PD11-06

PD11-06 Circulating tumor DNA association with residual cancer burden after neoadjuvant therapy in triple negative breast cancer in TBCRC 030

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Background. Patients (pts) with early triple negative breast cancer (eTNBC) are at increased risk of breast cancer recurrence and death. Recent studies have focused on escalation of therapy, with current treatment standard of at least five drugs – and associated toxicities - for eTNBC. Though presence of residual disease after neoadjuvant therapy (NAT) as measured by residual cancer burden (RCB) helps guide addition of adjuvant treatment, more effective tools to tailor therapy are limited. Persistence of circulating tumor DNA (ctDNA) in the setting of
residual disease is associated with high risk of distant recurrence. However, more sensitive minimal residual disease (MRD) assays are needed to potentially guide optimization of systemic therapy.

Methods. TBCRC 030 is a phase II randomized study of 12 weeks of NAT single agent cisplatin or paclitaxel for stage II-III TNBC, followed by surgery. The primary objective of the parent study was to correlate baseline biomarker for homologous recombination deficiency and RCB by study arm. From this group, responders (RCB 0/1) and non-responders (RCB 2/3) from both study arms who did not receive additional NAT prior to surgery were selected for analysis from the study cohort, matched on baseline nodal status and tumor size. As a post hoc study amendment, available pts were followed for event free survival (EFS). Plasma samples were collected prior to treatment initiation (W0), at three weeks (W3), and at twelve weeks, prior to surgery (W12). Whole genome sequencing (WGS) was performed on primary tumor tissue to identify somatic mutations and design for each pt a tumor-informed, ctDNA assay tracking up to 1000 mutations to detect MRD. Detection limit was computed for each tested sample as previously described. For each sample assayed, we report tumor fraction (TFx) when MRD was detected and the detection limit at 90% power when MRD was not detected.

Results. Of 139 study pts, 68 had complete tissue and plasma samples and no receipt of additional NAT. Of these, 22 were responders. These responders, and 22 matched non-responders were identified for analysis. Data from 22 pts – 11 responders, 11 non-responders - are described here; full analysis on all 44 pts will be presented at the meeting. Personalized ctDNA assays were designed targeting 434 to 1000 variants (median 1000) and applied to 66 plasma samples. At W0, 100% (22/22) were positive for ctDNA; 73% (16/22) and 55% (12/22) were positive at W3, and W12, respectively. In pts with T1-T2 tumors median TFx was 4.1e-3(7.8e-6, 3.4e-2) and 4.7e-1(4.3e-2, 9.0e-1) in pts with T3-T4 tumors. TFx decreased from W0 to W3 and from W0 to W12 in responders (Table 1). By W12, ctDNA had cleared in 7/8 pts with RCB 0, 1/3 with RCB 1, 2/8 with RCB 2, and 0/3 with RCB 3. Overall, ctDNA levels were broad with median TFx of 1.5e-3 (range 2.9e-6 to 0.90). Detection limit at 90% power for all tested samples was a median of 8.8e-6 (range 2.9e-6 to 6.8e-3).

To investigate whether ctDNA persistence after NAT was associated with BC recurrence, we analyzed a separate group of all 8 pts with known recurrence and with complete data and samples. All pts had persistent ctDNA at W12