous exposure to 150nM NER for 6 months. 10 mM stock solutions of FN (H7779-Sigma), AG (SML2665-Sigma) and NER (supplied by Puma Biotechnology, Inc) were made in DMSO. Proliferation was measured as percentage growth versus DMSO control using
an acid phosphatase based assay after 5 days drug exposure. The half-maximal inhibitory concentration (IC50) was calculated for each drug using CalcuSyn. The combination assays were performed using fixed ratios. The combination index (CI) values were calculated at the effective dose that inhibits 50% growth (ED50) using CalcuSyn. Values < 1 represent a synergistic effect, a value of 1 is additive and values > 1 represent an antagonistic effect. All data presented as the mean of biological triplicate experiments ± standard deviation. Results: This research found that the NR cell lines were >10-fold resistant to NER (HCC1569-NR IC50 0.44 ± 0.1 μM, HCC1954-NR IC50 0.198 ± 0.019 μM) compared to the parental HCC1569 (IC50 0.018 ± 0.015 μM) and HCC1954 (IC50 0.017 ± 0.001 μM) cell lines. Pan-RAR agonism by FN had a potent anti-proliferative effect in the HCC1569 (FN IC50 0.22 ± 0.02 μM) and the HCC1569-NR cell lines (FN IC50 0.28 ± 0.13 μM), with the HCC1954 and HCC1954-NR cell lines proving less sensitive (IC50 6.47 ± 1.3 μM and 1.9 ± 0.2 μM, respectively). When combined with NER, FN produced a strong antagonistic effect in the HCC1569 cell line (CI value: 15.63 ± 9.5) and a strong synergistic effect in the HCC1954 cell line (CI value: 0.42 ± 0.06). For the NR cell line models, the NER/FN combination proved synergistic (HCC1569-NR, CI value: 0.84 ± 0.46) or additive (HCC1954-NR, CI value: 0.97 ± 0.15). Next, we wanted to assess the impact of antagonising rather than activating RAR activity in our cell line models. All four cell lines were less sensitive to antagonist AG (IC50 >8μM for all cell lines) compared to FN. The addition of AG to NER resulted in responses diametrically opposed to the FN/NER combination. The AG/NER combination produced a strong synergistic effect in the HCC1569 cell line (CI value: 0.52 ± 0.17), an antagonistic effect in the HCC1954 cell line (CI value: 2.1 ± 0.4) and an antagonistic effect in both NR cell lines (HCC1954-NR, CI value: 2.69 ± 0.6 and HCC1569-NR, CI value: 1.58 ± 0.12). Conclusions: This pre-clinical study suggests involvement of the RAR signalling pathway in response to NER and the development of NR. Results also suggest pan-RAR agonism, rather than pan-RAR antagonism, as a potential therapeutic strategy to overcome NR. Further investigation is warranted to determine how targeting the RAR signalling pathway may assist in the treatment of HER2+ BC.

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INTRODUCTION: Breast cancer (BC) is the most prevalent malignant tumor in the female population, except for skin tumors. Despite therapeutic advances, over 20% of patients with localized disease will relapse. The research of epithelial-mesenchymal transition (EMT), tumor stem cells (TSC), and the biological mechanisms related to refractoriness and metastasis development is, therefore, an opportunity for new therapeutic strategies and better results.

OBJECTIVES: To identify breast cancer cellular markers related to EMT and TSC according to their histological subtypes, stage and to analyze their relationship with clinical outcomes.

METHODS: After selecting a public breast cancer patients database with interactome, we identified differentially expressed genes, their associated processes, coexpression networks and interactions with pathways related to the stem phenotype and epithelial-mesenchymal transition. The characterization of key genes and the correlation with histological subtypes and clinical outcome allowed us to determine a group of genes as potential breast cancer EMT/TSC prognostic markers. RESULTS: In the 989 patients studied, 1033 differentially expressed genes...
(DEGs) were found, categorized according to histological subtype (hormone receptor positive, HER2 positive, triple negative) and stage IV. Seven communities of gene coexpression were found, with the gray community showing greater interaction with hormone positive tumors, the green community with HER2 positive, and the turquoise community with the triple negative one. The hormone positive disease was related to extracellular matrix processes and neuronal communication, the HER2 positive to the extracellular matrix interaction and the triple negative tumors to mitotic processes. Investigation networks with EMT and TSC related genes demonstrated a strong correlation with HER2-positive and triple-negative tumors; being eight genes in HER2 positive subtypes correlated with survival (SYNDIG1, COL10A1, SLC24A2, LINC00922, KLKP1, MMP11 and ECM2); and one of the hormone positive subtype (ITIH5). ECM2 was highlighted in terms of EMT/TSC connectivity and survival. CONCLUSION: The EMT/TSC processes are significant in the various subtypes of breast cancer and impact on survival, especially in the HER2 positive subtype.

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Invasively distinct subpopulations cooperate via a laminin-332/Rac1 axis in triple-negative breast cancer

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Intratumoral heterogeneity poses a significant hurdle for cancer treatment, yet is under-characterized in the context of tumor invasion. Cancer cells from solid tumors can invade through two predominant modes: collective invasion, whereby cancer cells invade in multicellular packs or streams marked by intact cell-cell junctions; and single-cell invasion, whereby cells invade independently without intercellular adhesion. We have observed that collective and single-cell invasion co-occur within the same tumor microenvironment in triple-negative breast cancer, suggesting that invasive heterogeneity supports cooperative behavior between tumor subpopulations. To test this, we used a novel, published technique developed by the lab (SaGA) to isolate pure subpopulations of 4T1 cells that collectively invade (collectives) or single cells that invade alone (singles). 3-D spheroids of SaGA-purified collectives and singles exhibited almost exclusively collective and single-cell invasion, respectively, and these invasive phenotypes were retained over multiple passages. Integration of RNA sequencing and methylation array data obtained from RNA and DNA isolates, respectively, of collectives and singles revealed that collectives exhibit drastic overexpression and promoter hypomethylation of two laminin genes that form the laminin-332 complex, Lama3 and Lamc2. Additionally, an unbiased proteomic analysis of secreted proteins also revealed an overabundance of these laminins in collectives media. We found that singles have increased expression of integrin α6 and β4, which together have been found to specifically bind to laminin-332 to activate the Rac1 GTPase. Interestingly, our RNA sequencing data revealed a binary overexpression of a Rac1 GTPase, Prex1 in singles, suggesting that singles have enhanced Rac1 activation when compared to collectives with the potential for hyperactivation upon laminin-332 binding. Indeed, laminin-332 resulted in higher GTP-bound Rac1 in singles and subsequently increased invasion of singles in 3-D models. Additionally, laminin-332 induced cell elongation at the leading edge of single spheroids, which was reversible by treatment with a Rac1 inhibitor. Together, our data suggests that distinct subpopulations amidst a heterogeneous tumor cooperate via laminin-332 and Rac1 to facilitate tumor invasion in metastatic triple-negative breast cancer.

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Hope for OTHERS – An organ donation program for metastatic breast cancer research

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Background: Previous studies have shown that rapid autopsies (RA) provide a unique opportunity for tissue collection from patients who succumb to the disease. Because cancer patients are unable to donate their organs to other people, this program provides the patient an opportunity to leave a legacy by donating their body to research. These donations are vital for advancing breast cancer research. The UPMC/Pitt RA group revamped an existing program in 2018 through the formation of a larger multidisciplinary team that includes breast cancer laboratory and clinical researchers, pathologists, nurses, bioinformaticians, and tissue bankers. Because recruitment to the RA program was a challenge, we recently added patient advocates to the team to provide their essential perspective, and a dedicated research coordinator who serves as an ambassador for the program. Methods: Autopsy is performed by the Autopsy and Forensic Pathology Center of Excellence/Decedent Affairs Service of UPMC. Samples are banked in the Pitt Biospecimen Core (PBC), in addition to immediate processing including preparing of samples for sequencing and growing of organoids in the laboratory. Immunohistochemical (IHC) analysis is performed by UPMC/Magee Pathology. Results: The research coordinator quickly became an integral part of the program and closely interacts with care providers, patients and their families, pathologists on call, and manages interactions with transport services. Five breast cancer advocates have been instrumental in advising on additional changes to the program. The advocates attend regular team meetings and have formulated patient considerations for the the RA program, including appropriate and sensitive recruitment of patients, the role of physicians in decision making by the patient, registration for more than one RA program, potential issues with transporting a body across state lines and more. The advocates also developed the name for the program - “Hope for OTHERS” with Others standing for “Our Tissue Helping Enhance Research & Science”. As of June 2022, the team has completed 26 autopsies, and an additional 20 patients have consented to the program. The completed autopsies include patients with breast tumors representing different molecular and histological classes, ethnicities, and genders. The average disease-free survival and overall survival of patients that underwent autopsy was 81.6 and 127.8 months, respectively. Most patients passed outside the hospital (86%), with 62% in home hospice and 24% in inpatient hospice. Average time between death and start and end of autopsy was 4.56 hrs and 7.09 hours, respectively. The most common metastatic sites from which specimens are collected are liver, lung and lymph nodes. Per patient we collect on average specimens from 4
different organs. In addition to the metastatic lesions, we have access to primary tumor tissue and liquid biopsies obtained during the breast cancer disease progression for 44% and 73% of the patients, respectively. For a subset of the patients, tissue has been grown as patient-derived organoids or xenograft models. Preliminary IHC and sequencing analysis has provided insight into inter- and intra-patient and intra-tumor heterogeneity. Further molecular studies are ongoing. Conclusion In summary, over the last 5+ years, we have established a successful post-mortem tissue collection program, by addressing a series of barriers through the formation and work of a multi-disciplinary well-coordinated team. We are currently expanding our omics studies using state-of-the-art technologies to improve understanding how intra- and inter-tumor heterogeneity play a role in the clinical course of advanced breast cancer, to increase diversity of the patients enrolled in the RA program, and to support the successful implementation of other RA programs nationwide and worldwide.

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Oestrogen represses Noggin expression by interfering BMP/Smad signalling in ER positive breast cancer cells

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Background Bone morphogenetic proteins (BMPs) are members of Transforming Growth Factor β (TGF-β) superfamily. BMPs are actively involved in the disease progression and bone metastasis of breast cancer. As a natural antagonist of BMP, Noggin plays important roles in the regulation of BMP signalling. It can facilitate spread of breast cancer cells to bone and subsequent colonisation and formation of osteolytic bone lesions. The present study aimed to investigate the regulatory mechanism for Noggin expression in oestrogen receptor (ER) positive breast cancer cells. Method Noggin expression was analysed in The Cancer Genome Atlas (TCGA ER (+) n=763, ER (-) n=216) and E-MTAB-6703 (ER (+) n=733, ER (-) n=421) cohorts. Correlation between Noggin and ER was evaluated using Spearman test. The expression of Noggin in an ER positive breast cancer cell line MCF-7 was determined by depriving the cells from oestrogen using phenol red-free DMEM supplemented with 10% charcoal stripped foetal calf serum or adding 10-10M 17-β-oestradiol. Activation of Smad-1/5/8 and involvement of BMP receptors in the oestrogen repressed Noggin expression were further examined using recombinant human BMP7 and a BMP receptor inhibitor (LDN-193189). Influence of Noggin on cellular functions was evaluated in MCF-7 cells with Noggin overexpression using a lentiviral Noggin expression vector. Results Noggin expression was negatively correlated with ERα in both TCGA BRCA (r=-0.162, p < 0.01, n=1093) and E-MTAB-6703 (r=-0.078, p < 0.01, n=2302) cohorts. The expression of Noggin was increased in the MCF-7 cells upon a deprivation from oestrogen which was further validated by adding 17-β-oestradiol. This is in line with the increased expression of Noggin observed in the MCF-7 cells with ER silencing (GSE27473). Furthermore, an increased level of phosphorylated Smad1/5/8 was seen in the MCF-7 being hungered from oestrogen which was prevented by adding 17-β-oestradiol and LDN-193189, respectively. As a result, the oestrogen hunger induced Noggin expression was also decreased by adding 17-β-oestradiol and LDN-193189. To further investigate the influence of oestrogen on BMP-Smad signalling regulated Noggin expression, Noggin expression and phosphorylation of Smad1/5/8 and Smad3 were determined in MCF-7 cells which were treated with rhBMP7 and in combination with 17-β-oestradiol and LDN-193189, respectively. BMP7 induced Noggin expression and activation of Smad1/5/8 can be diminished by 17-β-oestradiol and LDN-193189. Noggin overexpression in MCF-7 cells resulted in an increase of proliferation. Conclusion Noggin expression can be repressed by oestrogen through an inference of the BMP- Smad signalling. Overexpression of Noggin promoted proliferation of MCF-7 cells. Further investigation is required to clarify the exact role of Noggin in ER positive breast cancer and its implication in the disease progression and current therapies.

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BACKGROUND Breast Cancer metastases develop via a series of complex steps that are often initiated through a cellular reprogramming called the epithelial-mesenchymal transition (EMT). One protein involved in the promotion of the EMT is Hypoxia-Inducible Factor-1 (HIF-1). The mechanisms by which HIF-1 initiates this process is unclear. Previous studies have demonstrated hypoxia to induce lipid metabolic reprogramming through HIF-1α-induced regulation of the fatty acid synthase (FASN). FASN produces palmitate which has been shown to post-translationally modify and stabilize oncoproteins like Sonic Hedgehog (Shh). I hypothesize that the mechanism by which HIF-1α fosters an EMT phenotype in breast cancer is through FASN-induced palmitoylation of Shh, which leads to activation of the Shh signaling pathway and its downstream targets.

MATERIALS AND METHODS HIF1 protein was stabilized in MDA-MB-231 triple negative breast cancer cells by exposing the cells to Dimethyloxallyl Glycine (DMOG). Stabilization confirmed via a Western Blot analysis. Cells were then exposed to a combination of DMOG and TVB-2640, FASN activity inhibitor, DMOG only, and a vehicle treatment. mRNA expression of HIF1, FASN, and SHH of these treatment groups were analyzed with qt-PCR.

RESULTS When MDA-MB-231 breast cancer cells were exposed to DMOG, mRNA expression of HIF-1, FASN, and SHH simultaneously increased. The DMOG-induced increase in SHH mRNA was prevented when FASN activity was inhibited.

CONCLUSION Increases in SHH mRNA expression levels are dependent on HIF1 stabilization and FASN activity. These result points to a potential mechanism connection between these proteins that could elucidate how the EMT is initiated.

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An early step in breast cancer progression is invasion of tumor cells into surrounding tissues. In many breast cancers, particularly ductal carcinomas, this invasion is accomplished by tumor cells migrating as a cohesive group. This often involves cells that take on heterogeneous roles as either leader or follower cells. While studies in common mouse and human breast cancer models have established that leader cells express high levels of keratin-14 (K14) and other basal epithelial markers, the molecular mechanisms regulating K14+ leader cell identity remain obscure. Here we performed time-sampled single cell RNA-sequencing in 3D type I collagen-embedded tumor organoids isolated from the MMTV-PyMT luminal B model of breast cancer. 11 distinct cellular transcriptional states were identified and correlated with K14 expression and invasive strand formation. Having identified the leader cell state we next asked what transcription factors were enriched, reasoning that transcription factors could be master regulators of leader cell fate. 30 different shRNAs targeting 10 genes were systematically evaluated for their effects on collective invasion. From this screen, suppression of Hes1, the downstream target of Notch signaling, yielded a marked switch from collective to single cell invasion. Disseminating single tumor cells maintained high expression of K14 in Hes1 knockdown organoids which was phenocopied by gamma-secretase inhibition in a human TNBC PDX model. Because K14+ tumor cells highly express the Notch ligand Jag1, these results support a model in which Notch signaling, specifically through activation of Hes1, dictates leader cell identity and spatial organization during collective invasion. Studies are ongoing investigating the impact of Hes1 dynamics on leader cell adhesion, hybrid EMT state, and preference for single versus collective metastasis. Because Notch suppression induces leader cell dissemination, we propose that Notch targeted therapy should be combined with therapies eradicating leader cells.

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Histopathological and immune characterization of liver metastases from patients with breast cancer

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Background: Liver metastases (LM) are ultimately present in ~50% of all patients with metastatic breast cancer (BC). Metastatic seeding to the liver relies on the interaction between cancer cells and the host microenvironment, resulting into two main histopathological growth patterns (HGPs): the replacement HGP (metastasis mimics the liver architecture and exploits liver vasculature) and the desmoplastic HGP (presence of a fibrotic rim separating the hepatocytes from the tumor cells). While the prognostic value of these HGPs is established for colorectal cancer, with the desmoplastic HGP being associated with better prognosis, investigation is needed for BC. It has also been reported that patients with LM have a poorer response to immune checkpoints inhibitors. A systematic evaluation of the HGP and LM-associated immune infiltrates (stromal tumor infiltrating lymphocytes, sTIL) is currently lacking. In this study, we aimed at: (i) investigating HGPs and sTIL in LM from patients with BC, and, (ii) evaluating the association of these HGPs and sTIL with standard variables and outcome.

Patients and methods: The study currently includes clinical data and samples from: 1) a retrospective cohort of 122 patients from 7 hospitals with surgically resected LMs (represented by 548 hematoxylin and eosin (H&E)-sections), further referred to as 'surgical cohort' and, 2) LMs from 2 institutional post-mortem tissue donation studies for a total of 23 patients (97 H&E-sections). All available H&E-sections were used to assess HGP and sTIL. HGPs were scored according to a standardized method (PMIDs: 35650276) and categorized per patient as pure-replacement (rHGP, i.e. 100% of the tumor-liver interface is replacement) or any-desmoplastic (dHGP, i.e. at least 1% of the tumor-liver interface is desmoplastic). sTIL are expressed as the percentage of stromal area covered by mononuclear immune cells at the metastasis-liver interface. Associations were assessed using Fisher exact and Wilcoxon tests. Univariable and multivariable Cox regression analyses stratified by center were used to evaluate the role of HGP on progression-free (PFS) and overall survival (OS).

Results: In the surgical cohort, 54 (44%) of patients displayed a rHGP and 68 (56%) a dHGP. Intra-patient, meaning inter-slide, heterogeneity of the HGP was observed in 24/122 (20%) of the patients suggesting that scoring multiple slides is needed for accurate assessment of the HGPs. We did not find any statistically significant association between HGP and clinico-pathological data. Higher sTIL were associated with dHGP (p=.003), as well as with a higher
histological grade (p=.087), estrogen receptor-positivity (p=0.062) and ductal histology (p=.08) of the primary tumor. rHGP was associated with worse PFS and OS, both at the univariable and multivariable level (Table).

In the post-mortem cohort, we observed a higher frequency of rHGP patients (19/23 patients, 83 %) and significantly lower levels of sTIL in the rHGP patients as compared to the rHGP patients from the surgical cohort (p=.009).

Conclusion: This study represents the largest study evaluating HGP and immune infiltrates of LMs from patients with BC. Approximately half of the surgically resected LMs have a dHGP, which is associated with higher sTIL and a better prognosis. The results from the LMs from the post-mortem cohort suggest that a more advanced stage of the disease is associated with an increase in rHGP and with a more immunosuppressed environment.

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<td>Time between BC and LM diagnosis (&gt;1year vs ≤1year)</td>
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Univariable and multivariable analyses

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Breast cancer is the leading cause of cancer death in women worldwide. Among the different subtypes of this disease, HER2-positive breast cancer is known to be one of the most aggressive and is linked to poor prognosis. This subtype is prone to develop metastases, reflecting a significant cellular plasticity. While the molecular machinery controlling actin dynamics is well implicated in cell invasion, the contribution of the microtubules is ill-defined.

We recently conducted a functional screen to identify such regulators, and characterized ACF7, a microtubule plus-end binding protein (+TIP), as a new promoter of invasion. Here, we aim to determine the in vivo contribution of ACF7 to tumor progression and to reveal the cellular and molecular mechanisms allowing this +TIP to promote metastasis. We analyzed the expression of ACF7 at the protein level across a panel of tumor microarrays and found that it is detectable in all breast cancer subtypes with the highest levels seen in HER2-positive. To study the role of ACF7 during tumor progression, we generated an ACF7 genetically engineered mouse model of breast cancer. We exploited a HER2-positive breast cancer mouse model (MMTV-NIC) that we bred with ACF7Flox mice. This approach allows for conditional deletion of ACF7 in mammary glands and represents a powerful model to define the roles of ACF7 in HER2-driven breast cancer. Our results show that ACF7 is not involved in tumor initiation and tumor growth as no difference between number of nodules per mouse, tumor mass or number of mammary intraepithelial neoplastic lesions was shown. However, our results show a significant decrease in lung metastasis in the ACF7cKO mice. To gain mechanistic insights into the roles of ACF7 in this specific process, we derived primary cell lines from tumors isolated from MMTV-NIC-ACF7WT and MMTV-NIC-ACF7cKO mice. We explored if ACF7 contributes to migration and invasion in a HER2 context. By using live-cell imaging, we demonstrated that ACF7-null cells display defects in both random and directed cell migration, as they show a delay in wound closure. We determined that ACF7KO cells show an increase in focal adhesions size, and exhibit defects in reorienting their actin and microtubules cytoskeletons parallel to the direction of migration. ACF7 was also found to promote cell invasion since ACF7KO cells were less efficient to cross a Matrigel membrane. To investigate the metastatic potential of ACF7-null tumors, we performed RNA-sequencing using RNA isolated from MMTV-NIC-ACF7WT and MMTV-NIC-ACF7cKO tumors. We identified a striking change in expression of genes involved in epithelial to mesenchymal transition (EMT), such as for example E-cadherin, Vimentin or the transcription factor Twist. These results suggest that ACF7 promotes metastasis through maintaining an EMT state in HER2 breast cancer cells. Collectively, our work demonstrates ACF7 as an important player in HER2 positive breast cancer progression via its functions in both cell migration and cell invasion. This works also suggests that developing approaches to
therapeutically target regulators of microtubule dynamics may reveal new opportunities to
decrease tumor progression and metastatic expansion.

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Epithelial/stromal cross talks that induce malignant transition of human ductal carcinoma in situ.

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Background: A large fraction of human DCIS (>50%) may not need the multimodality treatment options currently offered to all patients. More importantly, while we may be overtreating many, we cannot identify those most at risk for invasion/metastasis. Revealing the cellular and molecular mechanisms by which some DCIS remain indolent while others advance to invasive and metastatic breast cancers is currently a clinical unmet need. Methods: To address this gap, we developed the Mouse-INtraDuctal (MIND) model, by which patient-derived (PDX) DCIS epithelial cells are injected intraductally and allowed to progress naturally in mice. Single cell RNA-sequencing (scRNA-seq) was utilized to profile the DCIS epithelial and stroma cells in progressors vs. non-progressors. To distinguish between stromal (diploid) cells and tumor (aneuploid) cells, we calculated Copy Number Aberration (CNA) profiles from RNA using CopyKAT. Cell-type specific differential gene expression analysis of DCIS epithelial cells and microenvironment cell types in progressors and non-progressors was performed. We also predicted putative ligand:receptor interactions between the tumor cells and cell types in the microenvironment by CellPhoneDB. Results: Among 37 PDX DCIS MIND models followed for a
median of 9 months, 20 (54%) grafted into 95 glands, showed in vivo invasive progression (progressed) while 17 (46%), injected into 107 glands, remained non-invasive (non-progressed). ScRNA-seq was performed on 13 DCIS samples including 10 progressors and 3 non-progressors. Aneuploid cells were further analyzed to identify deferentially expressed genes that were upregulated in progressors compared to non-progressors (log2 fold=1, FDR p< 0.05). Notable genes included NEAT1, EIF4EBP1, SCGB2A2, TFF1 and TFF3 that were upregulated in the progressors. NEAT1, the core structural component of the paraspeckles, is frequently overexpressed in human cancers and its expression is correlated with worse survival in cancer patients. NEAT1 drives tumor progression by regulating genes involved in cellular growth, migration, invasion, metastasis, EMT, stemness, radio- and chemo-resistance, supporting its role as a potential biomarker and therapeutic target. TFF1/TFF3 mRNAs show increased expression in metastatic breast cancers. EIF4EBP1 is located on chrom 8p11-p12 which is frequently amplified in breast cancer and is associated with poor clinical prognosis. Further analysis using Cancer Hallmarks identified mitotic spindle, interferon signaling, DNA repair, oxidative phosphorylation and P53 pathway among the top signatures that were upregulated in the progressors. CellPhoneDB identified expression of several receptor/ligand interactions including CD74/MIF involved in epithelial/stromal and stromal/stromal cross talks that may play a role in DCIS invasive progression. Conclusions: Future studies will validate our findings using patient DCIS samples with known long-term outcome and in vivo MIND models to further refine risk associated biomarkers for invasion/metastasis and to identify more effective treatments.

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Non-canonical Wnt/Ror2 signaling regulates tumor cell invasion and dissemination in breast cancer through cell-matrix crosstalk

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BACKGROUND: Metastasis is the main cause of mortality for breast cancer patients. The early steps of cancer metastasis require that tumor cells actively invade and disseminate from the primary tumor to distant organs. Cell-extracellular matrix (ECM) interactions represent fundamental interactions during tumor invasion and metastasis, yet how particular signal-transduction factors prompt the conversion of tumor cells into migratory populations capable of systemic dissemination remains elusive. OBJECTIVES: Wnt signaling is a known regulator of cell fate, migration, and polarity during various key biological processes. We previously discovered an inverse correlation between the canonical Wnt signature and a non-canonical Wnt receptor, Ror2, across breast cancers in TCGA. The objective of this study is to investigate how canonical and non-canonical Wnt signaling orchestrate tumor cell behavior during cancer invasion and metastasis. METHODS: We used clinically relevant syngeneic TP53-null Genetically Engineered Mouse Model (GEMM) tumors that molecularly reflect the different breast cancer intrinsic subtypes. In vivo transplantation of GEMM models and in vitro 3D tumor organoids were employed to elucidate the molecular mechanism underlying the migration, invasion, and metastasis of tumor cells upon genetic perturbation of Wnt/Ror2 signaling. RESULTS/DISCUSSION: From 3-dimensional (3D) tumor organoid models, we identified novel transcriptional alterations encompassing cell-cell adhesion, cytoskeletal remodeling, and ECM organization upon Ror2 loss. At protein levels, we discovered a significant increase in collagen fibril organization and integrin-α5 and integrin-β3 expression following Ror2 depletion. In addition, the matrisomal protein fibronectin (FN) was concomitantly upregulated and assembled in Ror2-deficient tumor cells at sites of invasion. Consequently, we observed FAK activation
and actin cytoskeleton alterations in Ror2-deficient tumor cells, leading to a promigratory tumor cell behavior. The altered cytoskeleton and cell-ECM interaction enhanced the rigidity of the Ror2-depleted cells. Furthermore, Inhibition of either integrin or FAK activation abrogated the increased invasion driven by Ror2-loss. Unexpectedly, these changes were distinct from processes regulated by Wnt/β-catenin activation. From both spontaneous metastasis and experimental metastasis models, we discovered a shift from canonical to non-canonical Wnt signaling throughout the progression of lung metastasis, indicating that the balance of Wnt signaling may serve as a switch to dictate cell functions at different stages of metastatic development. Consistently, we found enhanced initial colonization in the lungs when Ror2 is depleted in these breast cancer cells. Together, these studies provide new insight into how canonical and alternative Wnt pathways coordinate cell-cell and cell-ECM exchanges during breast cancer progression and metastasis. Supported by grant NIH-CA016303

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While early detection of breast cancer (BC) has improved prognoses, there is an urgent need to improve outcomes for patients with distant metastatic disease. Higher expression of the Notch ligand JAG1 in primary BC tumors is strongly associated with lymph node metastasis and patient mortality, but causality is unclear. We show that JAG1 expression is higher in patients' metastatic BC cells colonizing lymph nodes than in primary tumors, suggesting that tumor cells with high JAG1 are preferentially able to metastasize to lymph nodes. JAG1 expression is higher in a derivative of BC line MDA-MB-231 selected for tropism to lymph nodes (MDA231-LN) than in the parental line or derivatives with other tropisms. To determine the mechanism(s) of JAG1-mediated metastasis, we generated clonal JAG1 knockout cell lines from MDA231-LN cells with corresponding JAG1 rescue lines. We investigated the role of JAG1 in spontaneous metastasis under clinically relevant conditions by orthotopically implanting JAG1 knockout and expressing cells, resecting the primary tumor, and following long-term metastatic spread in a mouse model. Quantification of tumor cells in blood showed that survival, metastatic burden, and JAG1 expression did not correlate with the number of circulating tumor cells. Conversely, JAG1 expression drove an increase in lymph node and body-wide metastatic burden and a trend toward decreased survival. In this model metastatic cells were abundant throughout lymph vessels, suggesting lymphatics are the primarily route of dissemination. Preliminary transcriptional analysis suggests that JAG1 alters interactions with lymphatic endothelial cells (LEC), potentially via VEGF signaling, leading us to examine downstream events in co-cultures of LEC with lymphatically invasive BC lines. Deciphering tumor-lymphatic endothelial signaling events may open new avenues to target BC metastasis.

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Exosome-mediated Circ-CRSP1 promotes tumor proliferation and metastasis through stabilizing ELAVL1 protein and suppresses anti-tumor immune response in regulating the progression of Triple-Negative Breast Cancer.

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Background: Triple-negative breast cancer (TNBC) is one of the most malignant subtype of breast cancer. Lacking targetable molecular drivers, chemotherapy is almost the only effective systematic treatment for TNBC. Compared with other types of breast cancer, TNBC shows a higher long-term recurrence rate and worse prognostic outcome, and its main cause of death is tumor metastasis. Therefore, there is an urgent clinical need to explore underlying molecular mechanisms and find novel targets for therapeutic intervention, as well as biomarkers for early clinical diagnosis.

Materials & Methods: To explore the signal pathways and target molecules related to tumor immunity by bioinformatics analysis of tissue samples [TNBC (n = 55), Her2 (n = 39), Luminal B (n = 30), Luminal A (n = 29), healthy (n = 11)]. Co-culture experiment was conducted to study the effect of TNBC-derived exosome-mediated molecules on the proliferation and migration of breast cancer. qRT-PCR assay was used to confirm the expression level of Circ-CRSP1 in tumor tissues, breast cancer cells, exosome derived from TNBC cells and serum exosomes of breast cancer patients. Overexpression and knockout experiments investigated the role of Circ-CRSP1 in promoting the proliferation and migration of TNBC cells. Protein molecular docking technique was used to predict the possible targeting binding protein ELAVL1, and molecular experiments and nude mice model were used to study the mechanism of Circ-CRSP1-ELAVL1 complex in tumor immunity.

Results: TNBC-derived exosome-mediated molecular transmission promotes the proliferation and migration of breast cancer, and may promote distant metastasis of breast cancer by changing the tumor microenvironment (TME) before metastasis. Bioinformatics analysis of TNBC tumor samples confirmed that TNBC is strongly associated with tumor immune-related biological processes and signal pathways. Circ-CRSP1 is highly expressed in TNBC tumor tissues, TNBC cells, exosome derived from TNBC cells and serum exosomes of TNBC patients, and is related to the poor clinical prognosis of TNBC patients. Overexpression of Circ-CRSP1 enhanced the proliferation and migration ability of TNBC cells, and the expression levels of EMT and cell-cycle related genes altered. Circ-CRSP1 binds to protein ELAVL1 at the physical level. The target gene of Circ-CRSP1-ELAVL1 complex is involved in the immune response, and the overexpression of Circ-CRSP1 significantly down-regulates the expression level of immune-related genes. Conclusion: Exosome-mediated Circ-CRSP1 promotes the transport of ELAVL1 from nucleus to cytoplasm through targeted binding with ELAVL1, and then regulates cytoplasmic proliferation and metastasis and inhibits the stability and translation of anti-tumor immune-related gene mRNA, thus finally promotes the proliferation, invasion and metastasis of TNBC. This study can further understand the mechanism of circRNA in the growth and metastasis of TNBC from the theoretical level, further explore the feasibility of Circ-CRSP1 as a molecular target for gene therapy, and provide theoretical basis and pre-clinical data for Circ-CRSP1 in serum exosomes as a high risk screening index and prognostic marker for TNBC patients.
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Evaluation of changes in sequencing quality and transcriptomic profiles with increasing post-mortem interval: results from an optimization experiment within the UPTIDER tissue donation program

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Background. Postmortem tissue donation programs can importantly enhance sample access for translational research on metastatic disease. However, this post-mortem setting poses logistical and technical challenges in terms of preserving nucleic acid quality and in particular RNA. Here we present the results of an experiment within our breast cancer tissue donation program UPTIDER (NCT04531696), aiming at assessing RNA degradation rates and expression profile changes in function of tissue type and sample-specific postmortem interval (ssPMI). Patients & Methods. For 7 patients, bulk RNA sequencing was performed using the Lexogen protocol on fresh frozen samples from healthy or tumour tissues taken repeatedly (at 1.5h time intervals) during the autopsy. ssPMI was defined as the time between the death of the patient and the freezing of the sample. Quality threshold was set at 0.5 million (M) of assigned reads (AR). Other quality metrics included number of expressed genes, evolution of proliferation-, hypoxia-, stromal- and immune-related transcriptional signatures (PMID:18698033, 20087356) with increasing ssPMI. Associations between quality metrics and ssPMI were assessed by linear regressions for longitudinal data, with quality metrics as dependent variable, time as independent variable and accounting for the clustering of the data by patient and organ using the generalized estimating equation method. Three nested models - with constant, linear and non-linear relationship - were compared using ANOVA testing strategy. Non-linearity was rendered by a restrict cubic spline with three knots. All tests were performed by the Wald test on regression coefficients. Results. Ninety samples (67 healthy, 23 tumour) were analyzed. Median ssPMI was 7.50 hours (range: 3.07-11.12). Most (87%) samples passed quality thresholds, with median AR being 1.70M (interquartile range: [0.70M-3.57M]). No association was found between quality metrics and time in healthy samples. In tumor samples, regarding sequencing quality, negative associations with increasing time were found for AR and for number of expressed genes with an average decay of 242308 reads per hour (95 confidence interval (95CI): [94415.62-390200.50], p-value=.001) and 251 genes per hour (95CI: [17.30-485], p-value=.035), respectively. At the transcriptomic level, potential subtle changes were observed regarding immune (e.g. STAT1 signature: -0.02, 95CI [-0.05;0.00]) and hypoxia-related signatures (e.g. PGAM1 signature: -0.03, 95CI [-0.05;-0.01]), while no effect of time was seen for the proliferation and stromal-related signatures. Sample size precluded organ specific analyses. Conclusion. A decrease in the number of AR and number of expressed genes with increasing ssPMI was found in tumor samples leading to subtle changes in few transcriptional programs. Healthy samples showed stable quality metrics over time possibly explained by a lower cell activity in healthy as compared to tumour cells. Knowledge derived from this study will be integrated in the upcoming transcriptomic analyses of the samples collected within UPTIDER.

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Association of baseline tumor-infiltrating lymphocytes and cell-cycle regulation markers on prognosis and mortality in patients with advanced breast cancer according to tumor characteristics and treatment type

We aimed to analyze the expression of cell-cycle regulation markers – minichromosome maintenance protein 2 (MCM2), Ki-67, Cyclin-A and phosphohistone-H3 (PHH3) and tumor-infiltrating lymphocytes (TILs) in pre-treatment core-biopsy samples of advanced breast carcinomas (ABC) in correlation with known predictive and prognostic factors. Consecutive breast cancer patients (n=398) treated during 2015-2019 were retrospectively analyzed. ABC was defined either as the first indication for locally recurrent, locally advanced or metastatic disease. TIL levels were evaluated of invasive tumor samples, and high expression was defined as TILs >15%. Immunohistochemistry was performed to analyze the expression of MCM2, Ki-67, Cyclin A and PHH3, which were correlated with the following clinicopathological parameters: clinical TNM, tumor grade, biological subtype, TILs, treatment type (chemotherapy-containing or non-chemotherapy). Univariate and multivariate analyses were used to assess factors associated with disease-free survival (DFS) and overall survival (OS). The multivariate analysis showed that patients with higher TIL levels had an improved 3-year DFS compared with those with low TIL levels, (79.5% vs. 63.7%, HR = 0.52, 95% CI = 0.32–0.78, p = 0.005), which may imply using the biomarkers to indicate initial treatment selection at the advanced stage. The effect was the most pronounced for triple-negative breast cancer (TNBC), and higher for HER2+ than hormone receptor positive breast cancer (HR+). Hormone receptor negative tumors showed significantly higher expression of the studied cell-cycle regulation markers Ki-67, MCM2 and Cyclin A compared with HR+ breast cancer, with TNBC showing the highest activity. Ki-67 and MCM2 were significantly associated with worse prognosis in HR+ breast cancer (p = 0.03; p = 0.04). Treatment type (chemotherapy vs. non-chemotherapy) as the initial treatment at the advanced stage influenced the 3-year DFS and OS in patients with high TIL levels in all molecular breast cancer subtypes. For those with low levels of TILs the difference was statistically non-significant. Our study showed that TIL and cell cycle marker testing could help to identify patients with more aggressive tumor types and the requirement of more aggressive treatment upfront. The proposed biomarker testing can help in selecting the appropriate treatment for increased disease-free survival.
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Advancing research on metastatic breast cancer: the UPTIDER post-mortem tissue donation program

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Background. Research in metastatic breast cancer is hampered by limited sample availability. Post-mortem tissue donation programs can help to overcome this problem but are logistically challenging and have thus far mainly focused on histopathological and genomic research. We here present the UPTIDER program (NCT04531696), aimed at the multilevel characterization of advanced breast cancer and generation of tumour models. Patients and Methods. Patients with stage IV breast cancer receiving their last line(s) of treatment are eligible for participation. Blood, urine and saliva samples are collected upon inclusion. Upon death, a post-mortem MRI (when possible) followed by a rapid autopsy is performed. Liquid biopsies from all body fluids and tissue samples from all macroscopically identified metastatic sites are collected. Samples are processed as mirrored biopsies in different conditions, such as fresh frozen for omics analyses, formalin fixed paraffin-embedded for histopathology, and slowly frozen in freezing medium or fresh for generation of xenograft and organoid models. Results. Since approval by the local Ethical Committee in November 2020, 22 patients have been enrolled and 15 autopsies have been performed. Mean interval between death and start of autopsy was 3h (range 2-6h), mean duration of the autopsies was 6h (4-9h). A post-mortem MRI was performed in 6 patients. Peripheral blood, central blood and bone marrow were collected from all patients; urine, ascites, cerebrospinal, pericardial and pleural fluid all in more than 2/3 of patients. On average, 232 (range 90-406) tissue samples of which 164 (45-303) pathological from 42 (15 – 79) metastases were collected for each patient. Most often sampled metastatic sites were lymph nodes, liver, bones, pleura and peritoneum. Samples from the primary tumour could be retrieved from all patients, either during the autopsy (n=6) or from historical archives. In total, 133 tumour samples were sent to collaborating partners for patient-derived xenograft creation. Already some have been successfully established and stored, including models derived from a patient with invasive lobular carcinoma (ILC) and one with metaplastic squamous cell carcinoma. When correlating microscopic and macroscopic findings, patients could largely be divided into three main categories. Eleven patients presented with overt and extensive disease burden, often characterized by diffuse visceral, pleural, peritoneal, bone and lymph node involvement. Two patients, both with ILC, presented with underestimated yet extensive disease burden.
burden. While gross examination and cross sectioning of organs did not reveal clear involvement, microscopical invasion of stomach and liver, amongst others, was found. Lastly, limited disease burden was seen in two patients, both with leptomeningeal involvement. In those patients, massive tumoral infiltration in the subarachnoid space and along the blood-brain barrier was seen microscopically, with no grey matter invasion. Conclusion. We successfully launched a new and comprehensive post-mortem tissue donation program for patients with metastatic breast cancer, enrolling ~ 1 patient per month. Post-mortem tumour samples already resulted in successful establishment of some patient-derived xenografts. From a clinical point of view, vast underestimation of the disease extent on imaging during life as well as macroscopically during the autopsy was observed in some patients with metastatic ILC. For patients with leptomeningeal metastasis, we showed that the highly aggressive nature of their disease might be explained by extensive meningeval infiltration disrupting the blood-brain barrier. Further insights into disease progression and heterogeneity will be generated by the ongoing multi-omics analyses.

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PD-L1 expression regulated by JAK/STAT signaling pathway contributes to cell migration and invasion in breast cancer

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Background: Programmed death-ligand 1 (PD-L1) implicated in tumor immune evasion and predictive biomarker in immunotherapy is widely recognized, however, the role of PD-L1 in modulating tumor invasion remains largely unexplored. PD-L1 expression on tumor tissue is usually limited by the invasiveness, tumor heterogeneity as well as insufficient tumor tissue samples, while PD-L1 expression on circulating tumor cells (CTCs) might overcome the limitation. In the present study, we aimed to investigate the role and mechanism of PD-L1 in regulating the migration and invasion of breast cancer cells and to evaluate PD-L1 expression on CTCs in metastatic breast cancer patients. Methods: The expression level of PD-L1 in MCF-7 cells and MDA-MB-231 cells was assessed by quantitative real-time RT-PCR and Western Blot. Gain-of-function and loss-of-function study on cell migration and invasion abilities were carried out by overexpression of PD-L1 or silencing PD-L1. PD-L1 expression on CTCs in thirty-six metastatic breast cancer patients were detected. A novel staining procedure which included fluorescent glucose analog staining for CTC enumeration and immunostaining targeting CD45, vimentin and PD-L1 were analyzed. Survival curves were estimated by the Kaplan-Meier method and the log-rank test was used to compare between groups. All tests were two-sided, and p values were considered significant at the 0.05 level. Results: Compared with MCF-7 cells, PD-L1 mRNA and PD-L1 protein expression were significantly increased in MDA-MB-231 cells. Down-regulation of PD-L1 expression in MDA-MB-231 cells inhibited the migration and invasion of MDA-MB-231 cells, while overexpression of PD-L1 in MCF-7 cells increased the migration and invasion of MCF-7 cells. In addition, we found that PD-L1 expression was regulated by JAK/STAT signaling pathway. PD-L1 expression on CTCs in metastatic breast cancer patients was associated with triple negative breast cancers subtype (P=0.013). High expression of PD-L1 on CTCs in metastatic breast cancer patients was correlated to poor overall survival (HR=3.165, 95%CI: 1.121-8.938, P=0.029). Conclusion: Our results indicate that high expression of PD-L1 contributes to cell migration and invasion in breast cancer cell possibly partially through JAK/STAT signaling pathway. The PD-L1 expression on CTCs might serve as a promising non-invasive prognostic biomarker in patients with metastatic breast cancer.

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Introduction. Claudin-9 (CLDN9), a member of the claudin protein family, is thought to play a role in the control of tight junctions (TJ) in various cell types. CLDN9 protein needs intracellular subcoat proteins, primarily the Zonula Occluden (ZO)-1 and ZO-3 to anchor to the cytoskeleton in order to form TJ with other proteins, including occludin. In the body, CLDN9 is highly expressed in endocrine tissues but is relatively low in mammary tissues. The role of CLDN9 is not well understood in cancer. In the present study, we have for the first time examined the pattern of CLDN9 expression at protein and transcript levels in breast cancer and explored its clinical and therapeutic implications. Methods. CLDN9 protein and CLDN9 transcript in fresh frozen human mammary tissues were evaluated by immunohistochemistry and quantitative transcript analyses and, together with the ZO family members and occludin in our database, correlated with clinical indicators. Assessment of expression in a range of cell lines was also determined. The levels of CLDN9 transcript, was also assessed against the therapeutic responses of the patients to chemotherapies by using a dataset from TCGA database. Results. Breast tumour tissues had high levels of CLDN9 transcript in tumours versus normal tissues. However, high grade breast tumours had significantly lower levels than low grade (p=0.02 and p=0.003, grade-2 and 3 vs grade-1 respectively). Patients with metastasis also had significantly lower levels than those without (p=0.0075). Patients who died of breast cancer had higher levels of the transcript than those who survived, although this was not significant. CLDN9 expression was significantly correlated with ZO-1 (r=0.20, p< 0.001) and ZO-3 (r=0.179, p< 0.01), but not ZO-2 in our cohort. There was significant correlation with another key TJ molecule, occludin (r=0.236, p=0.11). CLDN9, together with ZO-1 and ZO-3 significantly linked to the survival of patients (144 : 4.6 months for the low expressing group versus 113 : 8.2 months for the high expression group, p=0.013). The expression profile of the CLDN9/ZO1/ZO3 complex also indicated potential as an independent prognostic indicator (p=0.004, HR=2.033). The prognostic value was highly applicable to non-triple negative breast cancer patients. CLDN9 transcript also appeared to have a significant impact on treatment responses; patients...
who were sensitive to chemotherapies had a significantly lower levels of CLDN9 transcript than those who were resistant to treatment (p< 0.000001). In human cell lines, expression levels of CLDN-9 in ER (+) breast cancer cell lines, MDAMB361, MCF7 and BT474 were high; in a ER(-) breast cancer cell line MDAMB231, the expression level of CLDN-9 was lower. Conclusion. In conclusion, CLDN9 expression was differentially expressed in human breast cancer cells lines and appeared to reflect changes in ER status. It was apparent from levels of CLDN9 in a breast cancer cohort that expression was associated with grade and metastatic disease. Of significant notice was the finding that expression of CLDN9 in an expression profile with ZO1 and ZO3 has potential as a prognostic indicator, particularly in non-triple negative patients and in those who are chemotherapy resistant.

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Eleri Davies, n/a: No financial relationships to disclose
Bing Xu, n/a: No financial relationships to disclose
Tracey A. Martin, n/a: No financial relationships to disclose
Endomucins and their expression in breast cancer and the cellular and therapeutic impact

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Introduction. Endomucin-1 and endomucin-2 are two proteins structurally related, yet with low homology. The membrane bound sialoglycoproteins appear to play a key role in interfering with the formation of focal adhesion complexes (FAC) and matrix adhesiveness of cells, by mechanisms independent of the MUC1 repeat, which the endomucins do not possess. Endomucins are thought to be expressed at high levels in endothelium and haematopoietic cell lineages, although the levels in mammary tissues also seem high. Despite the seeming importance of endomucins in the adhesion and migration of cells, including cancer cells, the clinical value of endomucin in clinical cancer, including breast cancer, is largely unknown. The present study examined the expression profile of endomucins, together with the focal adhesion kinase FAK, in breast cancer and aimed to explore the cellular impact of endomucin on cancer cells. Methods. Human breast cancer cells MCF-7 and MDA MB-231 and a range of other cell types were used. An endomucin overexpression cell model was created and subsequently used to evaluate the function of the cells. The expression profile of the endomucin-1 and endomucin-2 transcripts and FAK, in an existing fresh frozen breast cancer tissue cohort, were quantified. Results. High levels of endomucins, particularly endomucin-1, are good indicators for the overall survival of the patient, p=0.021 for endomucin-1 and p=0.15 for endomucin-2. When expression levels of FAK were integrated into the survival analysis model, patients with high levels of both endomucins and low levels of FAK had the most favourable outcome, compared with those with most unfavourable outcome who had low level of endomucin and high FAK (survival during the follow up period respectively at 100% and 54%, p=0.013, Harzoud Ratio 0.298). Together with the Nottingham Prognostic Index, which independently predicts a poor
outcome (p=0.009, HR=7.6), the integrated expression profile of endomucin/FAK represents an
independent prognostic indicator for favourable overall survival (p=0.003, HR=0.13), and
indeed for a favourable disease free survival (p=0.008, HR=0.17). Mammary tissues, and
indeed breast cancer cell lines, expressed high levels of endomucin-2 transcripts and low levels
of endomucin-1 transcripts. High levels of endomucin-2 were also seen in fibroblasts and
vascular endothelial cells. We created a breast cancer cell submodel with MCF-7, by
overexpressing endomucin. It was shown that although endomucin over-expression had some
marginal impact on the adhesiveness of breast cancer cells, the over-expression however, had
significant impact on cells’ sensitivity to FAK inhibitor, with a markedly reduced adhesiveness to
matrix (p<0.001 control versus endomucin overexpression cells). Discussion. Endomucins
have a reduced expression in breast cancers and the reduction, together with low levels of focal
adhesion kinase, facilitate a favourable outcome for the patients. Together with the findings of
in vitro cell models, it would suggest that the expression profile of endomucins and FAK may be
a good indicator, not only for evaluating clinical outcomes, but also for choice of target
therapies.

Disclosure(s):
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Tracey A. Martin, n/a: No financial relationships to disclose
Lin Ye, n/a: No financial relationships to disclose
Andrew J. Sanders, n/a: No financial relationships to disclose
Fiona Ruge, Chief Technical Officer: No financial relationships to disclose
Jane Lane, n/a: No financial relationships to disclose
Eleri Davies, n/a: No financial relationships to disclose
Wen G. Jiang, n/a: No financial relationships to disclose
Effect of 3q oncogene SEC62 on migration and proliferation of triple-negative breast cancer cells

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Background Chromosome 3q26 amplifications represent a frequent alteration in various cancer entities including breast cancer. SEC62 – a 3q26 encoded gene – was identified as a potential onco- and tumor-driver gene for the pathogenesis of breast cancer. Although the precise physiological function of the respective protein Sec62 is not completely understood, Sec62 seems to induce an increased stress tolerance, enhanced cell migration and invasive potential in SEC62 overexpressing cells. SEC62 overexpressing breast cancer patients have been shown to have a higher rate of lymph node metastasis and poorer overall prognosis. Hence, we aimed to further evaluate the effect of Sec62 for triple-negative breast cancer by targeting cell migration and proliferation of triple-negative cell lines altered in their SEC62 expression.

Objectives The aim of this study was to investigate the role of Sec62 for triple-negative breast
cancer in cell culture using functional analyzes comparing cell migration and cell proliferation in triple-negative cell lines using the effects of siRNA-mediated Sec62 depletion in vitro. Material& Methods In this study, three SEC62 gene silencing experiments each with two different siRNAs directed against the SEC62 mRNA were carried out in comparison to a control siRNA in combination with cell proliferation and cell migration tests plus Western blots for the triple-negative breast cancer cell line CAL120 in order to determine the suspected causal relationship between SEC62- overexpression and an increased cell migration and thus an enhanced invasion potential of the cancer cells. The cell proliferation was examined in real time in the 96 well xCELLigence system and the cell migration using Fluoroblock without matrigel using fluorescence microscopy. Results In cell migration assays, the median migrated cell number in the control siRNA group was 263 (241-279), the cell number in the groups of the two siRNAs directed against the Sec62 mRNA was 72 (70-149) and 178 (96-276) (p < 0.01). In cell proliferation assays, the median cell index in the control siRNA group was 7.5 (7.4-7.6), while it was 7.4 (7.3-7.5) and 7.6 (7.5-7.7) (p=0.37). In the first analyzes of the medians of the three gene silencing experiments of the cell line CAL120, the expected negative effect of the SEC62-siRNA on cell migration is confirmed, while, as expected, the effect on cell proliferation remains unchanged with decreasing Sec62 content. Conclusion In this in vitro study using cell migration and cell proliferation assays we found a correlation between SEC62 overexpression and increased cell migration. This implies a potential association between Sec62 and an increased tumor cell invasion in triple-negative breast cancer.

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**Sven Lang, n/a:** No financial relationships to disclose
**Martin Jung, n/a:** No financial relationships to disclose
**Erich F Solomayer, n/a:** No financial relationships to disclose
**Julia C Radosa, n/a:** No financial relationships to disclose
12/9/2022
7:00 AM - 8:15 AM
Discussion 1 + Q&A: PD16-01 & PD16-02

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Jeri Francoeur, PA
12/9/2022
7:00 AM - 8:15 AM
Discussion 2 + Q&A: PD16-03, PD16-04, PD16-05 & PD16-06
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Jeri Francoeur, PA
Discussion 3 + Q&A: PD16-07 & PD16-08

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Country: United States
Jeri Francoeur, PA

Disclosure(s):

Aimilia Gastounioti, PhD: NIH / NCI: Contracted Research (Ongoing)
Poster Spotlight Discussion 16: Imaging to Diagnose Breast Cancer and Direct Its Treatment: Who, When, and How?

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  Country: United States
Introduction: The use of magnetic resonance imaging (MRI) prior to surgical treatment for breast cancer has greatly increased over the past decade. As MRI more accurately defines disease extent vs mammography and sonography, it is frequently utilized for staging women at elevated risk of occult disease due to young age, dense breast tissue, and/or lobular histology. However, it is not known whether women from different racial backgrounds and socioeconomic statuses have equal access to preoperative breast MRI. The goal of this study was to assess whether the use of preoperative breast MRI varies by race and insurance type.

Methods: We identified adult women who were diagnosed with Stage 0-III breast cancer within our mixed academic/community health system between 2016-2019 and were subsequently treated with surgical resection. We limited our analysis to non-Hispanic Black and non-Hispanic White women, as they comprised 93% of the eligible cohort. Patients who underwent breast MRI between their date of diagnosis and date of surgery were considered to have had a “preoperative MRI.” We used multivariable logistic regression to quantify the association between patient factors and receipt of preoperative MRI. Covariates included patient race, insurance type, age, year of diagnosis, clinical stage, histology, breast density, receptor subtype, and receipt of neoadjuvant systemic therapy.

Results: 1,268 women met inclusion criteria and had complete clinical information available for analysis. 362 (29%) were Black, and 906 (71%) were White. 718 (57%) had private insurance, 460 (36%) had Medicare, and 72 (6%) had Medicaid. Compared to White patients, a larger proportion of Black patients had Medicaid (15% vs. 2.0%), fatty or scattered density (i.e., level 1 or 2) breasts (69% vs 48%), and regional disease (26% vs 19%) (Table). Patients with Medicare had the highest proportion of fatty or scattered density breasts (67% vs private=46% vs Medicaid=56%), while patients with Medicaid had the highest proportion of regional disease.
(35% vs private=23% vs Medicare=15%).

The proportion of patients who received preoperative MRI was higher for White (49%) vs Black women (37%, p < 0.001). After adjustment, Black patients were 52% less likely to undergo preoperative MRI compared to White patients (OR 0.48, 95% CI 0.35-0.66, p < 0.001).

Compared to privately-insured patients, patients with Medicare had a similar likelihood of undergoing preoperative MRI (OR 0.81, 95% CI 0.54-1.22, p = 0.309), while patients with Medicaid may have had a lower likelihood of undergoing preoperative MRI (OR 0.55, 95% CI 0.30-1.00, p = 0.053).

Conclusions: Black patients with newly diagnosed breast cancer were less likely than White patients to undergo preoperative breast MRI, a disparity that persisted after controlling for insurance and clinical factors. Algorithmic use of preoperative MRI may mitigate provider- and system-level biases and promote more equitable resource utilization.

Characteristics of patients with non-metastatic breast cancer, diagnosed and treated at our institution (2016-2019)

Table. Characteristics of patients with non-metastatic breast cancer, diagnosed and treated at our institution (2016-2019).

<table>
<thead>
<tr>
<th></th>
<th>Black (n=362)</th>
<th>White (n=909)</th>
<th>All (n=1,260)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Mean age (SD)</strong></td>
<td>61.2 (12.8)</td>
<td>60.9 (12.9)</td>
<td>61.0 (12.9)</td>
<td>0.756</td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Private</td>
<td>182 (50)</td>
<td>556 (59)</td>
<td>738 (57)</td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>119 (33)</td>
<td>341 (35)</td>
<td>460 (35)</td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>54 (15)</td>
<td>18 (2)</td>
<td>72 (6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (2)</td>
<td>11 (1)</td>
<td>18 (1)</td>
<td></td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.389</td>
</tr>
<tr>
<td>Invasive ductal</td>
<td>211 (56)</td>
<td>504 (55)</td>
<td>715 (56)</td>
<td></td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>73 (20)</td>
<td>235 (26)</td>
<td>308 (24)</td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>57 (16)</td>
<td>111 (12)</td>
<td>168 (13)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21 (6)</td>
<td>56 (6)</td>
<td>77 (6)</td>
<td></td>
</tr>
<tr>
<td><strong>Receptor Status</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HER2+ / HER2-</td>
<td>95 (26)</td>
<td>277 (31)</td>
<td>372 (30)</td>
<td></td>
</tr>
<tr>
<td>HER2+ / HER2-</td>
<td>30 (8)</td>
<td>59 (6)</td>
<td>90 (6)</td>
<td></td>
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<tr>
<td><strong>Clinical Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>104 (29)</td>
<td>220 (24)</td>
<td>324 (26)</td>
<td>0.004</td>
</tr>
<tr>
<td>I</td>
<td>164 (45)</td>
<td>518 (57)</td>
<td>682 (54)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>72 (20)</td>
<td>143 (16)</td>
<td>215 (17)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22 (6)</td>
<td>25 (3)</td>
<td>47 (4)</td>
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<tr>
<td><strong>Breast Density</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 - microcalcida</td>
<td>24 (7)</td>
<td>42 (5)</td>
<td>66 (5)</td>
<td></td>
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<tr>
<td>2 - scattered</td>
<td>224 (62)</td>
<td>393 (43)</td>
<td>617 (45)</td>
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<td>3 - heterogeneous</td>
<td>101 (26)</td>
<td>394 (44)</td>
<td>496 (39)</td>
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</tr>
<tr>
<td>4 - extremely</td>
<td>13 (4)</td>
<td>77 (9)</td>
<td>90 (7)</td>
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<td><strong>Neoadjuvant Systemic Therapy</strong></td>
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<tr>
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<td>48 (13)</td>
<td>87 (10)</td>
<td>135 (11)</td>
<td></td>
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<tr>
<td>No</td>
<td>316 (87)</td>
<td>819 (90)</td>
<td>1135 (90)</td>
<td></td>
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<tr>
<td><strong>Preoperative MRI</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>133 (37)</td>
<td>445 (49)</td>
<td>578 (46)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>229 (63)</td>
<td>462 (51)</td>
<td>690 (54)</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>255 (70)</td>
<td>552 (61)</td>
<td>807 (64)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>107 (30)</td>
<td>354 (39)</td>
<td>461 (36)</td>
<td></td>
</tr>
</tbody>
</table>

*Biomarker data for 2019 cohort is pending

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Sara P. Ginzberg, MD: No financial relationships to disclose
Connor B. Grady, MPH: No financial relationships to disclose
Oluwadamilola (Lola) Fayanju, MD, MA, MPH, FACS: No financial relationships to disclose
Christine E. Edmonds, MD: No financial relationships to disclose
Introduction: Digital breast tomosynthesis (DBT) is increasingly utilized in breast cancer screening, including among women at high risk for breast cancer. While there is a lack of rigorous data from randomized controlled trials demonstrating superior efficacy compared to two-dimensional (2D) digital mammography, observational studies suggest that DBT might have lower rates of false-positive results and increased detection of invasive cancer than 2D mammography. However, uptake of DBT might be lower among racial/ethnic minorities, which could contribute to breast cancer disparities. We evaluated whether sociodemographic and breast cancer risk factors were associated with receipt of DBT vs. 2D mammography among a racially/ethnically diverse population of women undergoing screening mammography.

Methods: We conducted a respective cohort study among women, age 40-74 years, who underwent screening mammography at Columbia University Irving Medical Center (CUIMC) in New York, NY, from February 2020 to January 2022. We extracted data from the electronic health record (EHR) on age, race/ethnicity, first-degree family history of breast cancer (yes/no), prior breast biopsies (yes/no), and mammographic breast density (high vs. low), and calculated individual 5-year risks of invasive breast cancer according to the Breast Cancer Surveillance Consortium (BCSC) model. High risk was defined as a 5-year invasive breast cancer risk ≥ 1.67%. Our primary outcome was receipt of at least one DBT screening examination from 2020-2022 (yes/no). We conducted multivariable logistic regression analyses to assess the association between demographic/clinical factors and receipt of DBT.

Results: Among 5617 evaluable women, mean age was 55.4 years (SD, 9.5 years) and 56%
identified as non-Hispanic White, 10% as non-Hispanic Black, 17% as Hispanic, 8% as Asian, and 9% other/unknown. Over 60% of women had high breast density, and 34% met high-risk criteria. Seventy percent of women had at least one DBT from 2020-2022. In multivariable analyses (Table 1), women with high vs. low breast density were 2.5 times more likely to receive DBT (odds ratio [OR]=2.51, 95% confidence interval [CI]=2.19-2.88), while first-degree family history of breast cancer, prior breast biopsy, and age were inversely associated with DBT. Racial/ethnic minorities were less than half as likely to undergo DBT compared to non-Hispanic Whites; for example, Hispanic women were over 85% less likely to receive DBT (OR=0.14, 95% CI=0.11-0.16). Overall, there was no association between breast cancer risk status (high vs. low/average) and receipt of DBT (OR=1.00, 95% CI 0.92-1.08).

Conclusion: We observed that the majority of women undergoing screening mammography at CUIMC from 2020-2022 received DBT for breast cancer screening. However, racial/ethnic minorities, including non-Hispanic Blacks and Hispanics, were significantly less likely than non-Hispanic Whites to have received DBT. Breast cancer risk according the BCSC model was also not associated with receipt of DBT. Future studies should determine which subsets of women are more likely to benefit from DBT.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>Reference</td>
<td></td>
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<tr>
<td>50-59</td>
<td>0.86</td>
<td>0.73, 1.02</td>
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</tr>
<tr>
<td>60-69</td>
<td>0.80</td>
<td>0.67, 0.95</td>
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<tr>
<td>70-74</td>
<td>0.54</td>
<td>0.43, 0.69</td>
<td>&lt;0.001</td>
</tr>
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<td>Race/Ethnicity</td>
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<tr>
<td>Non-Hispanic White</td>
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<tr>
<td>Non-Hispanic Black</td>
<td>0.42</td>
<td>0.34, 0.51</td>
<td>&lt;0.001</td>
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<td>Hispanic</td>
<td>0.14</td>
<td>0.11, 0.16</td>
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<td>0.45</td>
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<td>Yes</td>
<td>0.67</td>
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<tr>
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<td>Yes</td>
<td>0.49</td>
<td>0.41, 0.58</td>
<td>&lt;0.001</td>
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</table>

Disclosure(s):

Julia E. McGuinness, MD: Seagen: Consulting Fees (e.g., advisory boards) (Ongoing)
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PD16-03
PD16-03 Use of post-neoadjuvant chemotherapy image-guided breast vacuum assisted biopsy to predict residual cancer in exceptional responders: A prospective cohort study

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Background: Post-neoadjuvant chemotherapy (NAC) image-guided biopsy of the residual imaging abnormality / tumor bed is increasingly used to assess residual disease in the breast and potentially identify exceptional responders who may not require surgical intervention. Previous studies have shown variable results on the diagnostic performance of this technique. The aim of this analysis was to assess the accuracy of post-NAC, image-guided vacuum assisted biopsy (VAB) to predict residual disease in the breast using a standardized assessment protocol. The findings could help further support the optimal design of trials omitting surgery in selected patients.

Methods: Prospective cohort study (BR154b) of consecutive patients with HER2 positive and triple negative (TN) invasive ductal carcinoma (IDC), treated with NAC, who underwent post-NAC VAB to aid surgical planning between 02/2018 and 06/2022 at one institution. Patients with complete / near complete imaging response (residual imaging abnormality ≤ 2cm) had a VAB to sample ≥ 90% of the breast residuum / tumor bed previously marked by clip insertion. Biopsy samples were defined as representative if pathology features suggestive of tumor bed or residual cancer were identified. Pathologic complete response (pCR) was defined as no residual invasive or in situ disease in
the breast (ypT0). Diagnostic accuracy of VAB was calculated using final surgical pathology as the reference standard. Simple descriptive statistics were used. Results: A total of 54 women met the eligibility criteria and underwent post-NAC VAB. This was not representative in 3 cases and therefore 51 women were included in the analysis. Median age was 49 years [interquartile range (IQR): 43 – 61]. The majority of cancers were grade 3 (n=31) or grade 2 (n=19). Subtype distribution was 21 (41.2%) for hormone receptor (HR) positive / HER2 positive, 13 (25.5%) for HR negative / HER2 positive and 17 (33.3%) for TN IDC. There was associated DCIS at diagnosis in 37.3% of cases. The majority of the cancers at presentation were T2 (n=35, 68.6%) with a median tumor size on imaging of 28 mm (IQR: 28 – 43). There were associated microcalcifications in 29 cases (n=11 extending beyond the main tumor). Sixteen women presented with cN+ disease. On completion of NAC, 19 women had complete imaging response, while in the remaining the median size of the residual imaging abnormality was 12 mm (IQR: 9 – 16). A post-NAC VAB was performed with ultrasound or stereo-guidance in 48 and 3 cases respectively. The median size (gauze) of needle used was 10 (IQR: 10) and the median number of cores obtained was 8 (IQR: 6-8). In the surgical specimen, the overall breast pCR rate was 58.8% (52.4% for HR positive / HER2 positive, 76.9% for HR negative / HER2 positive and 52.9% for TN). The axillary pCR rate was 81.25%. The false negative rate (FNR) of post-NAC VAB was 4.76% (1/51, 95% CI: 0.12 – 23.82%). The sensitivity and specificity for residual disease were 95.24% (95% CI: 76.18 – 99.88) and 93.33% (95% CI: 77.93 – 99.18) respectively. The negative predictive value was 96.55% (95% CI 80.49 – 99.48) and the overall accuracy 94.12% (95% CI: 83.76 – 98.77). Conclusions: This analysis suggests that a standardized assessment protocol using image-guided VAB in patients with HER2 positive or TN IDC and exceptional response to NAC (residual imaging abnormality / tumor bed measuring ≤ 2 cm) aiming to sample ≥ 90% of the breast residuum allows reliable prediction of residual disease and breast pCR with a FNR < 5%. These results further support the optimal design of de-escalation trials in NAC exceptional responders testing the safety of omitting surgery.

Disclosure(s):
Marios Konstantinos Tasoulis, MD, PhD, FEBS, FRCS: BMJ Publishing Group Limited: Contribution for online educational resource (Ongoing)
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Alicia F. Okines, MBChB, MD(Res), FRCP: Astra Zeneca/DS: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Gilead: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Lilly: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Roche: Consulting Fees (e.g., advisory boards) (Ongoing); Seagen: Consulting Fees (e.g., advisory boards) (Ongoing), Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); AstraZeneca: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing); BioRad: Contracted Research (Ongoing); Bristol Myers Squibb: Consulting Fees (e.g., advisory boards) (Ongoing); GlaxoSmithKline: Consulting Fees (e.g., advisory boards) (Ongoing); Guardant Health: Contracted Research (Ongoing); Invitae: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing); Invitae: Contracted Research (Ongoing); Lilly: Consulting Fees (e.g., advisory boards) (Ongoing); Merck Sharpe and Dohme: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing); Natera: Contracted Research (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing);
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Introduction: Neoadjuvant chemotherapy (NACT) represents an essential tool for the treatment of selected breast cancer patients aimed to reduce the tumor size for a more conservative resection and to gain early information about the sensitivity to applied treatment. An effective early response assessment helps both to change the therapeutic strategy for patients nonresponding to the treatment used and to avoid the toxicity related to ineffective treatment. We assumed that changing the chemotherapy regimen might avoid the residual cancer burden (RCB) III outcome and lead to the highest possible rate of pathological complete response (pCR) achieved. We examined the benefit of MRI as a preferred method for interim response assessment to NACT with a primary focus on the relation between the pattern of responses to NACT within the MRI-monitored and non-monitored patients and the pattern of final outcomes on the RCB scale. Methods: We present a real-life data-based retrospective analysis of 124 female patients with locally advanced breast carcinoma. All patients received NACT (anthracycline-based regimen followed by taxane-based regimen / early switch to taxanes after the 2nd cycle in nonresponders, and antiHER2 therapy if indicated) prior to surgery (mastectomy/breast-conserving surgery, sentinel lymph node biopsy/axillary dissection). Postoperative histopathological analysis of tumor specimens categorised 120 patients according to the RCB scale 0 – III. Four patients had surgery ex muros and were lost to follow-up. Patients were divided into two cohorts. Group A covered monitored patients with pre-treatment MRI and follow-up MRI after the 2nd cycle of NACT. If no response was detected, another follow-up MRI was indicated after the 2nd cycle of a new treatment. Group B comprised patients with no / incomplete MRI monitoring and patients without the change of therapy even though no response was detected by MRI after the 2nd cycle of NACT. Association between categorical variables was tested using chi-square tests. Statistical analysis was performed using StatsDirect® 3.3.5 (StatsDirect Ltd., Cheshire, UK). The data analysis was supported by a grant from the Cultural and Educational Grant Agency of the Ministry of Education, Science, Research, and Sport of the Slovak Republic (KEGA 041UK-4/2020). Results: MRI-monitored patients had two times the odds of being RCB 0 (OR = 2.02, P = 0.122) and almost three times the odds of being RCB 0 or RCB I (OR = 2.83, P = 0.0206) than patients with no monitoring. Changing the NACT after the 2nd cycle in the cohort of monitored patients with no response to initial therapy was significantly associated with better outcomes on the RCB scale (P = 0.0042). This result was confirmed by comparing the pattern of results in patients with no response
within the group of incompletely monitored patients with known MRI results after the 2nd cycle (P = 0.0257). Changing the ineffective NACT after the 2nd cycle significantly increased the proportion of RCB 0-I by 23.4%, confirming the benefit of response monitoring by MRI.

Conclusion Breast cancer constitutes a heterogeneity of tumor subtypes and it is acknowledged that their behaviour during NACT is highly variable and often unpredictable. MRI represents an effective tool for the assessment of tumor response to applied NACT. To achieve the most clinically meaningful impact of the selected treatment it is critical to monitor the tumor response within the first 3 cycles. Our data clearly confirmed that clinical decisions related to the detection of early response or no response (resulting in the change of NACT) lead to better treatment outcomes and less toxicity. The rate of pCR defines the applied treatment efficacy. Every single patient with results different from RCB III has a better prognosis, reduced need for further expensive treatment and also a more favourable quality of life. These key facts need to be carefully considered when discussing the cost and benefits of MRI monitoring.

Disclosure(s):
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PD16-05 Systemic staging in breast cancer patients receiving neoadjuvant chemotherapy

Introduction
Per NCCN guidelines, patients with stage I-III breast cancer should only have staging work up with CT chest, abdomen, and pelvis and bone scan if there are concerning symptoms, lab abnormalities, or physical exam findings. These patients do not require staging imaging because previous studies have documented the low incidence of metastatic disease found on systemic imaging, and the use of routine staging imaging has been shown to have a high false positive rate resulting in additional imaging and further work up with a low true positive rate. Despite the NCCN guidelines, extensive imaging is often performed prior to embarking on neoadjuvant therapy to look for evidence of metastatic spread of disease prior to surgery regardless of clinical stage and lack of symptoms.

Methods
We performed a retrospective analysis of patients at the University of Virginia diagnosed with invasive breast cancer who were recommended for neoadjuvant therapy and underwent systemic imaging to assess for the presence of distant metastatic breast cancer between 2012 and 2019. All receptor subtypes were included. Patients with signs/symptoms of metastatic disease at time of initial consultation were excluded. We evaluated the rate of metastatic breast cancer detected on systemic imaging. We also evaluated the rate of incidental findings on systemic imaging and how often this resulted in additional imaging or biopsy.

Results
328 patients met inclusion criteria and were recommended for neoadjuvant chemotherapy and underwent systemic staging. Of these, 8 patients had bilateral breast cancer at time of diagnosis. Included patients were 54.2% hormone receptor (HR) positive, 35.4% triple negative, and 23.2% HER2 positive; 74.1% were node positive (Table 1). Metastatic breast cancer was
identified in 9.1% (30 patients), which included 19 HR positive, 8 HER2 positive, and 7 triple negative patients. Of the patients found to have metastatic breast cancer, 80% had anatomic stage III disease at presentation and 93.3% were node positive. Two metastatic patients that were node negative had a cT2 or cT3 primary tumor. Systemic imaging identified incidental findings in 72.6% (238) patients. Most common incidental findings were pulmonary nodules (107), bone lesion or abnormality (71), hepatic lesions (55), and gynecologic lesions (50). Of the patients with incidental findings, 40.7% (98) underwent additional imaging for further work up or monitoring and 12.2% (29) underwent a biopsy or procedure for further work up. These biopsies identified benign or non-diagnostic results in 20 cases (69.0%) and identified an alternative malignancy in 9 cases (31%).

Conclusions
Within this study, asymptomatic metastatic disease was most commonly found in node positive stage III breast cancer, but was never or rarely found in stage I or II breast cancer patients. This validates NCCN recommendations that asymptomatic anatomic stage I or II breast cancer patients do not benefit from systemic staging. Yet, we did find a relatively high proportion of metastatic disease in asymptomatic patients with stage III breast cancer, indicating that systemic staging may be appropriate for this population. This must be balanced against the high probability of incidental findings with frequent additional imaging or biopsy, which has implications for patient anxiety, potential harm, and cost.

Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics</th>
<th>All Patients (n = 328)</th>
<th>Metastatic Breast Cancer Patients (n = 30)</th>
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</thead>
<tbody>
<tr>
<td>Bilateral Breast Cancer</td>
<td>2.4% (8)</td>
<td>0</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>52.8 (12.9)</td>
<td>55.3 (12.8)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>IDC</td>
<td>84.8% (285)</td>
<td>70.0% (21)</td>
</tr>
<tr>
<td>ILC</td>
<td>6.5% (22)</td>
<td>13.3% (4)</td>
</tr>
<tr>
<td>Mixed Ductal/Lobular</td>
<td>6.0% (20)</td>
<td>13.3% (4)</td>
</tr>
<tr>
<td>Other</td>
<td>2.7% (9)</td>
<td>3.3% (1)</td>
</tr>
<tr>
<td>Receptor Status</td>
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<td></td>
</tr>
<tr>
<td>HR+</td>
<td>54.2% (182)</td>
<td>63.3% (19)</td>
</tr>
<tr>
<td>HER2+</td>
<td>23.2% (78)</td>
<td>26.7% (8)</td>
</tr>
<tr>
<td>TNBC</td>
<td>35.4% (119)</td>
<td>23.3% (7)</td>
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<td>Grade</td>
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<tr>
<td>1</td>
<td>7.1% (24)</td>
<td>10.0% (3)</td>
</tr>
<tr>
<td>2</td>
<td>42.3% (142)</td>
<td>59.0% (15)</td>
</tr>
<tr>
<td>3</td>
<td>50.6% (170)</td>
<td>40.0% (12)</td>
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<tr>
<td>Anatomic Stage Prior to</td>
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<tr>
<td>Systemic Imaging</td>
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<tr>
<td>1</td>
<td>4.8% (16)</td>
<td>0</td>
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<tr>
<td>2</td>
<td>56.3% (189)</td>
<td>20.0% (6)</td>
</tr>
<tr>
<td>3</td>
<td>39.9% (131)</td>
<td>80.0% (24)</td>
</tr>
<tr>
<td>T Stage</td>
<td></td>
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<tr>
<td>cT1</td>
<td>15.8% (53)</td>
<td>0</td>
</tr>
<tr>
<td>cT2</td>
<td>49.4% (166)</td>
<td>30.0% (9)</td>
</tr>
<tr>
<td>cT3</td>
<td>23.8% (80)</td>
<td>40.0% (12)</td>
</tr>
<tr>
<td>cT4</td>
<td>10.1% (34)</td>
<td>30.0% (9)</td>
</tr>
<tr>
<td>N Stage</td>
<td></td>
<td></td>
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<tr>
<td>Node positive</td>
<td>74.1% (249)</td>
<td>93.3% (28)</td>
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</tbody>
</table>

Disclosure(s):
Courtney Lattimore, MD: No financial relationships to disclose
Squeo Gabriella, MD: No financial relationships to disclose
Christiana Brenin, MD: No financial relationships to disclose
Shayna Showalter, MD: No financial relationships to disclose
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PD16-06
PD16-06 Early MRI and PET biomarkers for hormone receptor-positive/HER2-negative early-stage breast cancer in the setting of neoadjuvant endocrine therapy and neoadjuvant chemotherapy in the I-SPY 2 TRIAL

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Purpose
Neoadjuvant endocrine therapy (NET) is increasingly used for patients with hormone receptor-positive (HR+) breast cancer. Dynamic contract-enhanced breast MRI is the most accurate modality to monitor tumor response during neoadjuvant chemotherapy (NAC)1, but there is limited research on response to NET.

The Endocrine Optimization Protocol (EOP) is a sub-study of the ongoing I-SPY 2 TRIAL testing amcenestrant (an oral selective estrogen receptor degrader [SERD]), with or without addition of abemaciclib (a CDK4/6 inhibitor) or letrozole (an aromatase inhibitor) in patients with stage 2/3, MammaPrint (MP) low-risk (index 0 to 1) or high-risk 1 (index -0.57 to 0), HR+/HER2-negative breast cancer. All I-SPY2 (including EOP) patients undergo MRI at baseline (T0), 3 weeks (T1), 12 weeks (T2), and 6 months, prior to surgery (T3). Functional tumor volume (FTV)2,3 is derived as a quantitative measure of tumor burden from each MRI. A subset of EOP patients also have 3 dedicated breast PET (dbPET) exams with 18F-fluoroestradiol (an estrogen receptor-targeted tracer, FES) at T0, T1, and T3. FES uptake on dbPET indicates the presence of functional estrogen receptor.

This study evaluates changes in FTV and FES uptake in patients receiving NET in the ongoing EOP trial. FTV changes in EOP were compared with those in a cohort of patients who received NAC in I-SPY 2.

Methods
The breast MRI and FES-dbPET images from patients in the EOP trial as of June 2022 were evaluated by a blinded central radiology team at a single institution. FTV was measured using standard procedure in I-SPY 2. Percent FTV change (ΔFTV) at Tn (n = 1, 2, or 3) was calculated by 100x(FTVTn-FTVT0)/FTVT0. FES uptake was quantified as standardized uptake value (SUV). Maximum SUV over the tumor volume (SUVmax) was measured using Osirix MD (Pixmeo SARL) and percent change (ΔSUVmax) was similarly defined. For comparison, FTV
was evaluated using curated imaging data of I-SPY 2 patients with stage 2/3, MP high-risk 1, HR+/HER2-negative cancer who completed standard NAC between 2010–2016.

Results
We included 55 EOP patients (NET cohort) and 68 I-SPY 2 patients (NAC cohort). At T0, median FTV was 9.8cc for the NET cohort and 10.1cc for the NAC cohort. Table 1 shows the longitudinal FTV change in the two cohorts. At T1, median FTV change was similar in the NET cohort (-33.8%) and NAC cohort (-33.9%). The NET cohort showed a dynamic range of FTV change from -65.4% (1st quartile) to -11.0% (3rd quartile), which covered the 1st to 3rd quartile ranges for the NAC cohort. At T2 and T3, FTV change was more gradual in the NET cohort compared to the NAC cohort.
Seven patients in the NET cohort underwent FES-dbPET. At T0, tumor FES uptake exceeded background uptake in all 7 patients with a median SUVmax of 8.2. At T1 and T3, tumor uptake decreased in all patients. Tumor uptake was indistinguishable from background for 3 patients (43%) at T1 and 5 patients (71%) at T3, despite evidence of residual tumor on MRI. The median change of SUVmax was -45.9% at T1 and -74.7% for T3 (Table 2).

Discussion
After 3 weeks of NET, we observed a large dynamic range of FTV change similar to that seen in NAC and a robust decrease in FES uptake. These results suggest the potential for combined use of early MRI change and FES-dbPET to provide scalable biomarkers to stratify response-based NET strategies.

Reference
Table 1: Longitudinal change of FTV (AFTV) in NET cohort and NAC cohort

<table>
<thead>
<tr>
<th>Imaging marker</th>
<th>Time point</th>
<th>NET cohort</th>
<th>NAC cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Median [1st, 3rd quartiles]</td>
<td>No. of patients</td>
</tr>
<tr>
<td>AFTV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>T1</td>
<td>55</td>
<td>-33.8% [-65, 4, -11, 0]</td>
</tr>
<tr>
<td>AFTV&lt;sub&gt;2&lt;/sub&gt;</td>
<td>T2</td>
<td>42</td>
<td>-64.4% [-81, 0, -45, 3]</td>
</tr>
<tr>
<td>AFTV&lt;sub&gt;3&lt;/sub&gt;</td>
<td>T3</td>
<td>18</td>
<td>-66.0% [-45, 6, -50, 0]</td>
</tr>
</tbody>
</table>

Table 2: Longitudinal change of SUV<sub>max</sub> (ASUV<sub>max</sub>) in NET cohort

<table>
<thead>
<tr>
<th>Imaging marker</th>
<th>Time point</th>
<th>NET cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Median [1&lt;sup&gt;st&lt;/sup&gt; and 3&lt;sup&gt;rd&lt;/sup&gt; quartiles]</td>
</tr>
<tr>
<td>ASUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>T1</td>
<td>7</td>
</tr>
<tr>
<td>ASUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>T3</td>
<td>7</td>
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</tbody>
</table>

Disclosure(s):

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Association of MRI morphologic phenotype from unsupervised learning with breast cancer subtypes and treatment response

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Background
Breast cancer is a heterogeneous disease and can be categorized into clinically or biologically meaningful subtypes. Predictive models built by MRI biomarkers performed better when they are optimized by breast cancer subtype than models optimized in the full cohort [1]. Functional tumor volume (FTV) measured from breast MRI has been used to assess tumor response to neoadjuvant therapy longitudinally in the I-SPY 2 TRIAL. Tumors show distinct morphological patterns, or phenotypes, on MRI. Previous studies demonstrated that either qualitative or quantitative measurements characterizing these phenotypes may provide additional information about treatment response [2,3]. In this study, we investigated if MRI morphologic phenotypes defined by unsupervised clustering is associated with breast cancer subtype and pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC).

Methods
A cohort of 990 patients enrolled in the I-SPY 2 TRIAL were included in this retrospective analysis. Patients were randomized to one of nine experimental drug arms or standard NAC, and pCR was assessed at surgery. DCE-MRI data acquired at pretreatment (T0) and early
treatment (T1) were analyzed. Four subtypes of breast cancer were defined by immunohistochemistry (IHC) based on hormone receptor (HR) and HER2 status.

Radiomic features were extracted by PyRadiomics [4] using FTV masks from DCE-MRI. MRI morphologic phenotypes were determined based on unsupervised hierarchical clustering approach on extracted radiomic shape features plus FTV using Pearson correlation with agglomerative ward linkage. The associations between the unsupervised clusters of radiomic features and FTV with four IHC subtypes and pCR were evaluated using χ² test of independence. Cramer’s V [5] were computed to measure the strength of association (higher Cramer’s V means stronger association). P-value < 0.05 was considered statistically significant.

Results

Three clusters were generated by unsupervised hierarchical clustering in a population of 910 patients included in our analysis (80 patients excluded due to missing pCR or DCE-MRIs). At T0, the unsupervised clusters showed statistically significant but weak association with pCR (Cramer’s V = 0.088, p = 0.029), but the association between the clusters and HR/HER2 subtypes did not reach significance (Cramer’s V = 0.055, p = 0.48). The unsupervised clusters based on T1 shape radiomic features showed statistically significant association with both pCR and HR/HER2 subtypes (p < 0.001 for both) with Cramer’s V of 0.231 and 0.154, respectively. Our results showed stronger association between pCR and cancer subtypes with MRI shape radiomic features at T1 than at T0.

Various pCR rates were observed in MRI clusters at T1. They were 56%, 36%, and 23% in Cluster 1, 2, 3, respectively. Table 1 shows pCR rates by HR/HER2 subtype in each cluster. In all sub-cohorts, pCR rate was highest in Cluster 1 and lowest in Cluster 3. In HR+/HER2-, the pCR rate in Cluster 1 was 2-fold of the pCR rates in Clusters 2 and 3-fold of Cluster 3. pCR rate was statistically significantly different depending on the MRI clusters in the sub-cohorts except for the HR/HER2+ sub-cohort: HR+/HER2-, p< 0.001; HR+/HER2+, p=0.021; HR-/HER2-, p=0.083; HR-/HER2+, p< 0.001.

Conclusion

MRI phenotype generated by unsupervised clustering using radiomic shape features at both pretreatment and early-treatment time points was associated with pCR outcome. Stronger association was observed at early-treatment time point. The association differed by subtype, with the strongest observed in HR+/HER2- and triple negative subtypes. Our results suggest that radiomic shape features derived from DCE-MRI may be helpful for early prediction of tumor response to NAC.

Citations

2. Tomography 6, (2020).

Table 1. pCR rate by HR/HER2 subtype in each MRI cluster at T1
<table>
<thead>
<tr>
<th>Cohort</th>
<th>MRI Cluster 1 (n = 146)</th>
<th>MRI Cluster 2 (n = 442)</th>
<th>MRI Cluster 3 (n = 322)</th>
<th>p-value ($\chi^2$ test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2- (n= 358)</td>
<td>38% (18/47)</td>
<td>17% (31/182)</td>
<td>12% (16/129)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HR+/HER2+ (n= 147)</td>
<td>55% (21/38)</td>
<td>39% (30/78)</td>
<td>23% (7/31)</td>
<td>0.021</td>
</tr>
<tr>
<td>HR- HER2+ (n = 75)</td>
<td>76% (16/21)</td>
<td>71% (27/38)</td>
<td>44% (7/16)</td>
<td>0.083</td>
</tr>
<tr>
<td>HR-/HER2- (n = 330)</td>
<td>68% (27/40)</td>
<td>49% (70/144)</td>
<td>31% (45/146)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Disclosure(s):

**Nu N. Le, n/a:** No financial relationships to disclose

**Natsuko Onishi, MD, PhD:** No financial relationships to disclose

**David C. Newitt, PhD:** Kheiron Medical Technology: research support to an institution outside the submitted work (Ongoing)

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**Efstathios Gennatas, n/a:** No financial relationships to disclose

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**Nola M. Hylton, PhD:** GE Healthcare: research support to an institution outside the submitted work (Ongoing)

**Wen Li, PhD:** No financial relationships to disclose
Purpose: To predict pathologic complete response (pCR) in breast cancer patients undergoing neoadjuvant chemotherapy (NAC), from baseline and early-treatment DCE-MRI scans, in the context of the ACRIN 6698/I-SPY 2 BMMR2 challenge.
Materials and Methods: The BMMR2 dataset consists of 191 patients undergoing NAC for locally advanced breast cancer as part of the ACRIN 6698/I-SPY 2 trial. DCE-MRI was obtained at time points T0 (pre-NAC), T1 (3 weeks), and T2 (12 weeks). The BMMR2 challenge provided the MRI scans, tumor annotations, and limited clinical and demographic information. The data were split 60/40; using the 60% training data, the task was to develop models to predict pCR; the competition was for best area under the curve (AUC) when applied to the 40% unseen test data.

Using the publicly available CaPTk software we calculated 3 types of radiomic features within the segmented tumor volume: 1) texture of the signal enhancement ratio (SER) kinetic map of T0 images; 2) texture of the difference between the T1 kinetic maps (PE, WIS, WOS, and SER) and corresponding T0 maps; 3) texture of the difference between the T1 kinetic maps and the corresponding T0 maps, with T1 scans deformably registered to T0 scans. ComBat harmonization was applied to the extracted features to account for MRI acquisition differences. We computed the tumor longest diameter, functional tumor volume (FTV), and clinical tumor size each at T0 and T1.

We modeled pCR via logistic regression. Using the training data alone, with the criteria of performance in univariable modeling and low collinearity, we selected radiomic features and clinical, demographic, and size covariates. We then performed PCA on the combined set of selected radiomic features and size covariates. We evaluated multivariable models including the selected clinical covariates in combination with the first few PCs via cross-validated AUC (5-fold, 200 repetitions) on the training data. The best models were submitted for independent evaluation on the unseen test data of the BMMR2 challenge.

Results: Of the available clinical covariates, only hormone receptor (HR)± and human epidermal growth factor receptor 2 (HER2)± had any association with pCR. We retained these in all models, and performed PCA on the set combining the best-performing features and the size variables FTV at T0, FTV at T1, and longest diameter at T1. Models based on the first few PCs, HR, and HER2, had training AUCs in 0.78–0.81. Our best-performing model had an AUC on test data of 0.84, using the covariates PCs 1–5, HR, and HER2 (Table 1).

Conclusions: Our preliminary results suggest that radiomic phenotyping of changes in tumor heterogeneity can accurately predict pCR early in the course of NAC. Future analysis with larger samples from ISPY-2 could also examine the effect of different therapies, including targeted therapy and immunotherapy.

Table 1: Performance of candidate logistic regression models on training and test data.
AUC: Area under receiver operating characteristic curve.

* Mean 5-fold cross-validated AUC across 200 replicates.
† Competition best-performing predictions.

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Elizabeth S. McDonald, MD, PhD: No financial relationships to disclose
Michael Feldman, n/a: No financial relationships to disclose

<table>
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<tr>
<th>predictors</th>
<th>AUC* on training data</th>
<th>AUC on testing data</th>
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</thead>
<tbody>
<tr>
<td>PC1, HRz, HER2x</td>
<td>0.8198</td>
<td>0.8210</td>
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<tr>
<td>PC1, PC2, HRz, HER2x</td>
<td>0.8032</td>
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<td>0.8269</td>
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<tr>
<td>PC1, PC2, PC3, PC4, PCS, HRz, HER2x</td>
<td>0.7787</td>
<td>0.837†</td>
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<tr>
<td>PC1, PC2, PC3, PC4, PCS, P08, HRz, HER2x</td>
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<td>0.8338</td>
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<tr>
<td>FTV, HRz, HER2x</td>
<td>0.7672</td>
<td>0.7562</td>
</tr>
</tbody>
</table>

Table 1: Performance of candidate logistic regression models on training and test data. AUC: Area under receiver operating characteristic curve.

SARCS abstract, University of Pennsylvania, I-SPY 2
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Poster Spotlight Discussion 17: Endocrine Therapy New Insights

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PD17-01 Genomic analysis of circulating tumor DNA (ctDNA) from patients with HR+, HER2-mutant metastatic breast cancer (MBC) enrolled in SUMMIT: mechanisms of acquired resistance to neratinib + fulvestrant + trastuzumab (N+F+T)

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Background: In the SUMMIT trial, original cohorts of patients with HR+, HER2-negative (locally assessed), HER2-mutant MBC received N alone or N+F, with promising clinical response rates but abbreviated duration. Clinical progression coincided with emergence of additional HER2 mutations and/or amplification of the mutant allele [Smyth et al. Cancer Discov 2020;10:198–213]. Addition of T to the combination was postulated to prolong response; the combination of N+F+T in heavily pretreated patients with HR+, HER2-mutant MBC who had received CDK4/6 inhibitors (n=51) yielded a confirmed overall response rate (ORR) of 35.3%, median duration of response (DOR) of 14.3 months, clinical benefit rate (CBR) of 47.1%, and median progression-free survival (PFS) of 8.2 months [Jhaveri et al. J Clin Oncol 2022;40:1028]. Seven of these 51 patients were part of a randomized (1:1:1) cohort who received N+F+T, F+T, or F alone. Patients randomized to F+T or F could crossover to N+F+T upon progression. No patients responded to F or F+T; however, one of four patients who crossed over to N+F+T upon progression on F+T responded to the triplet, as did two of six who crossed over upon progression on F. We undertook ctDNA sequencing in patients who responded to N+F+T upfront and after crossover. Methods: Patients with HR+, HER2-negative MBC with activating HER2 mutation(s) and prior CDK4/6i received N+F+T (oral N 240 mg/d with loperamide prophylaxis, im F 500 mg d1, d15, and d29 of cycle 1 then q4w, iv T 8 mg/kg initially then 6 mg/kg q3w) or F+T or F alone. Efficacy endpoints included investigator-assessed ORR and CBR (RECIST v1.1), DOR, and best overall response. ctDNA was collected at baseline, every third cycle during treatment, and at the end of treatment and analyzed by next-generation sequencing. Samples were analyzed using the TEMPUS xF assay. Results: Sequencing results from ctDNA analysis are pending at the time of this abstract submission. Baseline HER2 mutations and co-alterations will be reported and compared with those found in tissue samples. Genomic spectrum and variant allele frequencies in samples taken at baseline, on treatment, and at the end of treatment from patients who experienced complete or partial response to N+F+T and then progressed (n=25) will be sequenced and mechanisms of acquired resistance will be posited. ctDNA genomic profiles of serial time points from patients randomized to F or F+T before and after crossover to N+F+T (n=10) will also be evaluated. Conclusions: Similarities and differences between the mechanisms of acquired resistance to N+F+T, and those previously reported to be associated with progression on N or N+F, will be discussed.

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PD17-02 ctDNA Molecular Response based on breast cancer driver mutations predicts progression in aromatase inhibitor-sensitive first line treatment of oestrogen receptor-positive (ER+) HER2-negative (HER2-) advanced breast cancer.

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Background: The combination of a CDK4/6 inhibitor and an aromatase inhibitor (AI) is the gold standard for AI-sensitive first line treatment of ER+ HER2- advanced breast cancer. Nevertheless, some patients progress rapidly and may benefit from alternative strategies. Early ctDNA dynamics have been shown to predict disease course in several clinical situations. Here, we use samples from the PADA-1 trial to assess this strategy for patients receiving AI and palbociclib as first line treatment. PADA-1 was designed to assess the clinical utility of sequential analysis of ctDNA for emerging ESR1 mutations to trigger an early switch from AI plus palbociclib to fulvestrant plus palbociclib treatment. The study included 1,017 patients and was positive on its primary end-point. The objective of this translational study was to analyze the predictive value of 4-week molecular response (MR) for patient progression. Material & Method: First, a CLIA-validated targeted next-generation sequencing-based test (Guardant360 Response) was used to characterize changes in ctDNA level via detection of somatic single-nucleotide variants (SNVs), insertion/deletion mutations (indels), and gene fusions in 74 genes.
frequently mutated in cancer. A second analysis was restricted to cancer-associated mutations in 11 genes commonly mutated in breast cancer (PIK3CA, GATA3, TP53, AKT1, ERBB2, BRCA1, BRCA2, ATM, ESR1, PALB2 and RB1). The threshold for molecular response was defined as ≥ 50% decrease in ctDNA (MR score < 0.5). Subjects with ctDNA levels below the test’s limit of quantitation (ctDNA-low) were considered molecular responders. Results: 372 subjects with matched baseline and 4-weeks samples were available for analysis. Of these, 134 subjects (36%) were ctDNA-low, and 238 subjects (64%) quantifiable. Among the quantifiable subjects, 183 (77%) were molecular responders (MR+, MR < 0.5), and 55 (23%) were not (MR–, MR ≥ 0.5). PFS was moderately improved for both MR+ and ctDNA-low relative to MR– (HR=0.61 (95%CI 0.44-0.85), p< 0.01) over the full 29 months of follow up. Differential PFS event rate was observed only in the first 8 months following ctDNA assessment; during this time MR+ and ctDNA-low were associated with more significantly decreased risk of progression (HR 0.24, 95% CI 0.13 – 0.43, p=0.0001). Limiting ctDNA assessment to genes commonly mutated in breast cancer enhanced the predictive power of MR (HR=0.08, 95% CI 0.04 0.17, p< 0.001, for MR+ and ctDNA-low vs. MR– across 8 months post-assessment); however, fewer samples were quantifiable by this method (169 [45%] quantifiable; 203 [55%] ctDNA-low). Combining MR status with additional molecular features (e.g.tumor mutational burden and maximum mutation allele fraction) did not improve prediction of non-response.

Conclusion: Changes in ctDNA fraction during the first weeks of treatment are predictive of long term clinical benefit on an individual patient basis, particularly during the first year of therapy. Adjusting the MR threshold and/or limiting to genes known to be relevant in the specific tumor can tailor the assessment of ctDNA change to specific clinical scenarios where greater sensitivity or specificity may be required. The identification of patients at high risk for early clinical failure at the onset of treatment may allow for therapy escalation and/or change to improve outcome in this population. Funding : Pfizer and Guardant Health

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PD17-03

PD17-03 Cell-free DNA monitoring in a phase II study of adjuvant endocrine therapy with CDK 4/6 inhibitor ribociclib for localized HR+/HER2- breast cancer (LEADER)

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Background: While adjuvant endocrine therapy (ET) reduces recurrence risk in hormone receptor-positive (HR+) breast cancer, many patients still experience disease recurrence. Adjuvant therapeutic advances are needed to improve outcomes. Meanwhile, monitoring for circulating tumor DNA (ctDNA) in the adjuvant setting may detect molecular residual disease and/or emergences of molecular recurrence from tumor dormancy. Cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors have shown efficacy in HR+/HER2- metastatic breast cancer, and abemaciclib is now approved for adjuvant use in high-risk HR+/HER2- breast cancer. Adjuvant clinical trials have evaluated upfront use of adjuvant CDK 4/6 inhibition; however, the optimal timing of adding a CDK 4/6 inhibitor for HR+/HER2- breast cancer remains unknown. We conducted a prospective phase II clinical trial to evaluate the addition of the CDK 4/6 inhibitor ribociclib in patients with at least one remaining year of adjuvant ET regardless of duration of ET prior to trial enrollment, and we prospectively collected plasma for ctDNA analysis. Methods: Eligible patients had Stage I-III HR+/HER2- breast cancer and had been on adjuvant ET (any number of years) with at least one year of treatment remaining. Patients were randomized to one of two ribociclib schedules: continuous (400 mg daily, 28-day cycle) or intermittent (600 mg daily days 1-21, 28-day cycle) for one year. Patients were concurrently treated with an aromatase inhibitor (plus GnRH agonist, if premenopausal). Time to recurrence was calculated using the Kaplan-Meier method. ctDNA monitoring was performed using the SignateraTM platform, a tumor-informed assay based on whole exome sequencing of the primary tumor for multiplex PCR-NGS ctDNA assay design with targeting of up to 16 single nucleotide variants. Plasma samples were collected at the start of ribociclib/ET and serially during follow-up visits. Results: Among 81 patients treated with adjuvant endocrine therapy and the CDK4/6 inhibitor ribociclib, 42 patients had samples suitable for ctDNA analysis: 3 (7%) had a single ctDNA test, 17 (40%) had 2 serial ctDNA tests, and 22 (52%) had 3 serial ctDNA tests. After a median follow-up of 20 months, 2 patients who received ribociclib (intermittent dosing) experienced disease recurrence with recurrence-free survival of 100% at 1 year from study entry and 97% (95% CI 88-99%) at 2 years. ctDNA was detected exclusively in the only 2 patients that experienced recurrence, with lead times of 7 months and 8 months prior to clinical recurrence. Both patients had no detectable ctDNA at the start of ribociclib/ET. One patient had detectable ctDNA [mean tumor molecules/mL (MTM/mL) = 0.1] while on ribociclib/ET for 5 months, after which she completed a full 12 months of treatment. One month after completing ribociclib/ET (8 months after ctDNA detection), she presented with metastases in the liver and bones. The second patient had 2 negative ctDNA tests at days 0 and 147 while receiving ribociclib/ET and became ctDNA positive (MTM/mL = 0.1) at day 350. She developed CNS-only metastatic disease 7 months after completing ribociclib/ET. Among the other 40 patients who did not have detectable ctDNA, none have experienced recurrence. Conclusions: Overall, only 2 patients had detectable ctDNA, and both patients developed recurrent metastatic disease after completion of ribociclib with ET. Notably, one of these patients developed CNS-only disease.
While follow-up is early, the remaining patients did not have detectable ctDNA and have not developed recurrent disease. This study suggests monitoring for ctDNA may identify patients at increased risk for recurrence in the extended adjuvant period and potentially guide therapy escalation.

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PD17-04 WITHDRAWN
PD17-05 Development and Validation of a Composite Biomarker Predictive of Palbociclib + Endocrine Treatment Benefit in Early Breast Cancer: PENEOLE-B and PALLAS Trials

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Background: The PENELOPE-B (NCT01864746) and PALLAS (NCT02513394) trials are large prospective, randomized, phase III trials that evaluated adjuvant palbociclib (PAL) + endocrine treatment (ET) vs ET in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HER2–) early breast cancer (EBC). Both studies did not meet the primary endpoint of improving invasive disease-free survival (iDFS). We conducted biomarker analyses to identify patients who might benefit from PAL + ET in EBC. Methods: Resected tumor tissue was collected from consenting patients. Gene expression analyses were conducted using the HTG EdgeSeq Oncology Biomarker Panel including 2549 genes. Based
on 91 genes from the HTG panel, the intrinsic molecular subtypes were calculated using Absolute Intrinsic Molecular Subtyping (AIMS). Potential predictive treatment biomarkers were established in PENEOLOPE-B (n=906 with resected tissue) as the development set using an outcome-oriented approach based on iDFS with a selection procedure that maximized the log-rank statistic to estimate a standard Z score–based optimal cutoff. Independent validation was conducted on PALLAS (n=2085; PENEOLOPE-B-like with resected tissue and HTG data). Hazard ratios and corresponding 95% CIs were calculated using the Cox proportional hazards model, and iDFS distributions between treatment arms were compared using the log-rank test. Interaction between treatment and biomarker status was assessed. Results: Patient baseline characteristics were well balanced, with no differences in iDFS between the intent-to-treat set and the biomarker set for both trials. Approximately 73% of patients (PENEOLOPE-B [n=663] and PALLAS [n=1516]) had luminal A subtypes whereas only 7.1% (PENEOLOPE-B [n=64]) and 8.3% (PALLAS [n=172]) had a luminal B subtype. AIMS subtypes showed overall similar prognostic patterns for iDFS between PENEOLOPE-B and PALLAS. The biomarker-defined subgroup found in PENEOLOPE-B with optimal cutoff demonstrated a preferential benefit from PAL + ET (n=364 [96 events]; hazard ratio [95% CI], 0.63 [0.42, 0.95]; P=0.025). Independent validation of the PALLAS subgroup using the pre-defined optimal cutoff confirmed a significant benefit from PAL + ET (n=916 [70 events]; 0.55 [0.34–0.90]; P=0.015) while not in the rest of the patients (interaction p=0.0025). Significant treatment effects remained (0.55 [0.34–0.89]; P=0.015) after adjusting for the randomization stratification factors of PALLAS. Conclusions: The composite predictive biomarker defined from PENEOLOPE-B was independently validated in a prospectively defined retrospective analysis of a subset of patients selected from PALLAS. The composite biomarker identified a subset of EBC patients deriving benefit from the addition of PAL to ET. This patient stratification approach can potentially be applied to future adjuvant clinical trials for treatment of hormone receptor–positive/HER2–EBC.

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PD17-06 Immunohistochemical markers and determinants of clinical response in the Penelope-B trial

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Background: The Penelope-B trial did not show improvement in invasive disease-free survival (iDFS) with the addition of palbociclib to endocrine therapy (ET) in patients with high-risk early breast cancer (BC) after neoadjuvant chemotherapy (NACT). Biomarkers may be able to identify subgroups of patients deriving benefit from Palbociclib and guide future studies.

Estrogen-receptor (ER), progesterone-receptor (PgR) and Ki-67 might be helpful in identifying patients benefiting from palbociclib. Concordantly, tumors with elevated expression of Cyclin D1 and phosphorylated retinoblastoma protein (phospho-RB) may harbor more dependency on CDK4/6 and thus higher sensitivity to palbociclib. Methods: The percentage of positive ER and PgR cells and Ki-67 assessed in surgical specimens after NACT were combined to obtain the immunohistochemical score 3 (IHC3, Cuzick et al JCO 2011, low vs high based on the median IHC3 value). Cyclin D1 and phospho-RB Ser 807/811 immunoreactive (phospho-RB) scores were analyzed in residual tumors after NACT (range 0-12 each). Proportional hazard regression model was used to assess the predictive and prognostic value of IHC3 and treatment on iDFS. Subgroup analysis was performed according to BC intrinsic subtypes (luminal-A/normal-like, luminal-B/HER2-enriched/basal) and HER2-status (HER2 0, HER2 low). Cox/Fine-Gray regression was used to define the predictive and prognostic value of CyclinD1.
(≤1, >1), phospho-RB (≤2, >2) as dichotomized and continuous variables on iDFS, distant DFS (DDFS), locoregional invasive recurrence-free interval (LRRFI) and overall survival (OS). Multivariate analyses (MVA) were adjusted for age (≤50 vs >50), Ki-67 (≤15 vs >15), region (non-Asian vs Asian), ypN (ypN0-1 vs ypN2-3), risk status (CPS-EG=2 ypN+ vs ≥3), cT (cT1-2 vs cT3-4), ypT (ypT0-2 vs ypT3-4), and grade (G1-2 vs G3). The MVA for IHC3 includes all the covariates above except Ki-67. p< 0.05 was defined as statistically significant. Results: Data for ER, PgR, Ki-67, HER2, Cyclin D1 and phospho-RB were available for 1250 patients. Overall, 98.9% of the patients had ER+ tumors, 75.0% PgR+, 52.2% had HER2 low, 25.5% Ki-67>15, 50% had IHC3 score higher than median, 93.9% had Cyclin D1 >1, 57.8% had phospho-RB >2. Patients with IHC3 score high had a worse iDFS compared to patients with IHC3 score low (MVA HR 2.28 95%CI (1.78-2.91), p< 0.0001). Patients with luminal-A/normal-like tumors and IHC3 low had an improved iDFS with the addition of palbociclib to ET (MVA HR 0.35 95%CI (0.14-0.90), test for interaction p=0.01). No difference was observed according to HER2 status. Cyclin D1>1 has no predictive value but is prognostic for better iDFS (MVA HR 0.62 95%CI (0.41-0.94), p=0.023), LRRFI (MVA HR 0.50 95%CI (0.28-0.89), p=0.019). Similar results were obtained when Cyclin D1 was analysed as a continuous variable. Phospho-RB had neither predictive nor prognostic value. Phospho-RB highly correlates with Ki-67 (p< 0.001, Spearman correlation 0.248). Conclusions: Patients with high Cyclin D1 expression had a favorable prognosis independent of treatment arm, but patients with luminal-A/normal-like tumors and IHC3 low after NACT had an improved outcome when receiving palbociclib in addition to adjuvant ET. Theses exploratory studies suggest specific signatures/phenotypes could predict benefit from Palbociclib in high-risk early breast cancer.

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Background Hormone receptor–positive/HER2-negative (HR+/HER2-) breast cancer (BC) is associated with low % of stromal tumor-infiltrating lymphocytes (sTIL) and immune gene expression and poor response to immune checkpoint inhibitors. Evaluating the effect of letrozole and ribociclib (L+R) on the immune microenvironment may suggest new opportunities for immunotherapy-based approaches for HR+/HER2- BCs. Here, we present an exploratory correlative analysis from CORALLEEN, a trial that evaluated the efficacy of L+R (vs. chemotherapy [CHT]) in patients with high-risk PAM50 Luminal B BC (Prat et al. Lancet Oncology. 2022). Methods CORALLEEN is a randomized exploratory study in postmenopausal women with operable stage I-III breast cancer, HR+/HER2- and Luminal B by Prosigna®. Patients were randomized 1:1 to receive either 6 cycles of ribociclib (600mg; 3-weeks-on/1-week-off) plus daily letrozole or CHT: 4 cycles of AC followed by 12 doses of weekly paclitaxel. The primary endpoint was the rate of PAM50 Risk of Relapse (ROR)-low score at surgery in each arm. Samples were prospectively collected at baseline, day 15, and surgery. sTILs score, ki67 IHC and gene expression analysis were determined in all available samples. Complete cell cycle arrest (CCCA) was defined as Ki67≤2.7%. Gene expression profiling by mRNA sequencing (RNASeq) was evaluated. We applied a collection of 194 immune- gene expression signatures (iGES), representing multiple biological pathways and cell types, including. Results
106 patients were randomly assigned to receive neoadjuvant L+R (n=52) or CTH (n=54). Overall, Ki67, sTILs and RNA-seq was available in 95.4%, 96.7% and 83.1% of the samples across the 3 time-points. In terms of cell-cycle inhibition, L+R achieved a significant decrease in Ki67 protein expression and led to higher rates of CCAA at 2 weeks (89.6% vs. 43.2%, p<0.001) and surgery (45.9% vs 25.5%, P=0.054) compared with CHT. Interestingly, the 11-gene PAM50 proliferative score was significantly lower in tumors with CCAA than in those with non-CCCA (p<0.001) after L+R, but not after CHT (p = 0.682). In contrast, tumors with CCAA after CHT had a significantly lower rate of tumor cellularity compared to tumors with non-CCCA (p = 0.002). This was not observed in the L+R arm (p=0.141). Compared to baseline, no clear and significant patterns in % of sTILs were observed at week 2 and surgery. However, % of TILs at surgery in tumors with CCAA after CHT was higher than in tumors with non-CCCA (median 15% versus 1%, p=0.017). This was not observed in the L+R arm (median 1% and 5%, p=0.584). Interestingly, this inverse relationship between immune infiltration and CCAA was further confirmed by RNA-CTH compared to tumors with non-CCCA, whereas 174 (89.7%) of iGES were upregulated (FDR< 5%) in tumors with non-CCCA after L+R compared to tumors with CCAA. Finally, L+R and CHT treatment at week 2 and surgery showed an increase in adaptive immune signatures indicative of activated T-cell and B-cell phenotypes; however, CHT was uniquely associated with increased cytokine signaling, enhanced antigen presentation, dendritic, granulocyte, macrophage and NK cells and decrease in Th17, Th2 and Treg cells. Conclusion In early-stage Luminal B breast cancer, L+R induce a potent anti-proliferative effect compared to CHT. Both treatments generally increased T- and B-cell immune infiltration; however, an inverse relationship between immune infiltration and anti-proliferative response at surgery exists according to treatment, where immune infiltration is increased in residual tumors with non-CCAA when treated with L+R, but the opposite is observed with CHT. The prognostic value of immune and anti-proliferative effects of L+R in residual tumors is currently being evaluated in the prospective RIBOLARIS phase II clinical trial (NCT05296746).

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PD17-08

PD17-08 Pooled gene expression analysis and association with treatment response in patients with HR+/HER2- advanced breast cancer in the MONALEESA-2, -3, and -7 trials

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Background: The Phase III MONALEESA (ML)-2, -3, and -7 trials showed significant improvement in progression-free survival (PFS) and overall survival (OS) with ribociclib (RIB) + endocrine therapy (ET) over placebo (PBO) + ET in patients (pts) with HR+/HER2− advanced breast cancer (ABC); improvement in OS with cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) has been observed in some, but not all clinical trials. Gene expression analyses for each separate ML study were reported previously. Given the differences in CDK4 vs CDK6 inhibition between RIB and other CDK4/6i, we evaluated the association between cell cycle (CC)–related genes and outcomes based on pooled analysis of gene expression using tumor samples from the ML-2, -3, and -7 trials.

Methods: Gene expression data were generated from pre-treatment archival tumor samples (primary, 73%; metastatic, 27%) with a customized NanoString nCounter panel (781 genes) including genes involved in CC, other signaling pathways, and breast cancer biology. Samples were pooled from 1139 pre- and postmenopausal pts with HR+/HER2− ABC across the 3 ML studies, which included pts on first- and second-line therapy. Data were categorized into training (80%) and test (20%) datasets. The training dataset was used to analyze each gene (modeled continuously) individually for an association with PFS, and genes with a gene × treatment (tx) interaction P value <.10 were evaluated in the test dataset. Genes or gene signatures were classified by tertiles based on expression level (low/medium/high). For each tertile, median (m) PFS was calculated by the Kaplan-Meier method, and hazard ratios (HRs) of tx benefit (RIB vs PBO) were estimated. A Cox proportional hazards model adjusting for clinical covariates was used. A machine learning approach (elastic net survival model with stability selection), which used available gene expression data and select clinical factors and their interactions with tx arms, was applied to predict PFS.

Results: This report focused on CC-related genes and signatures. Gene expression levels of CDKN2B and the expression ratio of CCND1/CDKN2A showed a predictive relationship with benefit from RIB in both training and test sets (Table). PFS benefit with RIB was consistent regardless of the CDK4/CDK6 expression ratio or level of expression of CCNE1, CDK2, RB1, combined CC-related genes, E2F gene signatures, RB gene signature, combined DNA-replication genes, or combined proliferation-related genes. A machine learning approach identified a clinico-genomic signature that was prognostic for PFS benefit with RIB. Selected
variables included gene expression levels of FXBO5, PGR, RBBP8, and STC2 and several clinical features (tx arm, de novo disease, prior ET, and visceral disease). Pts with a low signature score had a longer mPFS vs pts with a high signature score, in the RIB (HR, 0.37; 95% CI, 0.22-0.62) and PBO (HR, 0.30; 95% CI, 0.15-0.59) arms.

Conclusion: In the largest pooled analysis of the association of gene expression profile data with CDK4/6i tx response in pts with HR+/HER2− ABC, the PFS benefit with RIB + ET over ET alone was consistent irrespective of expression levels of most CC genes. Variation in magnitude of RIB benefit was observed, depending on CDKN2B expression levels, CCND1/CDKN2A expression ratio, and machine learning–derived signature scores. The clinico-genomic CDK4/6i signature requires validation in additional datasets.

<table>
<thead>
<tr>
<th>Table. Progression-Free Survival by Gene Expression Subgroup</th>
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<tr>
<td><strong>Gene expression</strong></td>
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<tr>
<td>CDKN2B (training)*</td>
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<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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<td>CDKN2B (testing)*</td>
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<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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<td>CCND1/CDKN2A (training)*</td>
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<td>HR (95% CI)</td>
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<td>CCND1/CDKN2A (testing)*</td>
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<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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<td>CCNE1</td>
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<td>HR (95% CI)</td>
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<td>CDK2</td>
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<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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<td>CDK4/CDK6</td>
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<td>HR (95% CI)</td>
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<td>RB1</td>
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<td>HR (95% CI)</td>
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<td>Cell cycle-related genes</td>
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<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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<td>E2F gene signature</td>
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<td>RB gene signature</td>
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<td>HR (95% CI)</td>
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<td>DNA replication genes</td>
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<td>HR (95% CI)</td>
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<td>Proliferation-related genes</td>
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<tr>
<td>mPFS, mo</td>
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<td>HR (95% CI)</td>
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NR: not reached; m: median; PFS: progression-free survival; PBO: placebo; RIB: ribociclib.
* CDKN2B and CCND1/CDKN2A were evaluated in both training and testing sets and had a similar relationship with PFS.
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PD17-10
PD17-10 Genomic characterisation of hormone receptor-positive, HER2-negative breast cancer arising in young women: a secondary analysis of the SOFT trial

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Background Very young premenopausal women diagnosed with hormone receptor-positive, HER2-negative (HR+HER2-) early breast cancer (EBC) have higher rates of recurrence and death than their older counterparts, even when matched by intrinsic subtype. The reasons for this remain largely unexplained. Methods Genomic sequencing was applied to tumor samples from patients enrolled on the Suppression of Ovarian Function (SOFT) clinical trial in order to determine genomic drivers that are enriched in young premenopausal women. The SOFT clinical trial randomised 3066 premenopausal women with HR+ EBC to adjuvant endocrine therapy with tamoxifen alone, tamoxifen plus ovarian function suppression (OFS), or
exemestane plus OFS for 5 years. After exclusion of any HR-negative or HER2-positive tumors, genomic alterations were characterised using next-generation sequencing in primary tumours from a subset of 1,276 patients (deep targeted sequencing, N=1258; whole exome sequencing [WES] in a young-age, case-control subsample, N=82). We estimated copy number (CN) subgroups using the identification of key CN alterations from previously defined IntClust groups (Curtis et al. Nature 2012), including a CN-amplification-devoid subgroup and five CN-amplified groups. We utilised a modified “HRDetect” on samples that had successfully undergone WES to assess for genomic features suggestive of homologous recombination deficiency (HRD). Genomic alteration frequencies were compared between young premenopausal women (< 40 years) and older premenopausal women (≥ 40 years), and assessed for associations with distant recurrence-free interval (DRFI), and overall survival (OS). Eight year-estimated DRFI and OS are presented. Results Median follow up was 8 years. In the entire sequencing cohort (N=1,276), key gene-level copy number (CN) amplifications in CCND1, FGFR1 and MYC were associated with significantly worse DRFI and OS. Mutations in PIK3CA and MAP3K1 were numerically associated with better DRFI and OS but were not statistically significant. Using the IntClust-like subgroups, all CN-amplified subgroups (including one with multiple CN amplifications) had significantly worse DRFI and OS than the CN-devoid group, 81% vs 93% and OS estimate of 87 vs 95% respectively. Younger women aged < 40 years (N=359) compared with women aged ≥ 40 years (N=917) had significantly higher frequencies of mutations in GATA3 (19% vs 16%) and CN amplifications (47% vs 26%), but significantly lower frequencies of mutations in PIK3CA (32% vs 47%), CDH1 (3% vs 9%), and MAP3K1 (7% vs 12%). Additionally, there were significantly higher frequencies of genomic features suggestive of HRD (27% vs 21%), and a higher proportion of younger patients with PIK3CA mutations with concurrent CN amplifications (23% vs 11%).

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PD17-11

PD17-11 Circulating tumor DNA (ctDNA) reveals complex biological features with clinical relevance in metastatic breast cancer
PD17-12
PD17-12 Primary efficacy and safety results from the AMALEE trial evaluating 600 mg vs 400 mg starting doses of first-line ribociclib in patients with HR+/HER2− advanced breast cancer

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Background: In the Phase III MONALEESA (ML)-2, -3 and -7 trials, a 600 mg dose of ribociclib (RIB) demonstrated significant overall survival benefit in patients (pts) with HR+/HER2− advanced breast cancer (ABC) but was associated with QTcF (>480 ms, 3%-7%) and neutropenia (G3/4, 57%-64%) adverse events (AEs) which were managed by dose reductions. The Phase II AMALEE study was performed as a postmarketing commitment to assess whether reducing the starting dose of RIB from the recommended dose (3 wk on, 1 wk off) of
600 mg/day to 400 mg/day decreases QTcF prolongation without compromising the efficacy of first-line RIB in pts with HR+/HER2− ABC. Here, we present efficacy and safety results from the primary analysis of AMALEE. Methods: AMALEE is a randomized Phase II open-label study including pre- and postmenopausal pts with HR+/HER2− ABC with no prior therapy for ABC. Pts received RIB 400 mg + nonsteroidal aromatase inhibitor (NSAI) or RIB 600 mg + NSAI. The primary endpoint is to determine whether overall response rate (ORR) in the 400 mg arm is noninferior to the 600 mg arm. The key secondary endpoint is QTcF prolongation at cycle 1, day 15 (C1D15) 2 hours post dose. Additional endpoints included safety, progression-free survival (PFS), duration of response (DOR), time to response (TTR), and pharmacokinetics.

Results: A total of 376 pts were randomized 1:1 to receive RIB at either 400 mg or 600 mg doses. Baseline (BL) characteristics and prior antineoplastic therapy were balanced across treatment (tx) arms. At the time of the data cutoff (June 11, 2021), median follow-up was 14.9 mo (min, 6.1; max, 23.8), and all pts had been treated for ≥6 months from randomization or had discontinued study tx. ORR for RIB was 41.5% (95% CI, 34.4-48.7) with 400 mg vs 45.3% (95% CI, 38.1-52.6) with 600 mg (ORR ratio for RIB 400 mg vs 600 mg, 0.921 [90% CI, 0.757-1.121]). The lower 90% CI boundary did not meet the prespecified noninferiority (NI) margin of 0.814. Results for ORR by subgroups were consistent with the overall analysis set. RIB plasma exposure was lower at 400 mg than 600 mg; the geometric mean Cmax and AUC0-24h at C1D15 were approximately 28% and 43% lower in the 400 mg than the 600 mg arm (Cmax 1080 vs 1500 ng/mL and AUC0-24h 16400 vs 28600 ng×h/mL). This study met the key secondary endpoint, change in QTcF at C1D15 in the RIB 400 mg group with a 90% CI upper boundary of < 20 ms. Mean change in QTcF from BL to C1D15 2 hours post dose was lower in the 400 mg (12.5 ms, 90% CI, 10.9-14.1) than the 600 mg arm (19.7 ms, 90% CI, 17.4-22.0). QTcF ≥501 ms occurred in 1.6% of pts in the 400 mg arm vs 0.5% in the 600 mg arm. Rates of G3/4 neutropenia were lower in the 400 mg (31.4%) than the 600 mg arm (46.3%). Other safety results were consistent with those previously reported for RIB in the ML trials. Median duration of exposure to RIB was 8.0 mo (min, 0.1; max, 23.7) in the 400 mg arm vs 8.8 mo (min, 0.5; max, 20.8) in the 600 mg arm. Dose reductions of RIB were more frequent in the 600 mg group with 30.5% vs 13.8% of pts requiring 1 dose reduction in the 600 mg and 400 mg groups, respectively. Dose reductions were primarily attributable to AEs, with neutropenia being the most frequently reported AE requiring a dose modification. Rates of discontinuation due to AEs were similar in the 400 mg vs 600 mg arms (8.5% vs 9.6%). PFS, DOR, and TTR data are currently immature. Conclusions: RIB at the 400 mg dose shows a better safety profile vs 600 mg in terms of key AEs that are RIB concentration dependent (neutropenia and QTcF prolongation). ORR was 3.8% lower with 400 mg than 600 mg. The lower 90% CI boundary of the ORR ratio did not meet the NI margin, thus this study was unable to demonstrate statistical NI of the 400 mg vs 600 mg dose of RIB using ORR as the endpoint. Updated results with additional follow-up and the clinically relevant endpoint PFS will be presented at the congress.

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PD18-01

PD18-01 Adjuvant Trastuzumab Emtansine Versus Paclitaxel plus Trastuzumab for Stage I HER2+ Breast Cancer: 5-year results and correlative analyses from ATEMPT (TBCRC033)

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Background: The ATEMPT trial primary analysis found that one year of adjuvant trastuzumab emtansine (T-DM1) achieved a 3-year iDFS of 97.8% for patients with stage I HER2+ breast cancer, but was not associated with fewer clinically relevant toxicities (CRTs) compared with paclitaxel and trastuzumab (TH). In this end-of-study analysis, we report 5-year survival outcomes and correlative analyses from the trial. Methods: Patients with stage I centrally confirmed HER2+ breast cancer were randomly assigned 3:1 to adjuvant T-DM1 for one year or TH and received T-DM1 3.6 mg/kg IV every 3 weeks for 17 cycles or paclitaxel 80 mg/m2 IV with weekly trastuzumab IV followed by trastuzumab for 9 months. The co-primary objectives were to compare the incidence of CRTs between the 2 arms and to evaluate iDFS in patients receiving T-DM1. To investigate proteomic correlates of recurrence, spatial proteomic analyses were performed on samples from 13 patients experiencing iDFS events (cases) and 24 matched controls using the NanoString GeoMx Digital Spatial Profiler. The impact of HER2 heterogeneity on outcomes was investigated among 17 cases and 51 matched controls by fluorescence in-situ hybridization (FISH). HER2 genetic heterogeneity was assessed by scrutinizing the whole tumor area and defined as the occurrence of HER2 gene amplification in >5% but < 50% invasive tumor cells. The risk of recurrence was evaluated centrally with the HER2DX genomic assay from 225 primary tumor samples. Germline whole genome sequencing (WGS) was conducted among 55 patients experiencing T-DM1-induced thrombocytopenia and/or bleeding and 55 matched controls to identify genomic correlates for this side effect. Results: A total of 497 patients who initiated protocol therapy were included in this analysis (383 T-DM1 and 114 TH). After a median follow up 5.8 years, among patients receiving T-DM1 there were a total of 11 iDFS events, with 3 distant recurrences. The 5-year iDFS for T-DM1 was 97.0% (95% CI, 95.3-98.8%), the 5-year recurrence-free interval (RFI) was 98.6% (95% CI: 97.4-99.8%) and the 5-year overall survival (OS) for T-DM1 was 97.8 % (95% CI, 96.3-99.3%). Although the study was not powered to evaluate the efficacy of TH, among the 114 patients receiving TH, a total of 9 iDFS events were observed, including 2 distant events; the 5-year iDFS with TH was 91.3% (95% CI: 86.0-96.9%), 5-year RFI was 93.3% (95% CI: 88.6-98.2%) and 5-year OS was 97.9% (95% CI: 95.2-100%). A total of 56
samples were evaluable for heterogeneity analyses, among which 14% (n=8) harbored HER2 genetic heterogeneity. Spatial proteomic analyses found that NF1 (adjusted p=0.72 x10^{-6}) and CTLA-4 (adjusted p=0.15 x10^{-3}) were significantly upregulated in primary samples from cases, while cleaved caspase 9, CD25, GITR, ICOS, p53 and PD-L2 were significantly upregulated in controls (all with adjusted p<0.05). Germline WGS found that the top gene associations with thrombocytopenia and thrombocytopenia or bleeding were ALMS1 (p=0.19 x10^{-3}) and APBA3 (p=0.23 x10^{-3}), respectively, although none reaching the threshold for genome wide significance. rs62143195 and rs114169776 were the top single nucleotide polymorphisms associated with thrombocytopenia and thrombocytopenia or bleeding, respectively. Data on the impact of HER2 heterogeneity and of HER2DX score on survival outcomes will be presented. Conclusion: With longer follow-up, adjuvant T-DM1 confirmed outstanding long-term outcomes among patients with stage I HER2+ breast cancer, demonstrating a 5-year RFI of 98.6%. Spatial proteomic analyses identified a potential association between NF1 and CTLA-4 expression with recurrence. Details on the impact of HER2 heterogeneity and HER2DX assay on prognosis will be presented.

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PD18-02
PD18-02 Adjuvant Paclitaxel and Trastuzumab Trial (APT) for Node-Negative, Human Epidermal Growth Factor Receptor 2–Positive (HER2+) Breast Cancer: final 10-year analysis
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Background: The APT trial evaluated the activity of adjuvant paclitaxel and trastuzumab (TH) among patients with small, node negative HER2+ breast cancer. This regimen showed a 7-year invasive disease-free survival (iDFS) of 93%, a recurrence-free interval (RFI) of 97.5% with only four (1.0%) distant recurrences, and a 7-year overall survival (OS) of 95%. In this end-of-study analysis, we report the survival outcomes at 10 years and assess the role of HER2DX testing in predicting long-term outcomes with adjuvant TH.
Methods: APT was a single-arm multicenter investigator-initiated phase II study in which patients with HER2+ breast cancer with tumors ≤3 cm and negative nodes (one single micrometastatic node allowed) received IV weekly paclitaxel (80 mg/m2) with IV weekly trastuzumab for 12 weeks, followed by IV trastuzumab for 9 months. The primary endpoint was 3-year iDFS. Here we report 10-year iDFS, RFI, breast cancer–specific survival (BCSS) and OS. In an exploratory analysis, the risk of recurrence was evaluated with the HER2DX genomic assay.

Results: A total of 410 patients were enrolled from October 2007 to September 2010, of which 406 started the study treatment and were included in the intent to treat analysis. Median age at enrollment was 55 years (range, 24 to 85 years), and most patients (67%) had hormone receptor (HR)-positive disease. Fifty percent of patients had tumors 1.0 cm or smaller and only 9% of patients had tumors between 2 cm to 3 cm. Mean tumor size was 1.1 cm. After a median follow-up of 10.2 years (122 months), 36 iDFS events were observed, consistent with a 10-year iDFS of 89.7% (95% CI, 86.3%-93.1%). Ten-year iDFS was 90.2% (95% CI, 86.3%-94.3%) and 88.5% (95% CI, 82.4%-95.1%) for patients with HR-positive and HR-negative tumors at baseline, respectively. 10-year RFI was 96.8% (95% CI, 95.0%-98.7%), 10-year OS was 94.2% (95% CI, 91.6%-96.8%) and 10-year BCSS was 99.1% (95% CI, 98.1%-100.0%). Of the iDFS events observed in the trial, 6 were non-breast cancer related deaths and 9 were contralateral tumors, all but one locally found to be HER2-negative upon biopsy (Table 1). Among patients experiencing an iDFS event, 7 patients (1.7%) had distant recurrences, including 1 with a T2 tumor, 3 with a T1c tumor and 3 with a T1b tumor. At baseline, 6 of them had HR-positive disease, 1 had HR-negative disease, and 6 had high-grade disease. Upon biopsy of metastatic lesions, 5 of the 7 distant recurrences were locally found to be HER2+, 1 was HER2-negative and 1 had unknown HER2 status. HER2DX testing was conducted on available baseline archival tumor tissue and analyses of patients’ survival outcomes based on the HER2DX score will be presented.

Conclusion: After 10 years of follow-up, adjuvant TH confirmed excellent long-term outcomes for small, node-negative HER2+ breast cancer, with a 10-year RFI of 96.8% and a 10-year BCSS of 99.1%.

Table 1

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<th>DFS EVENT</th>
<th>ER-negative at baseline</th>
<th>ER-positive at baseline</th>
<th>N</th>
<th>Time to event (months)</th>
<th>N</th>
<th>Time to event (months)</th>
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<td>Local/regional recurrence</td>
<td>3</td>
<td>1 20</td>
<td>2</td>
<td>12, 153</td>
<td>2</td>
<td>0 37, 65</td>
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<td>- ipsilateral axilla (HER2+)</td>
<td>1</td>
<td>1 12</td>
<td>1</td>
<td>36** 59**, 84, 90</td>
<td>4</td>
<td>1 12, 56, 88, 106, 130</td>
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<tr>
<td>- ipsilateral breast HER2+</td>
<td>1</td>
<td>4 12</td>
<td>1</td>
<td>63**</td>
<td>6</td>
<td>27, 46, 54, 59, 81, 86</td>
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<td>Contralateral breast events</td>
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<td>5</td>
<td>1</td>
<td>4</td>
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<tr>
<td>- HER2+</td>
<td>4</td>
<td>36**, 59**, 84, 90</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>12, 56, 88, 106, 130</td>
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<tr>
<td>Death</td>
<td>6</td>
<td>42, 45, 52, 62, 62, 119</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td>14, 21, 48, 61, 62, 63</td>
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<td>- Breast-cancer related</td>
<td>6</td>
<td>42, 45, 52, 62, 62, 119</td>
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<td>Any recurrence or death</td>
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</table>

*HER2 status locally determined on a biopsy of the recurrent or contralateral tumor tissue
**Patient had subsequent breast cancer-related death, which was counted toward the calculation of breast cancer-specific survival

iDFS events with adjuvant paclitaxel plus trastuzumab after 10.2 years of follow up
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PD18-03 Final analysis of the Phase III PEONY trial: long-term efficacy and safety of neoadjuvant–adjuvant pertuzumab or placebo, plus trastuzumab and docetaxel, in patients with HER2-positive early or locally advanced breast cancer

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BACKGROUND
In the Phase II NeoSphere study (NCT00545688), dual HER2 blockade with pertuzumab (P) + trastuzumab (H) + docetaxel (D) significantly increased pathologic complete response (pCR) vs. H+D in the neoadjuvant setting for HER2-positive early breast cancer (EBC), locally advanced (LA) BC, or inflammatory BC, with supportive progression- and disease-free survival (DFS) data. Consistently, the randomized, multicenter, double-blind, placebo (Pla)-controlled Phase III PEONY trial (NCT02586025) significantly improved total pCR (tpCR; primary endpoint) with P+H+D vs. H+D in an Asian population, and safety data were in-line with the known P safety profile. We present the final analysis of long-term efficacy (at 3 and 5 years) and safety from the study.

METHODS
Patients had centrally confirmed HER2-positive EBC (T2–3, N0–1) or LABC (T2–3, N2 or N3; T4, any N) and were randomized 2:1 to four neoadjuvant P+H+D or Pla+H+D cycles every 3 weeks. P: 840 mg loading/420 mg maintenance doses (or Pla); H: 8 mg/kg loading/6 mg/kg maintenance; D: 75 mg/m². Patients then received three fluorouracil, epirubicin, and cyclophosphamide cycles, followed by 13 of P+H or Pla+H in the adjuvant setting for up to 1 year.

Long-term outcomes (event-free survival [EFS], DFS, overall survival [OS]; all secondary endpoints) were assessed by Kaplan–Meier methods, Cox proportional hazards models, and a two-sided log-rank test (stratified by disease category and hormone receptor status).

RESULTS
Data cut-off was Mar 14, 2022, and 329 patients were randomized; 219 to P; 110, to Pla. Safety populations were 218 and 110 patients, respectively. Baseline characteristics were well balanced. Most patients received the full HER2-targeted cycles. Median follow-up was 62.9 months. Long-term efficacy data are shown in the table.

During the overall treatment period, 70.6% of patients in the P+H+D arm and 68.2% in the Pla+H+D arm experienced grade ≥3 adverse events (AEs); the most common (in ≥5% of
patients in either arm) being neutropenia (59.2% vs. 55.5%), leukopenia (34.4% vs. 34.5%), and febrile neutropenia (5.0% vs. 3.6%). Of the most common any-grade AEs (in ≥30% of patients in either arm), diarrhea was more common in the P+H+D arm (40.8% vs. 17.3% in the Pla+H+D arm). Serious AEs were reported in 17.0% and 13.6% of patients, respectively. No primary cardiac events (heart failure [New York Heart Association grade III or IV] or significant decline of left ventricular ejection fraction) or secondary cardiac events occurred during any study periods.

CONCLUSIONS
Long-term efficacy endpoints (EFS, DFS, and OS) were supportive of the primary endpoint results (tpCR) and suggested a clinically meaningful improvement with P+H vs. Pla+H when administered before and after surgery for one year of anti-HER2- therapy. Safety data were in-line with the known P safety profile and generally comparable between arms, with the exception of diarrhea.
PEONY adds to the totality of data showing the benefit of the P+H+D regimen in HER2-positive EBC.

Long-term efficacy data
<table>
<thead>
<tr>
<th></th>
<th>P+H+D (n = 219)</th>
<th>Pla+H+D (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.53 (0.32–0.89)</td>
<td></td>
</tr>
<tr>
<td>Event-free rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>88.9%</td>
<td>79.7%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>9.2% (0.29–18.1); ( p = 0.043 )</td>
<td></td>
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<tr>
<td>5-year</td>
<td>84.8%</td>
<td>73.7%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>11.1% (1.2–21.0); ( p = 0.027 )</td>
<td></td>
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<tr>
<td><strong>DFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.52 (0.39–0.88)</td>
<td></td>
</tr>
<tr>
<td>Event-free rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>90.1%</td>
<td>81.1%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>9.0% (0.30–17.7); ( p = 0.043 )</td>
<td></td>
</tr>
<tr>
<td>5-year</td>
<td>86.0%</td>
<td>75.0%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>11.0% (1.2–20.7); ( p = 0.028 )</td>
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<tr>
<td><strong>OS</strong></td>
<td></td>
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<tr>
<td>HR (95% CI)</td>
<td>0.53 (0.23–1.19)</td>
<td></td>
</tr>
<tr>
<td>Event-free rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year</td>
<td>97.6%</td>
<td>91.0%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>6.0% (0.08–12.1); ( p = 0.053 )</td>
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<tr>
<td>5-year</td>
<td>93.6%</td>
<td>90.0%</td>
</tr>
<tr>
<td>( \Delta ) (95% CI); p-value</td>
<td>3.9% (2.9–10.7); ( p = 0.26 )</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; OS, overall survival; Pla, placebo.

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PD18-04 Prognostic implications of PIK3CA mutation by hormone receptor status and intrinsic subtype in early stage HER2-positive breast cancer: a correlative analysis from CALGB 40601.

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Paola Zagami MD1,2, Aranzazu Fernandez-Martinez MD, PhD1,3, Naim U. Rashid PhD 4, Katherine A. Hoadley PhD 1,3, Patricia A. Spears1, Charles M. Perou PhD1,3 and Lisa A. Carey MD1 1 Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA 2 University of Milan, Milan, Italy 3 Department of Genetics, University of North Carolina, Chapel Hill, NC, USA 4 Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA Background PIK3CA mutations have been described in 20-25% of early-stage HER2-positive breast tumors [1], and are associated with reduced pathologic complete response (pCR) rate after chemotherapy and anti-HER2 agents [2]. However, the independence of this finding and association with long-term outcomes within HER2+ patients is still largely unknown. Here, we studied the prognostic implications of PIK3CA mutations by hormone receptor (HR) status and intrinsic subtype in patients with early stage HER2+ breast cancer enrolled in CALGB 40601. Method In CALGB 40601, gene expression profiling by RNA sequencing (RNAseq) with PAM50-determined intrinsic subtype and PIK3CA mutations from
whole exome sequencing (WES) were obtained from 184/305 (60%) pretreatment core biopsies. We examined the association of PIK3CA mutations with pCR and event free survival (EFS) by HR status and intrinsic subtype using logistic and Cox regression analyses. Results PIK3CA mutations were found in 32 patients (32/184, 17%). The most frequent mutation was H1047R (12/32,38%), followed by E545K (7/32,22%) and E542K (5/32,16%). PIK3CA mutations were present in 20% and 15% of HR-positive and HR-negative BC subpopulations, respectively. Within Luminal-B, Luminal-A and HER2-Enriched breast tumors, PIK3CA mutations occurred in 36%, 10% and 19% respectively. In the overall population there was lower rate of pCR in mutated-PIK3CA patients than wild-type (34% vs 49%). Using only the subset of patients treated with neoadjuvant trastuzumab-based therapy as standard of care (excluding the lapatinib plus paclitaxel arm), we found a statistically significant lower pCR rate among PIK3CA-mutated tumors using logistic regression model (30% vs 54%, OR=0.30, p=0.0045). At a median follow-up of 9.1 years, the presence of PIK3CA mutation was significantly associated with worse EFS in the overall study population (HR 2.58, 95% CI 1.24-5.35, p=0.011). In a multivariable model including pCR status, HR status and intrinsic subtype (HER2-E vs. not), PIK3CA mutation was independently and significantly associated with worse EFS (HR 2.18, 95% CI 1.04-4.56, p=0.039). The negative impact of PIK3CA mutation on EFS was statistically significant only in patients with HR-positive (HR 3.6, 95% CI 1.45-8.96, p=0.06) and luminal breast tumors (HR 4.84, 95% CI 1.08-21.7, p=0.039), but not in HR-negative and non-luminal subtypes. Conclusion In our study, the presence of PIK3CA mutation was significantly associated with lower pCR rates in patients treated with chemotherapy plus trastuzumab. Moreover, in univariable and multivariable Cox models, PIK3CA mutations were associated with worse long-term survival, which appeared to be driven by HR-positive and luminal HER2-positive breast tumors. References 1. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature 2012;490:61–70. 2. Loibl S, Majewski I, Guarneri V, Nekljudova V, Holmes E, Bria E, et al PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol 2016;27:1519–25.

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PD18-05
PD18-05 MEN1611, a PI3K inhibitor, combined with trastuzumab ± fulvestrant for HER2+/PIK3CA mutant advanced or metastatic breast cancer: updated safety and efficacy results from the ongoing phase 1b study (B-PRECISE-01)

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Background: MEN1611 (MEN) is an oral PI3K inhibitor active on the p110α mutant and wild type, β and γ isoforms, while sparing the δ. B-PRECISE-01 is an open-label, 2-arm, phase 1b study investigating MEN1611 in combination with trastuzumab ± fulvestrant in patients with HER2 positive/PIK3CA mutated metastatic breast cancer (MBC). No dose-limiting toxicities were observed during the dose-escalation step and MEN1611 48 mg BID was selected as the recommended phase 2 dose (RP2D) for cohort expansion (CE). Methods: Eligible patients had HER2+/PIK3CA-mutated MBC and were treated with at least 2 prior lines of anti-HER2-based
therapy in the advanced/metastatic setting including trastuzumab. Patients received MEN1611 + trastuzumab (MEN+T); hormone receptor positive (HR+) postmenopausal women received M+ T + fulvestrant (MEN+T+F). Recruitment was closed in December 2021. Pooled safety and efficacy data from the two subpopulations of CE are presented herein. Results: As of June 2022, 62 female patients were treated: 56 of them with MEN1611 48 mg BID (25 MEN+T and 31 MEN+T+F). Median age 55.5 years (range 34-78), 21% premenopausal, ECOG PS 0-1: 95.2%. Median metastatic regimens 4; 71.0% had prior pertuzumab and 91.9% had prior T-DM1. Common treatment-emergent adverse events (TEAEs, ≥20%) were diarrhea 66.1%, nausea 45.2%, hyperglycemia 43.6%, anemia 35.5%, asthenia 29.0%, decreased appetite 27.4%, rash 25.8%, aspartate aminotransferase increased 22.6%, vomiting 22.6%, and pyrexia 22.6%. Common TEAEs with CTCAE grade ≥3 (≥10%) were hyperglycemia (22.6%) and diarrhea (11.3%). Most treatment-related AEs (TRAEs) were reversible and manageable by supportive care. TEAEs leading to permanent treatment discontinuation occurred in 9 patients (14.5%), the only TEAE occurring in more than one patient was lipase increased (3.2%). TEAEs caused temporary treatment interruptions in 32 patients (51.6%), the most common being hyperglycemia (21.0%) and diarrhea (9.7%). TEAEs leading to dose reduction occurred in 14 patients (22.6%), the most common being diarrhea (6.5%), hyperglycemia (3.2%) and stomatitis (3.2%). Serious TRAEs were experienced by 12 patients (19.4%): hyperglycemia 6 patients, diarrhea 3 patients, anemia, general physical health deterioration, generalized edema, lipase increased, ketoacidosis and pneumonitis (1 patient each). In the efficacy-evaluable population at the RP2D (n=41) 14 patients (34.1%) showed partial response (MEN+T 5/15, MEN+T+F 9/26), 1 patient (2.4%) had a complete response (MEN+T 1/15) and 23 patients (56.1%) had stable disease (MEN+T 6/15, MEN+T+F 17/26) as best response. At the RP2D, the median (95% CI) overall survival (OS) was 21.9 (11.9, NE) months and the median (95% CI) progression free survival (PFS) 5.6 (3.7, 7.2) months. In the MEN+T group, the median OS was 11.9 (5.7, NE) months and median PFS 3.9 (2.3, 6.7) months. In the MEN+T+F group the median OS was 21.9 (16.9, NE) months and median PFS 5.7 (3.7, 11.5) months. Five patients continue on treatment. Conclusions: Updated results from B-PRECISE-01 demonstrated that MEN1611 combined with trastuzumab ± fulvestrant continued to show a manageable safety profile with encouraging anti-tumor activity and duration of response in heavily pre-treated patients with HER2+/PIK3CA-mutated advanced or metastatic breast cancer.

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PD18-06

PD18-06 Image-guided optimization of neoadjuvant chemotherapy duration in stage II and III HER2-positive breast cancer: radiologic and pathologic complete response (pCR) rates in the multicenter phase 2 TRAIN-3 study (BOOG 2018-01)

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Background
pCR rates in stage II – III HER2-positive breast cancer have greatly improved since the addition of HER2 targeted agents to neoadjuvant chemotherapy and are associated with excellent long-term survival. While longer treatment regimens increase pCR rate, early complete responses are also common. We evaluated an image-guided approach to tailor chemotherapy duration based on the identification of early complete responders.

Methods
45 hospitals across the Netherlands participated in the phase 2 TRAIN-3 trial. Patients received neoadjuvant systemic treatment consisting of paclitaxel, trastuzumab, carboplatin and pertuzumab (PTC-Ptz). Response to treatment was monitored every three cycles and patients were referred for surgery in case of a radiologic complete response (rCR) or after a maximum of 9 cycles. RCR was defined as the absence of pathological enhancement on MRI breast plus negative vacuum assisted core biopsies in case of hormone-receptor positive (HR+) tumors. In addition, negative fine needle aspiration or lymph node biopsy was required in patients with nodal involvement at baseline. The primary endpoint was 3-year event-free survival (EFS). Here, we report locally assessed rCR and pCR rates after 3, 6 and 9 cycles, the negative predictive value of rCR assessment and the incidence of adverse events (AEs). Analyses are stratified by HR-status.

Results
We included 467 patients between April 2019 and May 2021. Median age was 51 years, 69% had stage II disease and 232 had HR+ tumors. 33.6% of HR- patients and 15.5% of HR+ patients achieved pCR after 3 cycles of PTC-Ptz (see table). The NPV was higher in HR- patients and independent of the number of cycles. AE evaluation is currently ongoing.

Conclusion
Three cycles of PTC-Ptz induce an early pCR in one in three HR- and one in six HR+ tumors in patients with stage II-III HER2+ breast cancer. Dynamic contrast enhanced MRI-based response evaluation identifies these patients with ±87% certainty in HR- disease and ±58% in HR+ disease. Continuation of PTC-Ptz after 6 cycles further improves pCR rates and can be considered to reduce the need for adjuvant T-DM1. Efficacy and safety of this image-guided approach to tailor treatment duration need to be confirmed with follow-up in EFS and OS analyses.

Cumulative rCR & pCR according to HR-status

<table>
<thead>
<tr>
<th>Table. Cumulative rCR &amp; pCR according to HR-status</th>
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<tbody>
<tr>
<td>HR- (n=235)</td>
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<tr>
<td>rCR</td>
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<td>pCR</td>
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<td>NPV (rCR &amp; pCR / rCR)</td>
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<td>pCR</td>
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<tr>
<td>rCR &amp; pCR</td>
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<td>NPV (rCR &amp; pCR / rCR)</td>
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*Including patients who underwent surgery for other reasons than rCR
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PD18-07

PD18-07 Omission of chemotherapy in the treatment of HER2-positive and hormone-receptor positive metastatic breast cancer – interim results from the randomized phase 3 DETECT V trial

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Background: Metastatic breast cancer (MBC) is an incurable disease and both the improvement of survival and maintenance of quality of life (QoL) are equally important aims of treatment planning. In patients with HER2-positive MBC, taxane-based chemotherapy in combination with dual HER2 targeted therapy with trastuzumab (T) and pertuzumab (P) is the standard of care first line therapy. However, adverse events are well-known side effects of any cytostatic treatment and can seriously impact the patients’ QoL. In addition, in HER2-positive MBC
activated estrogen receptor (ER) signaling is associated with primary or secondary resistance. Thus, for patients with HER2-positive and hormone-receptor (HR) positive MBC, the synergistic combination of dual HER2-targeted therapy plus endocrine therapy might offer a better treatment option compared to cytotoxic chemotherapy-based treatments. Methods: Between 9/2015 and 11/2022, the multicenter phase III DETECT V trial randomized patients with HER2-positive and HR-positive (i.e., ER positive and/or progesterone-receptor positive) MBC in the 1st-3rd line setting 1:1 to receive T and P combined with either endocrine therapy or chemotherapy followed by maintenance therapy with T, P and endocrine therapy. Chemotherapy and the endocrine agents could be chosen from a variety of available regimens according to physicians’ choice. Based on emerging data strongly suggesting an additional benefit of CDK4/6 inhibitors, an amendment came into effect in January 2019 with the addition of ribociclib to both treatment arms after 124 patients had been randomized. The primary objective of DETECT V is to compare tolerability between the chemotherapy-free and chemotherapy-containing treatment arm; secondary objectives comprise the comparison of PFS, OS and safety. Here we report results of an unplanned interim analysis with data cut off June 22th 2022. Results: The results reported here are based on 153 patients for whom end of study was documented at the time of data cut off for this interim analysis (120 patients randomized before and 33 patients randomized after the addition of ribociclib; 115 patients in the 1st line setting; 77 and 76 patients in the chemotherapy-free and chemotherapy-containing arm, respectively). Overall survival (OS) and progression-free survival (PFS) did not differ between patients receiving chemotherapy-free and chemotherapy-containing treatment (median OS not yet reached vs. 37.2 months, hazard ratio 0.87, 95% CI 0.51 – 1.50, p = 0.63; median PFS 15.6 vs. 14.9 months, hazard ratio 0.98, 95% CI 0.64 – 1.52, p = 0.93). Study treatment was terminated prematurely significantly less often in the chemotherapy-free treatment arm (43.9% vs. 72.2%, p = 0.001). Furthermore, tolerability was better for the chemotherapy-free treatment as there were less adverse events (AEs) of any grade (585 vs. 793; 70 vs. 71 patients affected), less AEs grade 3 or higher (66 vs. 90; 33 vs. 48 patients affected) and less serious adverse events (45 vs. 52; 28 vs. 29 patients affected) reported in the chemotherapy-free treatment arm as compared to the chemotherapy-containing treatment arm. Conclusion: These preliminary results suggest that chemotherapy-free treatment for patients with triple-positive MBC might be an effective and well tolerated option.

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Background: 1. The 3-drug combination therapy, trastuzumab, pertuzumab, and taxane chemotherapy is one of the standard treatment options for the first-line treatment of HER2-positive recurrent/metastatic breast cancer. 2. KN026 is a novel bispecific HER2-targeted antibody: Fully humanized, IgG1-like antibody binds to two distinct HER2 epitopes, the same domains as trastuzumab (ECD4) and pertuzumab (ECD2). IgG1 Fc fragment of KN026 binding FcγRIIIa mediates potent ADCC. 3. Preliminary safety and efficacy results from Phase 1 study data (data as of January 22, 2020) of KN026 monotherapy in HER2-positive advanced breast cancer were presented at ASCO 2020, showed promising efficacy and well tolerated safety. Herein, we present the results from the phase 2 trial. Methods: Eligible subjects with HER2-positive and first-line systemic treatment-naive (relapse ≥12 months after the end of...
neoadjuvant/adjuvant therapy) recurrent or metastatic breast cancer were enrolled in this study. Subjects received KN026 30 mg/kg combined with docetaxel 75 mg/m² Q3W until disease progression, unacceptably toxicity, withdrawal of informed consent from subjects, or other circumstances that require drug discontinuation. The primary endpoints were ORR and duration of response (DoR). The secondary endpoints included safety, PFS and OS. Results: At data cut-off date (Mar 26, 2022), the median follow-up was 13.8 months (Interquartile Range [IQR] 12.22, 14.00). 57 subjects were enrolled, the median age was 52 years, 100% were female, and 89.5% (51/57) were stage IV. Of the 55 subjects evaluable for efficacy, 21 had received prior taxane, 4 had received prior trastuzumab in combination with taxane, 30 without any prior trastuzumab and taxane. Nearly half of the subjects (25/55) had previously received trastuzumab and/or taxane chemotherapy. The confirmed ORR within 55 evaluable subjects was 76.4% (95% CI: 62.98, 86.77) and DoR was 18.1 months (95% CI: 12.45, NE). Median PFS was 19.3 months (95% CI: 13.86, NE) and median OS was not reached. Median PFS is not yet mature. The 12-, and 18-month OS rates were 93.5% (95% CI: 80.79, 97.89), and 88.3% (95% CI: 68.93, 95.92), respectively. The confirmed ORR was 80% in 30 trastuzumab-and taxane-naïve subjects. Among these subjects, OS rates at 12, and 18 months were 100% (95% CI: 100,100), and 90.0% (95% CI: 47.30, 98.53), and the median PFS was 19.3 months (95% CI:13.77, NE). Treatment emergent adverse events with incidence rate ≥20% and TEAE≥Grade 3 were neutropenia (n=23, 40.4%) and leucopenia (n=16, 28.1%), respectively. The incidence of serious adverse events was 15.8%(9/57), including 5.3%(3/57) for febrile neutropenia, 3.5% (2/57) for leucopenia, and less than 2% for other SAEs. There were no deaths due to KN026 drug-related AEs in this study. Conclusions: KN026 in combination with docetaxel is well tolerated and has shown promising clinical benefit as a 1L treatment for HER2-positive advanced breast cancer. At data cut-off date (Mar 26, 2022) median PFS was 19.3 months while 18-month OS rate was 88.3%, which is very encouraging. Efficacy and safety require large-scale phase III studies to verify.

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PD18-09 ACE-Breast-03: Efficacy and safety of ARX788 in patients with HER2+ metastatic breast cancer previously treated with T-DM1

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Background: Amplification of the human epidermal growth factor receptor 2 (HER2) gene with consequent HER2 protein overexpression occurs in approximately 20% of breast cancers (BC) and is a major driver of tumor development and progression. The HER2-targeted ADC trastuzumab emtansine (T-DM1) has been approved for the treatment of HER2-positive metastatic BC (mBC) after prior trastuzumab and taxane therapy. However, disease progression occurs in all patients requiring additional therapeutic options. The use of second-generation anti-HER2 ADCs using alternative molecules is being investigated to overcome drug resistance. ARX788 is a next-generation ADC using a technology platform whereby a HER2-specific monoclonal antibody is conjugated with Amberstatin269, a potent cytotoxic tubulin inhibitor. Site-specificity, high homogeneity, and stable covalent conjugation of ARX788 lead to its slow release and prolongation of the peak serum pAF-AS269 concentration, which may contribute to the lower systemic toxicity and increased targeted delivery of payload to tumor cells at a lower effective dose compared to other HER2 ADCs. Here, early evidence of activity of ARX788 in patients previously treated with T-DM1 is shown.
Methods: ACE-Breast-03 (NCT04829604) is an ongoing global, phase 2, single-arm study evaluating ARX788 in patients with HER2+ mBC whose disease has progressed following T-DM1, T-DXd, and/or tucatinib-containing regimens. The ARX788 is administered with an initial dose of 1.5 mg/kg Q4W and subsequent doses of 1.3 mg/kg Q4W. Eligibility criteria included central laboratory confirmed HER2+ mBC per ASCO/CAP guidelines, measurable disease, and adequate organ function. Stable treated brain metastases are allowed. Patients with interstitial lung disease (ILD) or pneumonitis in prior 12 months; active ocular infections or any chronic corneal disorder; are excluded. The primary endpoint is overall response rate (ORR).

Results: At the data cutoff of 11-Jul-2022, 7 patients were enrolled in ACE-Breast-03 (v1.0) who previously experienced disease progression on T-DM1 and had response-evaluable disease. Pts had a median age of 59 years and had received a median of 5 lines of prior anti-HER2 cancer therapy (range: 2-8). None of the pts in this subset had received T-DXd or tucatinib. 5 pts were previously treated with HER2-targeted TKIs (neratinib and lapatinib), as well as an investigational HER2 ADC and responded to ARX788 (3 PR; 2 SD). Two patients had hormone receptor (HR)-positive disease and 5 had HR-negative mBC. Treatment with ARX788 remains ongoing with the median time of ARX788 therapy of 4.5 months. The confirmed ORR was 57.1% (4/7 pts) and an unconfirmed ORR of 71.4% (5/7 pts) as one pt experienced an unconfirmed response with PR after 2 cycles. The disease control rate (DCR) was 100% (7/7 pts). No drug-related grade ≥3 AEs were reported; 57.1% (4/7 pts) reported ocular AEs including grade 1 events in 3 pts (i.e., dry eye, blurred vision) and a grade 2 event in one pt (lagophthalmos). No pneumonitis or ILD was observed. ARX788 was well-tolerated, and AEs were manageable.

Conclusion: In this small cohort of patients previously treated with T-DM1, ARX788 had a manageable AE profile and demonstrated promising clinical activity (confirmed ORR 57%; DCR 100%).

ACE-Breast-03 Spider Plot for patients with mBC who were previously treated with T-DM1
ARX788 demonstrated promising clinical activity in patients previously treated with T-DM1.

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PD18-10
PD18-10 Treatment of HER2-positive (HER2+) hormone-receptor positive (HR+) metastatic breast cancer (mBC) with the novel combination of zanidatamab, palbociclib, and fulvestrant

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Background: HER2+ mBC remains incurable, with a need for new HER2-directed therapies and regimens, including chemotherapy-free options. Zanidatamab (zani) is a novel HER2-targeted bispecific antibody that binds HER2 in a unique trans configuration, driving multiple mechanisms of antitumor activity, including complement-dependent cytotoxicity. A CDK4/6 inhibitor combined with endocrine therapy is an approved treatment for HER2-negative/HR+ mBC and this combination has also demonstrated encouraging antitumor activity when paired with HER2-targeted therapy(ies) in HER2+/HR+ mBC. Here, we report results from ZWI-ZW25-202 (NCT04224272), an ongoing single-arm phase 2 study of zani combined with palbociclib (palbo) and fulvestrant (fulv) in pts with HER2+/HR+ mBC. Methods: Eligibility requirements include: HER2+/HR+ unresectable, locally advanced BC or mBC; ECOG PS of 0 or 1; prior treatment with trastuzumab, pertuzumab and T DM1 (additional prior HER2-targeting agents are permitted); and no prior treatment with CDK4/6 inhibitors. Part 1 of the study evaluated the safety and tolerability of the zani/palbo/fulv combination and determined the recommended doses for use in Part 2, where the antitumor activity of the combination is being evaluated. Endpoints include safety outcomes, progression-free survival at 6 months (PFS6), confirmed objective response rate (cORR) per RECIST v1.1; disease control rate (DCR=complete response [CR] plus partial response [PR] plus stable disease [SD]); duration of response (DOR); PFS; and overall survival. Results: As of 24 Feb 2022, 34 pts (33 HER2+/HR+ per central analysis) with a median age of 52 (range 36-77) have been treated. In the metastatic setting, pts had received a median (range) of 4 (1-10) prior systemic regimens, including 3 (1-8) different prior HER2 targeted therapies, and 1 (0-4) endocrine therapy. Seven pts (20%) had T DXd treatment and 7 pts had prior fulv treatment. All pts received zani (20 mg/kg Q2W) and standard doses of palbo and fulv. Eighteen pts (53%) remained on treatment; median duration of zani treatment was 6.9 mo (range 0.5-16.3). A dose-limiting toxicity (DLT) of neutropenia occurred in 1 of 7 DLT-evaluable pts in Part 1. Among all pts (n=34), the most
common (>20%) treatment (zani, palbo and/or fulv)-related adverse events (TRAEs) were diarrhea (74%), neutrophil count decreased/neutropenia (62%), stomatitis (41%), asthenia (26%), nausea (24%), and anemia (21%). Grade (Gr) ≥3 TRAEs in 2 or more pts included neutrophil count decreased/neutropenia (50%), anemia (6%), diarrhea (6%), and thrombocytopenia (6%). AEs of special interest were all Gr ≤2 and included 4 pts with cardiac events (LVEF decrease of ≥10% from baseline) and 1 pt with infusion-related reaction. There were no treatment-related serious AEs. Palbo was discontinued for 1 pt due to an AE (AST increase); no pt discontinued zani treatment as a result of AEs. Two deaths occurred: 1 due to disease progression and 1 due to an unrelated AE of pneumonia caused by COVID-19. In 29 pts with measurable disease, the cORR was 34.5% (95% CI: 17.9, 54.3), all responses were cPRs, of which 1 is pending CR confirmation. DOR ranged from 2.3 to 14.9+ mo, with 8 confirmed responses ongoing, and the DCR was 93.1% (95% CI: 77.2, 99.2). Interim median PFS was 11.3 mo (range 0.03-16.7; 95% CI: 5.6, not estimable). PFS6 analysis is planned following the completion of enrollment. Conclusions: Zani in combination with palbo and fulv shows encouraging antitumor activity with durable responses in heavily pretreated pts and a manageable safety profile. This regimen has the potential to be a chemotherapy-free treatment option in pts with HER2+/HR+ mBC. Enrollment in the study is continuing.

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Institution (Ongoing); Elucida Oncology: Research Funding to Institution (Ongoing); EMD Serono: Research Funding to Institution (Ongoing); Fochon: Research Funding to Institution (Ongoing); FujiFilm: Research Funding to Institution (Ongoing); G1 Therapeutics: Research Funding to Institution (Ongoing); Greenwich Lifesciences: Consulting Fees to Institution (Ongoing); H3 Biomedicine: Consulting Fees and Research Funding to Institution (Ongoing); Harpoon: Research Funding to Institution (Ongoing); Hutchinson MediPharma: Research Funding to Institution (Ongoing); Immunogen: Research Funding to Institution (Ongoing); Immunomedics: Research Funding to Institution (Ongoing); Incyte: Research Funding to Institution (Ongoing); Infinity Pharmaceuticals: Research Funding to Institution (Ongoing); InvestisBio: Research Funding to Institution (Ongoing); iTeos: Consulting Fees to Institution (Ongoing); Jacobio: Research Funding to Institution (Ongoing); Janssen: Consulting Fees to Institution (Ongoing); Karyopharm: Research Funding to Institution (Ongoing);Leap Therapeutics: Research Funding to Institution (Ongoing); Lilly: Consulting Fees and Research Funding to Institution (Ongoing); Loxo: Consulting Fees to Institution (Ongoing); Lycera: Research Funding to Institution (Ongoing); MabScience: Research Funding to Institution (Ongoing); Macrogenics: Research Funding to Institution (Ongoing); MedImmune: Research Funding to Institution (Ongoing); Merck: Consulting Fees and Research Funding to Institution (Ongoing); Mersana: Consulting Fees and Research Funding to Institution (Ongoing); Merus: Research Funding to Institution (Ongoing); Millennium: Research Funding to Institution (Ongoing); Molecular Templates: Research Funding to Institution (Ongoing); Myraid Genetic Laboratories: Research Funding to Institution (Ongoing); Novartis: Consulting Fees and Research Funding to Institution (Ongoing); OncoMed: Research Funding to Institution (Ongoing); Onconova Therapeutics: Research Funding to Institution (Ongoing); ORIC Pharmaceuticals: Research Funding to Institution (Ongoing); Orinove: Research Funding to Institution (Ongoing); Orum Therapeutics: Consulting Fees to Institution (Ongoing); Pfizer: Consulting Fees and Research Funding to Institution (Ongoing); PharmaMar: Research Funding to Institution (Ongoing); Pieris Pharmaceuticals: Research Funding to Institution (Ongoing); Pionyr Immunotherapeutics: Research Funding to Institution (Ongoing); Plexxikon: Research Funding to Institution (Ongoing); Propella Therapeutics: Consulting Fees to Institution (Ongoing); Puma Biotechnology: Consulting Fees to Institution (Ongoing); Radius Health: Research Funding to Institution (Ongoing); Regeneron: Research Funding to Institution (Ongoing); Relay Therapeutics: Consulting Fees and Research Funding to Institution (Ongoing); Repertoire Immune Medicine: Research Funding to Institution (Ongoing); Rgenix: Research Funding to Institution (Ongoing); Roche/Genentech: Consulting Fees and Research Funding to Institution (Ongoing); SeaGen: Consulting Fees and Research Funding to Institution (Ongoing); Sermonix Pharmaceuticals: Research Funding to Institution (Ongoing); Shattuck Labs: Research Funding to Institution (Ongoing); Silverback: Consulting Fees and Research Funding to Institution (Ongoing); StemCentRx: Research Funding to Institution (Ongoing); SynBio: Research Funding to Institution (Ongoing); Syndax: Research Funding to Institution (Ongoing); Syros: Research Funding to Institution (Ongoing); Taiho: Research Funding to Institution (Ongoing); TapImmune: Research Funding to Institution (Ongoing); Tesaro: Research Funding to Institution (Ongoing); Tolmar: Research Funding to Institution (Ongoing); Torque Therapeutics: Research Funding to Institution (Ongoing); Treadwell Therapeutics: Research Funding to Institution (Ongoing); Verastem: Research Funding to Institution (Ongoing); Vincerx Pharma: Research Funding to Institution (Ongoing); Zenith Epigenetics: Research Funding to Institution (Ongoing); Zymeworks: Research Funding to Institution (Ongoing)

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PD18-11

PD18-11 Dose-Expansion Study of Trastuzumab Deruxtecan as Monotherapy or Combined With Pertuzumab in Patients With Metastatic Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer in DESTINY-Breast07 (DB-07)

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Background: In trials of HER2+ metastatic breast cancer (mBC), trastuzumab deruxtecan (T-DXd) monotherapy showed durable efficacy (DESTINY-Breast01) and significantly prolonged progression-free survival vs trastuzumab emtansine (DESTINY-Breast03). T-DXd is approved in the US for patients with HER2+ unresectable/mBC who received ≥1 prior anti-HER2–based treatment (tx) in the metastatic or neo-/adjuvant setting and recommended for approval in the EU as 2nd-line tx. Preclinical data suggest that T-DXd used in combination with other anticancer tx may lead to improved efficacy. The purpose of DB-07 is to assess the safety and efficacy of T-DXd alone or with other anticancer tx for patients with HER2+ mBC. Here we report preliminary data from the DB-07 dose-expansion phase for T-DXd monotherapy and T-DXd + pertuzumab (P) as 1st-line (1L) tx in mBC.

Methods: DB-07 (NCT04538742) is an ongoing, phase 1b/2, 2-part (part 1: dose finding; part 2: dose expansion), modular, open-label trial of T-DXd alone or with other anticancer tx in patients with HER2+ mBC. In part 2, patients in module (mod) 0 received T-DXd 5.4 mg/kg every 3 weeks (Q3W) and in mod 2, T-DXd 5.4 mg/kg + P 420 mg Q3W (loading dose: 840 mg), the recommended phase 2 dose. Patients in these mods must be mBC tx naive. For part 2, the primary objective is to assess safety and tolerability. A secondary objective is to assess the objective response rate (ORR) per local investigators by Response Evaluation Criteria In Solid Tumors v1.1. We report results for patients randomized before Oct 13, 2021 to mods 0 and 2 of part 2 (data cutoff [DCO]: Mar 4, 2022); recruitment is ongoing. Based on the distinct mechanism of action of T-DXd and P, we conducted preclinical studies with the drugs in HER2-overexpressing cell lines to elucidate their potential synergies. To assess the effects on T-DXd internalization, live cell imaging was performed using pH-dependent fluorescently labeled T-DXd. To assess the effects on HER2 signaling, total and p-HER2 levels and downstream substrates were evaluated by immunoblot.

Results: 23 patients were enrolled in the T-DXd monotherapy mod; 20 (87.0%) were receiving tx and 3 (13.0%) discontinued tx (withdrawal by patient, n=2; adverse event [AE], n=1) by DCO.
22 patients were enrolled in the T-DXd + P mod; 20 (90.9%) were receiving tx and 2 (9.1%) discontinued tx (AE, n=1; disease progression, n=1) by DCO. All patients experienced AEs (Table); 1 patient in each mod died. The unconfirmed ORR (80% CI) with T-DXd monotherapy and T-DXd + P was 82.6% (68.2%-92.2%) and 77.3% (61.9%-88.5%), respectively; updated data will be presented. Preclinical studies showed that T-DXd was more rapidly and effectively internalized in combination with P than when administered alone. Immunoblotting of cell lysates showed a greater reduction in total HER2 and HER2 signaling in response to combination tx than with T-DXd or P alone.

Discussion: In summary, 1L T-DXd monotherapy and T-DXd + P safety profiles and antitumor activity were consistent with those previously reported for T-DXd. Mature data in these mods are awaited, and other T-DXd combinations are being investigated in additional mods. Preclinical studies showed the potential for P to induce greater internalization of T-DXd and inhibition of HER2-driven signaling. These results support investigation of T-DXd in larger ongoing trials (eg, NCT04784715).

<table>
<thead>
<tr>
<th>Table. Summary of treatment duration and safety data</th>
<th>T-DXd monotherapy (n=23)*</th>
<th>T-DXd + pertuzumab (n=22)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual treatment duration, median (range), months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-DXd</td>
<td>5.6 (0.7-9.3)</td>
<td>5.5 (0.9-9.7)</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>NA</td>
<td>5.5 (0.9-9.7)</td>
</tr>
<tr>
<td>Any-grade AEs, n (%)</td>
<td>23 (100)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Any-grade AEs (≥30% in either module), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (73.9)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (26.1)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11 (47.8)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (30.4)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (21.7)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (17.4)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Grade ≥3 AEs, n (%)</td>
<td>6 (26.1)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Grade ≥3 AEs in &gt;1 patient in either module, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (4.3)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>2 (8.7)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>AEs of special interest, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjudicated interstitial lung disease/pneumonitis</td>
<td>1 (4.3)*</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>2 (8.7)*</td>
<td>0</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>1 (4.3)*</td>
<td>1 (4.5)*</td>
</tr>
</tbody>
</table>

AE, adverse event; NA, not applicable; T-DXd, trastuzumab deruxtecan.
* All patients were female. * Interstitial lung disease/pneumonitis was possibly related to T-DXd, was grade 2, and led to discontinuation of T-DXd. † Left ventricular dysfunction was possibly related to T-DXd, was grade 2 in both patients and led to T-DXd interruption in 1 patient. ‡ Death was due to disease progression (assessed by brain magnetic resonance imaging). † Death was due to disease under study (per autopsy report).

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AACR Outstanding Investigator Award for Breast Cancer Research

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GS4-02 Oncological Outcomes Following Omission of Axillary Lymph Node Dissection in Node Positive Patients Downstaging To Node Negative with Neoadjuvant Chemotherapy: the OPBC-04/EUBREAST-06/OMA study

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Background: Data on the oncologic safety of omission of axillary lymph node dissection (ALND) in node positive (N+) patients who downstage to ypN0 with neoadjuvant chemotherapy (NAC) is sparse. Additionally, there is no consensus on which axillary staging procedure should be used in this setting, sentinel lymph node biopsy (SLNB) alone or in combination with localization and retrieval of the clipped positive node, also known as targeted axillary dissection (TAD). Whether the reduction in the false negative rate observed with TAD translates into a significant reduction in the rate of axillary recurrence is unknown. We sought to evaluate oncologic outcomes after omission of ALND in a large, real-world cohort of breast cancer (BC) patients and to compare rates of axillary recurrence after SLNB with dual tracer mapping vs. TAD.

Methods: Data were collected from 19 centers in the Oncoplastic Breast Consortium (OPBC) and EUBREAST networks. Patients with T1-4 biopsy-proven N1-3 BC who underwent NAC followed by axillary staging with either SLNB with dual tracer mapping or TAD and who were pathologically node negative (ypN0) were included. ypN0 was defined as the absence of any tumor or isolated tumor cells. Competing risk analysis was performed to assess the cumulative incidence rates of axillary recurrence, locoregional recurrence, and any invasive (locoregional or distant) recurrence. Two-year cumulative incidence rates were compared between TAD and SLNB using the Gray’s test. Type I error rate was set to 0.05 (α).

Results: We included 785 patients (565 treated with SLNB and 220 with TAD) treated with NAC followed by surgery from 01/2014-12/2020. Median patient age was 50 years. The majority (57%) of patients had clinical T2 tumors, and 95% had N1 disease. Most (55%) were HER2+, and 21% were triple negative. Most patients (81%) received anthracycline and taxane-based chemotherapy regimens, but NAC regimens differed between patients treated with TAD and those treated with SLNB (Table 1). All patients with HER2+ tumors received anti HER2 therapy. Nodal radiotherapy was administered to 76% of patients, and was more common in patients who underwent TAD (82% TAD vs 74% SLNB, p=0.017). Breast pathologic complete response (ypT0/is) was more frequent among those patients that had TAD (80% TAD vs. 66% SLNB, p< 0.001). TAD localization was with wire in 46%, radioactive seed in 40%, ultrasound in 5%, tattoo in 2%, and with a combination of these techniques in 7%. The clipped node was successfully retrieved in 94% of TAD cases. The median number of lymph nodes removed was lower in the TAD group compared to the SLNB group [3 (IQR 3-5) vs 4 IQR 3-5), p< 0.001], as
was the median number of sentinel lymph nodes [3 (IQR 2-4) vs 4 IQR 3-5), p< 0.001] (Table 1).
The 5-year rates of any axillary recurrence, locoregional recurrence, and any invasive recurrence in the entire cohort were 1.1% (95%CI 0.39-2.4%), 3.1% (95%CI 1.6-5.3%) and 10% (95%CI 7.6-13%), respectively. The two-year cumulative incidence of axillary recurrence did not differ between patients treated with TAD compared to SLNB (0% vs 0.9%, p=0.19).

Conclusion: Early axillary recurrence after omission of ALND in patients who successfully downstage from N+ to ypN0 with NAC is a rare event following both SLNB or TAD, and was not significantly lower in TAD than SLNB. Although longer follow-up is needed to confirm these findings, the main advantage of TAD seems to be a reduction in the number of lymph nodes removed. Overall, these results support omission of ALND in patients who successfully downstage to node negative disease after NAC.

Table 1

<table>
<thead>
<tr>
<th>Table 1: Clinicopathological Features of the Study Cohort, Stratified by Axillary Staging Technique</th>
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<td>Full cohort (n=748)</td>
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<td>Number of positive nodes removed, median (IQR)</td>
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Frequency (row percent) reported for categorical variables, and median (IQR) reported for continuous variables.
*Node-negative HER2-negative,5: node-negative, pCR T0/pT0, and HER2-negative.
**Node-negative HER2-positive: node-negative, pCR T0/pT0, and HER2-positive.
†Applicable to HER2-positive patients only (n=492)
‡Applicable to HER2-negative patients only (n=650)
§Applicable to mastectomy patients only (n=472)
$Applicable to mastectomy patients only (n=501)
\$Applicable to mastectomy patients only (n=375)
Clinicopathological Features of the Study Cohort, Stratified by Axillary Staging Technique

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EMBARGOED GS4-03 Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy
GS4-04 Population-based Estimates of contralateral Breast Cancer Risk among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2

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Purpose To estimate the risk of contralateral breast cancer (CBC) among women in the general population with germline pathogenic variants (PVs) in ATM, BRCA1, BRCA2, CHEK2, and PALB2. Methods Among 15,104 prospectively followed women within the CARRIERS study treated with ipsilateral surgery for invasive breast cancer, a subset of 14,237 women were identified from population-based studies. The risk of CBC was estimated for PV carriers in each gene compared to women without PVs in a multivariate proportional hazard regression analysis accounting for the competing risk of death and adjusting for patient and tumor characteristics. The primary analyses focused on the overall cohort and on women from the general population. Secondary analyses examined associations by race/ethnicity, age at primary breast cancer diagnosis, menopausal status, and tumor estrogen receptor status. Results Germline BRCA1, BRCA2, and CHEK2 PV carriers with breast cancer were at significantly elevated risk (Hazard ratio ≥ 1.9, p< 0.05) of CBC, whereas only the PALB2 PV carriers with ER-negative breast cancer had elevated risks. In contrast, ATM PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Among premenopausal women, the 15-year cumulative incidence of CBC was >20% for BRCA1, BRCA2 and CHEK2 PV carriers with breast cancer, and for PALB2 PV carriers with ER-negative breast cancer. The 15-year cumulative incidence of CBC among postmenopausal PV carriers was < 20% for PV carriers in any of the 5 genes. Conclusions Women diagnosed with breast cancer and known to carry germline PVs in BRCA1, BRCA2, CHEK2, or PALB2 are at substantially increased risk of CBC and may benefit from enhanced surveillance and risk-reduction strategies.

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GS4-05 Phase II randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy

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Purpose/Objectives: Proton therapy is under investigation in breast cancer as a strategy to reduce heart and lung exposure, which is associated with late cardiopulmonary adverse events and secondary malignancy. To date, studies investigating postmastectomy radiotherapy (PMRT) with protons have used conventional fractionation. We hypothesized that condensing treatment to 15 fractions would be safe based on evidence that breast cancer is more sensitive to higher dose fractions than surrounding normal tissues. Materials/Methods: We conducted a randomized non-inferiority phase II trial comparing conventional and hypofractionated proton PMRT with primary endpoint of 24-month complication rate (defined as grade 3 or higher late adverse events using CTCAE, v 4.0 and/or unplanned surgical intervention in patients undergoing mastectomy with reconstruction). With a 10% non-inferiority margin the study ensured 80% power and had a one sided-type I error rate of 0.05. Cardiotoxicity was assessed with serial transthoracic conventional and 2-dimensional speckle tracking echocardiography (2D-STE). Eligibility included age ≥ 18 years with non-inflammatory breast cancer resected by mastectomy with indications for PMRT. Assignment of treatments was balanced with respect to immediate breast reconstruction (IBR). Conventional fractionation group received 50 Gy in 25 fractions of 2 Gy, and hypofractionation group received 40.05 Gy in 15 fractions of 2.67 Gy (RBE 1.1). Target volume included the chest wall and axillary, supraclavicular, and internal mammary lymph nodes. All patients were treated with multi-field optimized pencil beam scanning (intensity modulated proton therapy). Results: Between 2016 and 2018, 82 patients were enrolled and randomized (41 conventional, 41 hypofractionation). Median patient age was 52 years. 32.9% were staged T3-T4 and 79.3% node positive at diagnosis. 57 of 82 patients (69.5%) elected IBR. The median mean heart dose was 0.49 Gy and the median ipsilateral lung volume receiving 40% of prescription or greater (V40%) was 13.6%. No significant changes on conventional or 2D-STE at end-of-treatment or 3-month follow-up compared to baseline were observed. The rate of ≥ grade 2 acute dermatitis was lower with hypofractionation (44% vs 15%, p = 0.006). Other ≥ grade 2 acute adverse events including esophagitis (0 vs 5%), infection (5% vs 2.4%) and skin hyperpigmentation (7.3% vs 4.8%) were not significantly different between the two arms. With a median follow-up of 38.3 months, the 24-month complication rate was conventional 14.6% vs hypofractionation 17.1% (absolute difference 2.4%, p=0.17, 95% CI [-0.9, 15.7%]). In patients with IBR, 6 of 28 (21.4%) conventional and 7 of 29 (24.1%) hypofractionated patients developed complications (p =0.80). There was no significant difference in 3-year disease-free survival between the conventional (89.4%; 95% CI 80.0 – 99.8%) and hypofractionated (92.4%, 95% CI 84.5 – 100.0%) arms (p = 0.91). One local recurrence occurred in the hypofractionated arm simultaneous with regional and distant relapse. The remaining 6 recurrences were isolated distant events. Conclusions: Proton PMRT provided excellent locoregional control and normal tissue sparing. There were no subclinical echocardiographic changes indicative of radiation-induced cardiac dysfunction. Hypofractionation resulted in comparable disease control, tolerability and reconstruction outcomes as conventional fractionation. Although non-inferiority of hypofractionation could not be established based on the upper bound of the 95% confidence interval for complication rate being greater than 10%, both conventional and hypofractionation may be considered appropriate regimens for ongoing phase 3 randomized trials comparing photon and proton radiotherapy.

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GS4-06 Radiomic phenotypes of breast texture and association with breast cancer risk and masking

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Breast parenchymal patterns on radiologic images are associated with breast cancer risk. Radiomic features have been proposed as quantitative measures of parenchymal patterns. We defined intrinsic imaging phenotypes of breast parenchymal patterns based on radiomic features extracted from full field digital mammography (FFDM) in breast screening populations and assessed whether these phenotypes are associated with breast cancer risk and masking. We selected 30,000 women with 4-view FFDM exams from Hologic machines from three institutions (Hospital of the University of Pennsylvania, Mayo Clinic, and San Francisco Mammography Registry), randomly split into a training (20,000 women) and test set (10,000 women). In total, 390 radiomic features were automatically extracted from each image using a validated software pipeline, standardized, and adjusted for site differences using ComBat. We used two methods, hierarchical clustering and Principal Components (PCs) analysis, to classify significant variation among the features in the training set and replicate among the test set.

Next, we applied the replicated clusters and PCs to an independent nested case-control set [1082 invasive breast cancer (BC) cases (of which 151 were Black and 883 White women, 38 other race) matched to 2837 controls (411 Black and 2345 White women, 81 other race) on age, race, timing of images, and site]. We examined associations of the clusters and PCs with invasive breast cancer risk, as well as masking [defined as a false-negative (FN) screen (124 cases and 319 matched controls) and additionally the subset with symptomatic interval cancer (IC) within 12 months of negative screen (88 cases and 223 matched controls)] using conditional logistic regression. We evaluated their association with breast cancer alone, and with adjustment for age, body mass index (BMI) and breast density assessed by Breast Imaging Reporting and Data System (BI-RADS) using likelihood ratio tests. We estimated discrimination using area under the curve (AUC) and compared AUCs for models that included the radiomic clusters and PCs with the model that included only age, BMI and density. We also stratified analyses by race (Black/White).

From hierarchical clustering, we defined six statistically significant phenotype clusters (each of at least 1000 women) in the training set which were replicated in the test set. For PC Analysis, we identified six PCs in the training set, explaining 85% of the variation in texture features and reproduced these in the test set. The six radiomic phenotype clusters (P< 0.001) and six PCs (P< 0.001) were both associated with invasive BC, including after adjusting for age, BMI, and density (cluster P=0.004; PCs P< 0.001). Improvements in discrimination of invasive BC with inclusion of PCs or clusters were more pronounced among Black women (Table). Further, the PCs (P< 0.001) and clusters (P< 0.001) were significantly associated with FN overall and for symptomatic IC (PCs P< 0.001; clusters P=0.001), but only PCs remained significant after adjusting for age, BMI and density (PCs P=0.004 for FN; PCs P=0.007 for symptomatic IC).

Discrimination of masking also improved with inclusion of both clusters and PCs (Table). We identified reproducible radiomic phenotypes that are associated with invasive BC risk, above and beyond breast density with the strongest associations for invasive BC among Black women and symptomatic interval cancers.

<table>
<thead>
<tr>
<th>Group</th>
<th>AUC (95% CI)</th>
<th>AUC (95% CI)</th>
<th>AUC (95% CI)</th>
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<tr>
<td></td>
<td>Age+BMI+BIRADS 5+6 Clusters</td>
<td>Age+BMI+BIRADS 5+6 Clusters</td>
<td>Age+BMI+BIRADS 5+6 Clusters</td>
</tr>
<tr>
<td>Invasive BC - Overall</td>
<td>.601 (.585, .621)</td>
<td>.613 (.595, .631)</td>
<td>.616 (.598, .634)</td>
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<tr>
<td>Black Women</td>
<td>.627 (.580, .674)</td>
<td>.646 (.600, .693)</td>
<td>.685 (.640, .730)</td>
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<tr>
<td>White Women</td>
<td>.603 (.583, .623)</td>
<td>.506 (.586, .626)</td>
<td>.515 (.595, .634)</td>
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<tr>
<td>False Negative BC</td>
<td>.636 (.584, .689)</td>
<td>.611 (.619, .722)</td>
<td>.705 (.655, .755)</td>
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<tr>
<td>Symptomatic Interval</td>
<td>.686 (.625, .747)</td>
<td>.740 (.682, .797)</td>
<td>.762 (.706, .818)</td>
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GS4-08 10-year results of a phase 3 trial of low-dose tamoxifen in non-invasive breast cancer

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We have previously shown in a phase 3 trial that tamoxifen 5 mg/day for 3 years decreased by 52% the incidence of recurrence of invasive breast cancer or DCIS after a median follow-up of 5.1 years in women with excised non invasive breast disease, including atypical ductal hyperplasia, DCIS or LCIS (DeCensi et al. JCO 2019; 37:1629). Toxicity was negligible with only an extra hot flash per day in the tamoxifen arm compared with the placebo arm. These findings were incorporated into the ASCO clinical practice guidelines for breast cancer risk reduction as an alternative option to standard doses and duration of tamoxifen or aromatase inhibitors in women with non-invasive disease (Visvanathan et al. JCO 2019; 37:3152). In the present study we update the findings on breast cancer recurrence after a median of 9.14 years (interquartile range, IQR, 7.16-10.73) and a total of 10.57 person years of follow up to see if the treatment effect is retained with more events and after a median of approximately 6 years from treatment cessation. We conducted a national multicenter randomized trial of tamoxifen, 5 mg/d or placebo administered for 3 years after surgery in women with hormone-sensitive or unknown breast intraepithelial neoplasia, including atypical ductal hyperplasia and lobular or ductal carcinoma in situ. The primary end point was the incidence of invasive breast cancer or ductal carcinoma in situ. Between November 1, 2008, and March 31, 2015, 1,160 women were
screened and 500 aged 75 years of age or younger were included in the study. Women with high-grade or comedo/necrotic DCIS received adjuvant radiotherapy of 50 Gy in 25 courses. The mean age was 54 years (standard deviation, 9 years), and 55% of participants were postmenopausal. The mean (SD) body mass index, kg/m², was 25.7 (4.8) on tamoxifen and 25.3 (4.2) on placebo. Twenty percent had ADH, 11% had LCIS, and the remaining 69% had DCIS. After a median follow-up of 9.14 years, there were 22 neoplastic events (invasive breast cancer or DCIS) with tamoxifen and 37 with placebo (annual rate 11.09, 95% CI, 7-30-16.84 on T vs 19.71, 95% CI, 14.28-27.21 on P per 1,000 person-years; hazard ratio, 0.56; 95% CI, 0.33 to 0.95; P = .03), which resulted in a 5-year number needed to treat of 18. Overall, 71% of the recurrences were invasive breast cancer. The follow-up was updated with the most recent visit within 12 months in two thirds of the participants, so an update of all participants will be performed by Sept 30th with full analysis of neoplastic events, annual risk rate ratio, serious adverse events and deaths. Moreover, an updated analysis of potential effect modifiers will be conducted, including menopausal status, baseline estradiol levels, menopausal symptoms, BMI, smoking status and Ki-67 of the primary lesion. In conclusion, our findings indicate that low dose tamoxifen given for 3 years still significantly prevents recurrences from non-invasive breast cancer after a median of 6 years from treatment cessation, providing a valid prevention/interception option in this disease group. Supported by Ente Ospedaliero Ospedali Galliera, Genova, Italy, the Italian Ministry of Health (RFPS-2006-1-339898), the Italian Association for Cancer Research (IG 2008 Grant No. 5611), and the Italian League against Cancer (LILT 7-08).

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EMBARGOED GS4-09 Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer: Primary Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13)
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GS5-01 Addition of platinum to sequential taxane-anthracycline neoadjuvant chemotherapy in patients with triple-negative breast cancer: A phase III randomized controlled trial

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Background: Despite several studies, the impact of adding platinum on long-term outcomes in triple-negative breast cancer (TNBC) has not been definitively established. We conducted a single-centre randomized phase III trial to evaluate the efficacy and toxicity of adding platinum to standard neoadjuvant chemotherapy in these patients. Methods: Patients with histopathological diagnosis of TNBC without evidence of distant metastases who were planned to be treated with neoadjuvant chemotherapy (NACT) were randomized to experimental or control arms after stratification by menopausal status (premenopausal or perimenopausal, and postmenopausal) and stage [operable breast cancer (OBC, clinical T1-3, N0-1, M0), and locally advanced breast cancer (LABC, cT4 or N2-3, M0)]. NACT in control arm included paclitaxel 100 mg/m2 once per week for 8 weeks followed by doxorubicin (60 mg/m2) or epirubicin (90 mg/m2) plus cyclophosphamide (600 mg/m2) once every 21 days for 4 cycles while in experimental arm carboplatin (area-under-curve 2) was added once per week for 8 weeks with paclitaxel. After NACT patients received standard surgery for primary tumor and axillary lymph nodes (LN) followed by radiotherapy. The primary endpoint was disease-free survival (DFS) and the secondary endpoints were overall survival (OS), pathological complete response (pCR, absence of invasive cancer from breast and LN), and toxicity. Results: Between April 2010 and January 2020, 720 (355 control, 365 experimental) patients with a median age of 46 (25-69) years [< 50 years, 502 (69.7%), premenopausal 418 (58.2%)], were included in the study, of whom 285 (39.6%) had OBC and 435 (60.4%) had LABC, with a median clinical tumor size of 6.0 (1.2- 20.0) cm. At a median follow-up of 67.6 (18.9-142.2) months, in the experimental and control arms, the 5-year DFS were 70.6% (95% CI 65.7-75.5%) and 64.5% (95% CI 59.4-69.6%), respectively (HR 0.79, 95% CI 0.61-1.02, p=0.073), 5-year OS were 74.0 (95% CI 69.3-78.7%) and 66.7% (95% CI 61.6-71.8%), respectively (HR 0.75, 95% CI 0.57-0.98, p=0.034), and pCR were 55.2% (95% CI 49.7-69.5%) and 41.5% (95% CI 36.2-47.0%), respectively (p=0.0004). In subgroup analyses, the benefit of carboplatin was confined to patient's < 50 years, with significant interaction between treatment and age. In women < 50 years of age, in experimental versus control arms, 5-year DFS and OS were 74.5% vs 62.3% (p=0.003, interaction p=0.003) and 76.8% vs 65.7% (p=0.003, interaction p=0.004), respectively. Addition of carboplatin had a significant beneficial impact on OS after adjusting for baseline clinical tumor size and age in a Cox model (HR 0.75, 95% CI 0.58-0.98, p=0.038). In experimental and control arms, numbers of patients with any grade >/=3 toxicity were 140 (38.5%) and 107/355 (30.14%), respectively, (p=0.02), grade >/=3 neutropenia were 2/364 (0.55%) and 1/355 (0.28%), respectively, grade >/=3 thrombocytopenia were 1/364 (0.27%) and 0 (0%), respectively, and febrile neutropenia were 26/364 (7.14%%) and 18/355 (5.07%), respectively (p=0.25). Conclusions: This study, to our knowledge the largest reported trial of neoadjuvant platinum in TNBC thus far, suggests that addition of carboplatin to sequential taxane-anthracycline neoadjuvant chemotherapy results in substantial and clinically meaningful improvement in disease-free and overall survival in young patients with TNBC and should be the standard of care in these patients.

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GS5-02 Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study

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Background: The GeparOLA study was designed to evaluate the efficacy and safety of the combination of paclitaxel (P) plus olaparib (O) as part of neoadjuvant chemotherapy (NACT) in patients with human epidermal growth factor receptor 2 (HER2)-negative, either hormone receptor (HR)-positive or HR-negative and homologous recombination deficiency (HRD) defined as having a g/tBRCA mutation and/or a high HRD score. Primary analysis showed a pCR rate of 55.1% (90% CI 44.5%-65.3%) with PO and 48.6% (90% CI 34.3%-63.2%) with P plus carboplatinum (Cb). The PO combination could not exclude a pCR rate of ≤55% in the PO arm but was significantly better tolerated. Analysis on the stratified subgroups showed higher pCR rates with PO in the cohorts of patients < 40 years and HR-positive tumors (Fasching Ann Oncol 2020). Here, we report long-term data. Methods: GeparOLA (NCT02789332) was a non-comparative, multicenter, prospective, randomized, open-label, phase II trial. Patients with primary HER2-negative breast cancer, HRD and indication for chemotherapy (cT2-cT4a-d or cT1c and cN+ or cT1c and pNSLN+ or cT1c and TNBC or cT1c and Ki-67 >20%) were randomly assigned to receive either P 80 mg/m2 weekly plus O 100 mg twice daily for 12 weeks or P plus Cb area under the curve 2 (AUC2) weekly for 12 weeks, both followed by four cycles of either 2-weekly or 3-weekly epirubicin 90 mg/m2 plus cyclophosphamide 600 mg/m2. Primary endpoint was pCR (ypT0/is ypN0) rate after NACT with PO followed by EC. Long-term efficacy endpoints included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival (OS). The time-to-event endpoints analysis is planned with median follow-up of at least 4 years and a follow-up completeness of at least 80%. Results: Between September 2016 and July 2018, 274 patients were screened, of whom 107 were randomized
and 106 (PO N=69; PCb N=37) started treatment. The median age was 47.0 years (range 25.0-71.0); 32 patients were aged < 40 years; 36.2% of patients had cT1 tumors and 31.8% were cN-positive; the majority (86.8%) had grade 3 tumors and a Ki-67>20% (89.6%). Seventy-seven patients (72.6%) had TNBC. After a median follow-up of 49.8 months (range 0.1-69.1), 18 (15 in PO; 3 in PCb) iDFS events and 7 (6 in PO; 1 in PCb) deaths were reported. The 4-year survival rates are shown in the table below. iDFS (HR PO to PCb=2.86 [95%CI 0.83-9.9], log-rank p=0.081), DDFS (HR =3.03 [95%CI 0.67-13.67], log-rank p=0.129), and OS (HR=3.27 [95%CI 0.39-27.2], log-rank p=0.244) tended to be inferior with olaparib. Patients without g/tBRCA mutation seem to benefit from the use of carboplatinum (7/30 iDFS/DDFS events in PO; 0/16 in PCb, log-rank p=0.037, HR n.a.). Conclusions: In patients with HER2-negative and HRD breast cancer the use of olaparib instead of carboplatinum although showing comparable pCR rates, tended to result in an overall inferior outcome. This was mainly driven by the patients without a g/tBRCA mutation. In patients with a g/t BRCA mutation no difference between olaparib and carboplatinum was seen. Key words: Olaparib, HER2-negative breast cancer, HRD, survival

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GS5-03 Evaluation of anti-PD-1 Cemiplimab plus anti-LAG-3 REGN3767 in early-stage, high-risk HER2-negative breast cancer: Results from the neoadjuvant I-SPY 2 TRIAL

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Background: I-SPY2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes defined by hormone-receptor (HR), HER2, and MammaPrint (MP) status to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer. The primary endpoint is pathologic complete response (pCR). Cemiplimab is an anti-PD-1 inhibitor approved for the treatment of NSCLC and cutaneous basal and squamous cell CA. Lymphocyte activation gene 3 (LAG-3) binds MHC class II leading to inhibition of T-cell proliferation and activation and is often co-expressed with PD-1. REGN3767 is a fully humanized mAb that binds to LAG-3 and blocks inhibitory T-cell signaling. Concurrent blockade of LAG-3 with an anti-PD-1 may enhance efficacy of an anti-PD-1.

Methods: Women with tumors ≥ 2.5cm were eligible for screening. Only HER2 negative (HER2-) patients were eligible for this treatment; HR positive (HR+) patients had to be MP high risk. Treatment included Paclitaxel 80 mg/m2 IV weekly x 12 and Cemiplimab 350 mg and REGN3767 1600 mg both given q3weeks x 4, followed by doxorubicin/cyclophosphamide (AC) every 2 weeks x 4. The control arm was weekly paclitaxel x 12 followed by AC every 2-3 weeks x 4. Cemiplimab/REGN3767 was eligible to graduate in 3 of 10 pre-defined signatures: HER2-, HR-HER2-, and HR+/HER2-. The statistical methods for evaluating I-SPY 2 agents has been previously described. To adapt to changing standard of care, we constructed “dynamic controls” comprising ‘best’ alternative therapies using I-SPY 2 and external data and estimated the probability of Cemiplimab/REGN3767 being superior to the dynamic control. Response predictive subtypes (Immune+ vs Immune-) were assessed using pre-treatment gene expression data and the ImPrint signature.

Results: 73 HER2- patients (40 HR+ and 33 HR-) received Cemiplimab/REGN3767 treatment. The control group included [357 patients with HER2- tumors (201 HR+ and 156 HR-) enrolled since March 2010. Cemiplimab/REGN3767 graduated in both HR-/HER2- and HR+/HER2- groups; estimated pCR rates (as of June 2022) are summarized in the table. Safety events of
note for Cemiplimab/REGN3767 include hypothyroidism 30.8%, adrenal insufficiency (AI) 19.2%, hyperthyroidism 14.1%, pneumonitis 1.3%, and hepatitis 3.8%. All were G1/2 except for 6 (7.7%) G3 AI and 3 (3.8%) G3 colitis. Rash occurred in 62.8%, 9% G3 and 2 pts (2.6%) had pulmonary embolism. X% of adrenal insufficiency cases required replacement therapy. 40 patients (11 HR+ and 29 HR-) in Cemiplimab/REGN3767 were predicted Immune++; 32 (29 HR+ and 3 HR-) were predicted Immune-. In the HR+ group pCR was achieved in 10/11 (91%) patients with Immune+ subtype compared with 8/29 (28%) with Immune- subtype. Additional biomarker analyses are ongoing and will be presented at the meeting.

Conclusion: The I-SPY 2 study aims to assess the probability that investigational regimens will be successful in a phase 3 neoadjuvant trial. Dual immune blockade with a LAG-3 inhibitor and anti-PD1 therapy resulted in a high predicted pCR rate both in HR-/HER2- (60%) and HR+/HER2- (37%) disease. The novel Imprint signature identified a group of HR+ patients most likely to benefit from this active regimen.

<table>
<thead>
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<th>Signature</th>
<th>Estimated pCR rate</th>
<th>Probability Cemiplimab/REGN3767 Superior to Control</th>
<th>Predictive Probability of Success in Phase 3</th>
<th>Probability Cemiplimab/REGN3767 Superior to Dynamic Control</th>
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<tr>
<td>HER2-</td>
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<td>0.211</td>
<td>&gt;0.999</td>
<td>0.960</td>
</tr>
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<td>0.145</td>
<td>&gt;0.999</td>
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Estimated pCR rates

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GS5-04 Identification of symptoms that are associated with irAEs in the I-SPY clinical trial

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Title. Identification of symptoms that are associated with irAEs in the I-SPY clinical trial

Background. Immunotherapy has emerged as an important component of neoadjuvant therapy for some patients with breast cancer (BC). As a result, immune-related adverse events (irAEs) are increasing and have effects on both short and long term symptoms significantly impacting patient quality of life. BC patients may develop new conditions including arthralgias, gastrointestinal issues, endocrinopathies, and fatigue during or after cancer therapy that may be acute or long-lasting in nature. Monitoring for early onset and severity of symptoms, and adjusting treatment and symptom management could optimize therapy for a particular patient, maximizing potential efficacy while mitigating toxicity. We sought to identify patient demographic characteristics and symptom patterns associated with risk for development of irAEs in the context of a randomized trial for patients with early-stage high-risk breast cancer.

Methods. I-SPY2 is a multi-center, phase 2 trial using response-adaptive randomization for high-risk early-stage women with BC. The study population for this analysis includes enrolled patients receiving combinations of experimental immunotherapy and chemotherapy. Groups considered for statistical comparisons included those that developed an irAE versus those that did not develop an irAE up until the surgery timepoint. In I-SPY adverse events are documented through the Common Terminology Criteria for Adverse Events (CTCAEv5.0). Hypothyroidism, adrenal insufficiency, and pneumonitis were the irAEs considered in this study. A chi-square test was used to assess associations between race and ethnicity (White, Asian, Black, non-Hispanic) and irAEs. One-way ANOVA was used to evaluate the association between age (>50 vs < 50) and irAEs. 33 symptoms reported at CTCAE grade 2 or higher were included in the analyses and a symptom burden score was calculated using area under curve (AUC) which combined the duration of each symptom between baseline and week 6 of treatment, and grade of adverse event. Regularized regression using leave-one out cross validation was used to evaluate early symptoms (as quantified by the symptom burden score) as predictors, and irAEs as surrogate responses. Results. Out of 461 patients, percentages of patients with irAEs of interest included hypothyroidism (13%), adrenal insufficiency (9%), and pneumonitis (4%). Demographic information was available for 333 patients, of which 270 (81%) were White, 23 (7%) were Asian, 37 (11%) were African American (AA) and 278 (17%) were non-Hispanic. There were proportionately higher number of white patients that developed hypothyroidism than non-white patients (35 of 265 (13%) vs 2 of 63 (3%), P < 0.04). Pneumonitis was more common in patients over 50 years old than under 50 years old (35 of 265 (13%) vs 2 of 63 (3%), P < 0.04). Pneumonitis was more common in patients over 50 years old than under 50 years old (P < 0.02). Symptoms that were most commonly reported up to week 6 of treatment among patients who developed an irAE included: diarrhea (36%), fatigue (15%), dizziness (12%) and shortness of breath (SOB) (11%). Symptoms associated with the development of hypothyroidism included fatigue (15%, mean AUC=11.8 vs 5.8 for those that did not develop irAE), SOB (11%, 4.3 vs 2.8), and blurry vision (1%, 1.0 vs 0.12). Development of adrenal insufficiency was associated with early reports of diarrhea (36%, 19.0 vs 10.5), SOB (11%, 7.8 vs 2.6), joint pain (3%, 2.29 vs 0.58), decreased
appetite (3%, 3.55 vs 0.91), and constipation (1%, 3.6 vs 0.02). No significant early symptoms emerged for pneumonitis due to a limited number of events. Conclusion. Our study utilizes an analysis framework that is aimed to determine symptom clusters that predict the development of irAEs. We describe specific symptoms presenting early with the development of hypothyroidism and adrenal insufficiency, in recognition of allowing physicians to be more diligent in active and post treatment monitoring.

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GS5-05 ZNF689 deficiency promotes intratumor heterogeneity and resistance to immune checkpoint blockade in triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) is an aggressive disease characterized by remarkable intratumor heterogeneity (ITH), which poses a significant therapeutic challenge. However, the key determinants and underlying mechanisms of ITH in TNBC remain to be fully elucidated. Methods: We used multi-omics data from our cohort (n = 260) and The Cancer Genome Atlas (n = 134) cohort to comprehensively characterize ITH at the genetic and histologic levels. Transcriptomic differences between high ITH and low ITH tumors were compared to identify the core genes contributing ITH in TNBC. Xenograft models were used to examine the role of key determinants in TNBC ITH. The molecular mechanism was investigated by mass spectrometry, coimmunoprecipitation, pull-down, RNA-seq, long interspersed element-1 (LINE-1) reporter, ATAC-seq, luciferase reporter assays, chromatin immunoprecipitation, flow cytometry and coculture assay. Results: We found that high ITH was associated with poor patient survival and immune checkpoint blockade (ICB) resistance, which were validated in four independent ICB-treated trials. Further analysis indicated zinc finger protein 689 (ZNF689) deficiency as an important determinant of TNBC ITH. Mechanistically, the ZNF689-TRIM28 complex directly bound to the promoter of LINE-1, inducing H3K9me3-mediated transcriptional silencing. ZNF689 deficiency reactivated LINE-1 retrotransposition to exacerbate genomic instability, which promoted ITH. ZNF689 deficiency-induced ITH inhibited antigen presentation and CD8+ T cell infiltration, leading to ICB resistance. Pharmacological inhibition of LINE-1 retrotransposition reduced ITH, augmented antitumor immunity, and eventually sensitized ZNF689-deficient tumors to ICB. Consistently, ZNF689 expression positively correlated with favorable prognosis and ICB responsiveness in clinical samples. Conclusions: Our study uncovers a new mechanism underlying ZNF689 deficiency-induced ITH and suggests LINE-1 inhibition combined with ICB as a novel treatment strategy in TNBC.

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GS5-06

GS5-06 InteractPrint predicts clinically meaningful interactions between cancer epithelial cells and immune cells: Lessons from a single-cell breast cancer atlas

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BACKGROUND: While immunotherapy has revolutionized the treatment of many solid tumors, the efficacy of immunotherapy regimens is comparatively lower in breast cancer. Immunotherapy efficacy is often negatively correlated with intratumor heterogeneity. Novel immunotherapy approaches in breast cancer should leverage how cancer epithelial cell heterogeneity affects immune cells in the tumor microenvironment. However, current definitions of cancer epithelial cell heterogeneity in breast cancer have limited resolution. Single cell RNA-seq (scRNA-seq) provides an unprecedented opportunity to further define cancer epithelial cell heterogeneity and identify how heterogeneity influences interactions with immune cells.

METHODS: We generated a novel scRNA-seq dataset of 236,363 cells from 119 primary breast tumors biopsied from 88 patients taken from 8 publicly available datasets, currently the largest published scRNA-seq dataset in breast cancer. To define cancer epithelial cell heterogeneity, we performed unsupervised clustering and supervised clustering based on molecular subtype and expression of clinical target genes on all cancer epithelial cells. This identified 11 gene elements (GEs), which reflect key molecular features that vary between cancer epithelial cells. Receptor-ligand pairing analysis allowed us to determine how cells that
highly express each GE interact with various immune cells. We developed InteractPrint, a score to predict the predominant tumor-interacting immune cells, based on the GE composition of an individual patient tumor. RESULTS: In our dataset, 17% of samples were HER2+, 41% were HR+, and 42% were TNBC. This dataset was statistically powered to characterize cancer epithelial cell heterogeneity. For each of the 11 GEs, we predicted interactions with immune cells. Experimentally, GEs with predicted NK cell interactions showed sensitivity to NK cell cytotoxicity. In a spatially resolved transcriptomics dataset, GEs with predicted T cell interactions demonstrated colocalization with CD8+ T cells, while those with limited predicted T cell interactions did not. To infer GE-immune interactions at the patient level (GEs define cell-level interactions), we developed InteractPrint. To validate InteractPrint, we assessed the accuracy of the T cell InteractPrint in predicting response to anti-PD-1 therapy. Across two trials and all breast cancer subtypes, T cell InteractPrint demonstrated significant improvement over PD-L1 in predicting response to anti-PD-1 therapy. In an scRNA-seq dataset of samples from patients treated with pembrolizumab, we observed AUC of 85% (p < 0.005) for T cell InteractPrint vs. 61% (p > 0.05) for PD-L1 in predicting response to anti-PD-1 therapy. In patients treated with paclitaxel + pembrolizumab in the I-SPY 2 trial, we observed AUC of 81% (p < 0.00001) for T cell InteractPrint versus 72% (p = 0.001) for PD-L1. CONCLUSIONS: Our results demonstrate considerable cancer epithelial cell heterogeneity across primary breast tumor samples and clinical subtypes. We defined this heterogeneity and leveraged it to predict immune cell interactions within a patient’s tumor. We developed T cell InteractPrint to capture heterogeneous interactions between cancer epithelial cells and CD8+ T cells. T cell InteractPrint is predictive of response to anti-PD-1 immune checkpoint inhibition at higher AUC than PD-L1. This provides a path forward for the interpretation of cancer epithelial cell heterogeneity in a clinically meaningful way.

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Background: Younger women with breast cancer have increased risk of development of brain metastases irrespective of the tumor subtype. We have shown that pre-menopausal levels of 17-β-Estradiol (E2) contributes to the promotion of brain metastases by influencing the tumor microenvironment. E2 promotes brain metastasis (BM) of estrogen receptor negative (ER−) BC cells by inducing neuroinflammatory ER+ astrocytes in the brain niche to secrete pro-metastatic factors critical for early brain colonization. Ovariectomy (OVX) in combination with the aromatase inhibitor (Letrozole) prevented brain colonization of triple negative (TNBC) (ER-PR-HER2-) human xenografts (MDA231BR/NSG) and murine models (E0711/C57Bl6, 4T1/BALBc) through paracrine activation of EGFR and TRKB, pathways involved in increased invasion and early tumor initiation. Yet, the extent to which E2-depletion therapies can decrease progression of established BM in combination with current standard of care for brain metastasis remains unknown. Goal: Current standard of care (SOC) for patients with TNBC brain metastasis includes irradiation (SRS, whole brain) and immunotherapy (PD-1/PDL-1 inhibitors). The goal of this study was to assess how E2-depletion therapies affects brain immune function in the context of SOC for brain metastatic progression of TNBC. Results: To assess whether E2-depletion could decrease BM progression in a model that mimics standard of care for BM, TNBC E0771-GFP-luc cells were injected intracardially in syngeneic ovariectomized (OVX)-
female C57BL6 mice supplemented with pre-menopausal levels of E2. Seven days after injection (when cancer cells have colonized), mice received a single 15Gy dose brain irradiation and were randomized to continue receiving E2, E2 withdrawal (E2WD) or E2WD plus the aromatase-inhibitor letrozole (E2WD+LET). Brain metastatic burden significantly decreased in E2WD and E2WD+Letrozole treated mice as compared to E2-treated mice. Injection of E0711 cells in immunocompromised NSG mice or in the absence of brain irradiation abolished this effect, suggesting that E2-depletion therapies decrease BM progression through boosting radiation-induced anti-tumor immunity. Accordingly, there were no differences in BM progression in E2, E2WD or E2WD+let treated mice in a xenograft model (F2-7 TNBC cells) in NSG mice, even in the presence of brain irradiation. Immune-profiling of brains from OVX+E2, OVX and OVX+Let C57BL6 mice carrying BMs showed dynamic changes in immune populations at early and late stages of brain metastatic colonization. At early stages post brain colonization (3 days post ic injection) E2-treated mice showed a decreased fraction of CD11b+CD45Int CD206+ microglia/CNS macrophages as compared to OVX+LET-treated mice, without significant changes in the fraction of infiltrated lymphocytes, suggesting E2 represses early immunosurveillance through repression of microglia/CNS macrophage activation. At later stages of brain colonization (7 days post ic injection), E2-treated mice showed an increased fraction of proinflammatory microglia and decreased fraction of T and B cells as compared to OVX or OVX+let treated mice. While E2-depletion increased the recruitment of T cells to the brain niche, the fraction of CD279 (PD1+) brain T cells was similar among groups. Ongoing studies assess the efficacy of E2-depletion therapies in combination with brain radiation and PD-1 inhibitors to decrease metastatic burden and improve survival in preclinical models. Conclusion: Our results support the hypothesis that estradiol promotes brain metastatic progression by stimulating an immunosuppressive brain microenvironment. As such, FDA-approved E2-depletion therapies (aromatase inhibitors and selective-estrogen modulators) could be used in combination with brain irradiation and PD-1 inhibitors to promote a more effective anti-tumoral immune response.

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GS5-08 Soluble E-cadherin: a novel prognostic biomarker and driver of brain metastasis in inflammatory breast cancer

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Background: Inflammatory breast cancer (IBC) is a highly aggressive form of breast cancer with rapid onset and a strong propensity to spread to distant organs. Five-year overall survival (OS) rates remain poor, in part because of the high risk of brain metastasis: 19% of patients with IBC have brain metastases within the first 2 years after diagnosis. Our hypothesis for this study was that soluble E-cadherin (sEcad), an 80-kDa extracellular proteolytic fragment of full-length E-cadherin - a tumor promoter in IBC, is crucial for driving brain metastasis in IBC. Methods: We analyzed serum sEcad levels in from 348 IBC patients by ELISA. Four IBC cell lines [ER–/HER2+ (MDA-IBC3; SUM190) and ER–/HER2– (SUM149; BCX010)], human brain microvascular endothelial cells, and immortalized human astrocytes were used in this study. Stable overexpression of sEcad in IBC cell lines was achieved using lentiviral vectors. Mass spectrometry and Bio-ID-based proteomics assays, and RNA sequencing were used to identify sEcad-interacting proteins and potential mechanisms. In vivo, we studied tumor growth and brain metastasis in mice by injecting IBC cells into the mammary fatpad or tail vein, respectively, of SCID/Beige mice. Results: In IBC patients, higher serum sEcad levels correlated with poorer OS (p=0.02), earlier development of metastasis (p=0.006), and development of brain metastasis (p=0.04). On multivariable analysis, sEcad independently predicted OS (hazard ratio [HR]=2.07 [95% CI 1.19-3.60], p=0.01). In vitro, sEcad overexpression in IBC cell lines promoted anchorage-independent growth, migration, invasion, and resistance to anoikis. In vivo, sEcad-overexpressing SUM149 cells promoted primary tumor growth (p=0.007). Mice injected with sEcad-overexpressing MDA-IBC3 cells also had higher incidence of brain metastasis (100% vs 50%, p=0.03), metastatic burden (p=0.02) and number of metastases per mouse (p=0.0009), and had worse OS (p=0.0016), and brain metastasis-free survival (p=0.04), relative to controls. We further found that sEcad increased cancer cell adhesion to brain endothelial cells (p=0.01) and promoted induction of reactive astrocytes (as identified by high glial fibrillary acidic protein levels) in vitro and in vivo. Mechanistically, mass spectrometry and Bio-ID assays identified X-linked inhibitor of apoptosis protein (XIAP), a potent inhibitor of apoptotic cell death, as a novel binding partner of sEcad, which was validated through co-immunoprecipitation. Further analysis showed that sEcad bound to the BIR2 domain of XIAP. XIAP is the most potent and best-defined anti-apoptotic IAP family member, and it could induce NF-kB activation to inhibit tumor cell apoptosis. Gene set enrichment analysis of RNA-seq profiling data showed activation of NF-kB signaling and downregulation of apoptotic pathways in the sEcad-overexpressing SUM149 cells compared with controls. Immunoblotting revealed that sEcad enhanced XIAP expression, activated NF-kB signaling, and inhibited cleavage of caspase-3 in IBC cells. Conclusions: We found that higher serum sEcad correlates with development of brain metastases and independently predicts poor OS in patients with IBC. We further found that sEcad promotes tumor growth and brain metastasis, perhaps via activation of XIAP/NF-kB signaling in breast cancer cells and promotion of endothelial cell adhesion and reactive astrocytosis in the brain microenvironment. These findings uncover a novel and crucial role for sEcad in brain metastasis and provide new insights and potential therapeutic targets for patients with metastatic IBC.

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GS5-10 Utility of the 70-gene MammaPrint test for prediction of extended endocrine therapy benefit in patients with early-stage breast cancer in the IDEAL Trial

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Background: The IDEAL trial showed no significant benefit of 5 years extended endocrine therapy (EET) using letrozole in postmenopausal patients with hormone receptor positive (HR+) breast cancer (BC) versus 2.5 years. Genomic classifiers may assist with treatment decisions by predicting EET benefit. The 70-gene MammaPrint (MP) test classifies tumors as having a higher or lower risk of distant metastasis in HR+ early-stage BC. A MP lower risk result can be further classified as either Ultra-Low risk or Low risk of distant metastasis. In the NSABP B42 trial, MP predicted a statistically significant absolute benefit from EET in patients with a MP Low Risk result. Here, we aimed to determine the utility of MP in identifying a subgroup of patients enrolled in the IDEAL trial for which 5 years of EET is beneficial compared to 2.5 years.

Methods: A total of 869 patients had available primary tumor tissue for testing. MP results were available for 545/869 patients, of which 515 did not have an event at 2.5 year after randomization and were used for our analyses. The MP result for each patient was calculated by Agendia while blinded to patient clinical outcomes. The primary endpoint was distant recurrence (DR). Secondary endpoints were recurrence free interval (RFI) and breast cancer free interval (BCFI) as defined by STEEP criteria. Patients were classified as higher risk (score -1.000 - 0) or lower risk (score 0.001 - 1.000). Lower risk tumors were further classified as either MP Ultra-Low (score > 0.355) or MP Low Risk (score ≥ 0.001, ≤ 0.355). Likelihood ratio test based on stratified Cox proportional hazards (PH) model were used to evaluate treatment
by risk group interaction. Differences in endpoints between treatment groups were assessed by stratified log-rank tests. Hazard ratios (HR) and 95% Confidence Intervals (CI) were computed based on the stratified Cox PH model.

Results: The clinical characteristics of the 515 IDEAL samples with a MP result were comparable to the whole IDEAL cohort (n=1820). Within the 2.5 year EET group, 50.6% (n=134) were MP higher risk and 49.4% (n=131) MP lower risk, of which 14.5% (n=19/131) were MP Ultra-Low. Within the 5 year EET group, 50.0% (n=125) were MP higher risk and 50.0% (n=125) MP lower risk, of which 11.2% (n=14/125) were MP Ultra-Low. Among patients with MP lower risk tumors, 5 years vs. 2.5 years of EET resulted in a significant absolute benefit of 9.8% for DR (HR=0.42, [95% CI 0.174-0.996]), 9.8% for RFI (HR=0.43, [95% CI 0.198-0.934]), and 8.8% (HR=0.53, [95% CI 0.264-1.055]) for BCFI, whereas patients with MP higher risk tumors did not derive significant benefit (Table 1). Within the MP lower risk group, 5 year vs 2.5 year EET benefit was more pronounced in MP Low tumors, which exhibited a significant benefit of 10.1% for DR (HR=0.32, [95% CI 0.116-0.866]), 11.7% for RFI (HR=0.35, [95% CI 0.147-0.824]), and 9.7% for BCFI (HR=0.48, [95% CI 0.225-1.015]); MP Ultra Low tumors did not derive significant benefit. Treatment-by-risk group interaction was statistically significant for RFI.

Conclusion: A significant EET benefit was observed for MammaPrint lower risk tumors but not for MP higher risk tumors. MammaPrint Low tumors exhibited the largest absolute benefit of 5 years of EET compared to 2.5 years. Consistent with the findings in the NSABP B42 trial, the results from this second randomized trial provide clinically meaningful implications in patient selection for extended endocrine therapy.

Table 1. IDEAL: 10-year outcome analysis comparing 5 years vs. 2.5 years of EET using letrozole stratified by MP risk.
Table 1. IDEAL: 10-year outcome analysis comparing 5 years vs. 2.5 years of EET using letrazole stratified by MP risk.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MammaPrint Result</th>
<th>10-yr outcome 2.5y EET (%)</th>
<th>10-yr outcome 5y EET (%)</th>
<th>Absolute benefit (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
<th>P interaction**</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>Higher Risk (n=259)</td>
<td>90.0</td>
<td>90.9</td>
<td>0.9</td>
<td>0.882</td>
<td>0.305</td>
<td>1.968</td>
<td>0.758</td>
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<td></td>
<td>Lower Risk (n=256)</td>
<td>82.5</td>
<td>92.3</td>
<td>9.8</td>
<td>0.416</td>
<td>0.174</td>
<td>0.666</td>
<td>0.049</td>
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<tr>
<td></td>
<td>MP Low (n=223)</td>
<td>85.2</td>
<td>95.3</td>
<td>10.1</td>
<td>0.317</td>
<td>0.116</td>
<td>0.666</td>
<td>0.025</td>
</tr>
<tr>
<td>RFI</td>
<td>Higher Risk (n=259)</td>
<td>90.1</td>
<td>86.5</td>
<td>-3.6</td>
<td>1.283</td>
<td>0.617</td>
<td>2.067</td>
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</tr>
<tr>
<td></td>
<td>Lower Risk (n=256)</td>
<td>82.5</td>
<td>92.3</td>
<td>9.8</td>
<td>0.435</td>
<td>0.158</td>
<td>0.624</td>
<td>0.033</td>
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<tr>
<td></td>
<td>MP Low (n=223)</td>
<td>81.5</td>
<td>93.2</td>
<td>11.7</td>
<td>0.346</td>
<td>0.147</td>
<td>0.624</td>
<td>0.016</td>
</tr>
<tr>
<td>BCFI</td>
<td>Higher Risk (n=259)</td>
<td>87.0</td>
<td>84.8</td>
<td>-2.2</td>
<td>1.101</td>
<td>0.567</td>
<td>2.136</td>
<td>0.777</td>
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<tr>
<td></td>
<td>Lower Risk (n=256)</td>
<td>80.9</td>
<td>89.7</td>
<td>8.8</td>
<td>0.528</td>
<td>0.204</td>
<td>1.065</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>MP Low (n=223)</td>
<td>80.6</td>
<td>90.3</td>
<td>9.7</td>
<td>0.478</td>
<td>0.225</td>
<td>1.015</td>
<td>0.055</td>
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</table>

**MammaPrint Lower Risk & Higher Risk (n=515) and *** MammaPrint Low Risk & High Risk (n=482)**

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GS5-11 Sacituzumab Govitecan (SG) vs Treatment of Physician’s Choice (TPC): Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients (Pts) With HR+/HER2− Metastatic Breast Cancer (mBC)

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Background: HR+/HER2– mBC, the most common subset of breast cancer, is treated with sequential endocrine therapy + targeted agents followed by sequential single-agent chemotherapy (CT), with increasingly shorter benefit duration with each subsequent treatment. High Trop-2 expression is observed in breast cancer regardless of subtype. SG is a Trop-2-directed antibody-drug conjugate approved for pre-treated metastatic triple-negative breast cancer. In the phase 3 TROPICS-02 study, SG showed both significant progression-free survival (PFS) benefit (HR, 0.66; P<0.001; median 5.5 vs 4.0 mo; JCO 2022) at the primary analysis and overall survival (OS) benefit (median 14.4 vs 11.2 mo; HR, 0.79; P=0.02; ESMO 2022) at the 2nd planned interim OS analysis vs TPC in pretreated HR+/HER2- mBC. Here we compare efficacy outcomes for SG and TPC by Trop-2 expression. Methods: Eligible pts had HR+/HER2- locally recurrent inoperable or mBC; received ≥1 prior taxane, endocrine therapy, a CDK4/6 inhibitor; and received 2-4 prior CT regimens for mBC. Pts were randomized 1:1 to receive SG (10 mg/kg IV on d 1 and 8, every 21 d) or TPC (eribulin, gemcitabine, capecitabine, or vinorelbine) until disease progression or unacceptable toxicity. The primary endpoint was PFS by independent review per RECIST v1.1; OS and objective response rate (ORR) were key secondary endpoints. ORR was assessed by blinded independent central review per RECIST v1.1. Membrane Trop-2 expression on archival tumor tissue was assessed by immunohistochemistry and expressed as a histochemical score (H-score; range, 0-300); efficacy outcomes were assessed in H-score <100 and ≥100 groups. The H-score <100 group was further divided into H-score ≤10 and >10- <100 subgroups to assess the activity of SG in pts with very low Trop-2 expression. Results: Data cut-off was January 3, 2022 for PFS (median follow-up, 10.2 mo) and July 1, 2022 for OS (median follow-up, 12.5 mo). In total, 543 pts were randomized to receive SG (n=272) vs TPC (n=271). Pts had a median of 3 prior CT regimens for mBC; 95% had visceral metastases. There were 238 (88%) vs 224 (83%) Trop-2-evaluable pts in the SG vs TPC groups, respectively; of these, 95% had tumors with Trop-2 H-score >0. Of Trop-2-evaluable pts, 192 (42%) and 270 (58%) had H-scores <100 and ≥100, respectively. Disease response was observed in the 34 pts with H-score ≤10 who received SG. In pts who received SG, those with H-score ≤10, >10- <100, and ≥100 had ORRs of 24%, 18%, and 23%, respectively. The safety profile for SG by Trop-2 H-score was consistent with previous reports. Conclusions: In this TROPICS-02 post-hoc analysis, improved efficacy with SG vs TPC was observed regardless of Trop-2 expression, and there was no clear level of Trop-2 expression at which a better treatment effect for SG was observed. These results support SG as an effective novel treatment option for patients.
with pretreated, endocrine-resistant HR+/HER2- mBC, and reinforce that Trop-2 testing is not required for SG treatment.

<table>
<thead>
<tr>
<th>Trop-2 expression, H-score</th>
<th>n (SG/TPC)</th>
<th>Median PFS (SG vs TPC), mo</th>
<th>PFS HR (95%CI)</th>
<th>Median OS (SG vs TPC), mo</th>
<th>OS HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>96/96</td>
<td>5.3 vs 4.0</td>
<td>0.77 (0.54-1.09)</td>
<td>14.6 vs 11.3</td>
<td>0.75 (0.54-1.04)</td>
</tr>
<tr>
<td>≥100</td>
<td>142/128</td>
<td>6.4 vs 4.1</td>
<td>0.60 (0.44-0.81)</td>
<td>14.4 vs 11.2</td>
<td>0.83 (0.62-1.11)</td>
</tr>
<tr>
<td>≤10</td>
<td>34/45</td>
<td>5.5 vs 4.3</td>
<td>0.89 (0.51-1.57)</td>
<td>17.6 vs 12.3</td>
<td>0.81 (0.34-1.98)</td>
</tr>
<tr>
<td>&gt;10–&lt;100</td>
<td>62/61</td>
<td>5.0 vs 3.5</td>
<td>0.67 (0.42-1.07)</td>
<td>13.7 vs 11.0</td>
<td>0.81 (0.54-1.23)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>204/179</td>
<td>5.6 vs 4.0</td>
<td>0.62 (0.49-0.89)</td>
<td>14.1 vs 11.1</td>
<td>0.82 (0.58-1.04)</td>
</tr>
</tbody>
</table>

H-score, histological score. PFS, progression-free survival. SG, sacituzumab govitecan. TPC, treatment of physician’s choice.

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Background HRBC is a phase III randomized open label study of adjuvant radiotherapy in patients with breast cancer. In this study we compared a 3 weeks radiation schedule with 2 weeks. Materials and methods Patients with breast cancer, stage I-III, post mastectomy or after breast conservative surgery who needed adjuvant locoregional radiotherapy were randomized to 34Gy in 10 fractions over 2 weeks (study arm) or 35Gy in 15 fractions over 3 weeks to the chest wall and 40Gy/15#/3wks to breast and supraclavicular fossa (control arm). Boost dose when indicated was 8Gy/2# in both the arms. Patients were planned on simulator with 2 tangential fields to breast/chest wall and incident supraclavicular fossa field. Acute toxicity was assessed using a RTOG grading system. Assessment was carried out weekly during radiotherapy and at 4 weeks after treatment by the physician. Cosmetic outcome was assessed using Harvard/NSABP/RTOG scale. The toxicity between the two arms was compared using Fisher’s exact test. The trial was approved by institutional ethics committee. This trial is registered with ClinicalTrials.gov, number NCT04075058. Results This study included 1121 patients. Median follow up was 35 months (range 6-84 months). Mean age was 48 year (range 24-80 years). The patient characteristics were comparable between the two arms except for more mastectomies in the 3 week arm and more node positive patients in the 2 week arm. There were more oestrogen receptor positive tumors in the 3 week arm. Acute skin toxicities were comparable between the two arms. Grade 2 and 3 skin toxicity was 98(17%) and 82(15%); and 16(3%) and 10(2%) in the 3 week and 2 week arm (p=0.15), respectively. Cosmetic outcome was significantly better in 2 week arm 94% as compared to 90% in the 3 week arm (p=0.016). Conclusion The two radiation schedules were comparable in terms of acute skin toxicity. Cosmetic outcome was better in the 2 week schedule.

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Updates in the pathology of PABC

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Updates in the Pathology of Pregnancy Associated Breast Cancer (PABC)

Pregnancy associated breast cancer is defined as a breast cancer diagnosed during gestation, lactation and within 1 to 5 years postpartum. While the development of malignancy during pregnancy is rare, the incidence is increasing; breast cancer is one of the most common cancers diagnosed during pregnancy and the postpartum period occurring in up to 1 in 3000 deliveries. Of interest, breast cancer is the leading cause of cancer death in US women age 15-29. Pregnancy has a dual effect on breast cancer development: on one hand cancer protective and on the other cancer promoting. While a number of hypotheses have been proposed over the years to explain these effects, the most likely hypothesis for the development of PABC is the involution hypothesis. This hypothesis proposes that the involution pathways activated during pregnancy and the immediate postpartum period are remodeling programs similar to wound healing and inflammation that may be associated with tumor development and progression. Although PABCs can be any subtype of breast carcinomas, they are usually invasive ductal carcinomas of high tumor grade and large tumor size with higher stage at presentation and higher rates of lymph node involvement. Most PABCs are hormone receptor negative tumors with high Ki-67 proliferation rates; most frequently, they are either triple negative or HER2-positive carcinomas. A number of studies have shown that PABCs have different genomic signatures than the non-PABC tumors with PABCs having an increased expression of immune response mediators. Better understanding of the molecular pathways of tumor initiation and progression and prompt diagnosis and state-of-art treatment protocols in PABC is expected to lead to better outcomes for these young breast cancer patients.
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**Oncofertility and other quality of life issues**

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The current availability of effective systemic treatment strategies has significantly improved the prognosis of patients with early breast cancer. However, this survival gain is often obtained at the cost of higher toxicity. The increase in life span among breast cancer survivors calls for the need to address both early and late potential adverse effects of anticancer therapies to maximize their quality of life. Among them, the potential gonadotoxicity of anticancer therapies and its implications on fertility and ovarian function need to be discussed with all young patients. According to available guidelines, oncofertility counseling should now be considered mandatory in the care of young women with newly diagnosed cancer. This counselling should focus on the risk of developing treatment-induced premature ovarian insufficiency and on the available techniques to preserve fertility and/or ovarian function. Oocyte/embryo cryopreservation, or ovarian tissue cryopreservation in those not eligible for gamete cryopreservation, are standard strategies to be offered to young patients interested in preserving fertility, i.e. to increase their chances of post-treatment pregnancies. Ovarian suppression with gonadotrophin-releasing hormone agonists (GnRHa) during chemotherapy can be offered to premenopausal patients interested in ovarian function preservation, i.e. to decrease their risk of developing chemotherapy-induced early menopause.

Current available data confirm that pregnancy occurring following proper treatment for breast cancer and period of follow-up is safe, both in terms of long-term clinical outcomes for the patients and safety for the babies. However, there is a slightly higher incidence of obstetric and birth complications that require the need for a closer monitoring of these pregnancies.

Beyond fertility and pregnancy-related issues, a long-term follow-up of young women with breast cancer by the oncofertility unit is recommended for improving the management of other additional gynecological-related issues faced by these women. Among them, contraception should be considered during active treatment and in the follow-up of women who do not wish to get pregnant. Moreover, in the current era of more complex endocrine therapy approaches with a major negative impact on the quality of life of premenopausal patients with breast cancer, it is essential to properly and proactively care about their treatment-related side effects. Among them, menopause related-symptoms and sexual dysfunction may be better managed by implementing a close collaboration between oncologists and gynecologists within the oncofertility unit.

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Overview of the current state of the art – what patients and oncologists need to know

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While radiation therapy plays a significant role in the treatment of breast cancer for many patients, the nuances of modern day radiation therapy are often poorly understood by both patients and referring providers. Radiation therapy techniques to reduce toxicity and improve treatment accuracy have rapidly evolved in the past decade. This session will introduce non-radiation oncologists to recent innovations that allow increased personalization of treatment based on anatomical variations. Methods to improve patient positioning will be discussed. Frequently utilized dosimetric techniques for breast radiotherapy will be described and compared, including Volumetric Modulated Arc Therapy (VMAT), Intensity Modulated Radiation Therapy (IMRT), and 3D conformal planning. New methods for patient monitoring during treatment and the purpose of respiratory gating will be reviewed. Finally, the impact of surgical therapies on radiation planning and delivery will also be examined. Attendees should leave the session having a greater understanding of the current available options for radiotherapy and rationale for the choice of treatment technique.
Over the past decade, breast cancer radiotherapy has increasingly focused on techniques to improve treatment precision and limit toxicity. Surface guided radiotherapy and respiratory gating has allowed for improved cardiac sparing and the elimination of permanent skin tattoos in women receiving breast radiation, while rapid developments in the technological delivery of radiation via both volumetric arc therapy and proton beam radiation have shown promise in further improving target coverage and normal tissue sparing for breast cancer patients. Cutting edge innovations, including MR-guided radiotherapy and FLASH technology are now being explored as means to further improve treatment precision and decrease toxicity. The purpose of this talk is to highlight and discuss these advances in radiotherapy, review the existing evidence to support their use in the treatment of breast cancer, and detail specific patient populations that are most likely to benefit. Discussion will also focus on ongoing and future research aimed at improving our understanding and utilization of these novel advances in care.
In this seminar I will discuss how breast cancer DTCs modify the metastatic microenvironment to favor seeding and dormancy. In order to extravasate efficiently and form metastasis, cancer cells have to become migratory and coordinate both invasive and proliferative programs at distant organs. High-resolution lattice light-sheet with adaptive optics imaging in living cells revealed that DTCs extravasate from the blood vessels by forming actin-rich invadopodium protrusions. We have identified a population of breast cancer DTCs with pro-invasive and pro-dormancy capacities. These cells downregulate srGAP1, a GTPase regulator, favoring dissemination and dormancy at metastatic organs. Our findings describe a novel mechanism mediating the shift from a proliferative to an invasive/dormant phenotype in breast cancer cells in vivo. srGAP1 is a new regulator of dormancy that regulates the formation of dormancy-permissive microenvironments through increased secretion of TGFb2 and SMAD2 activation.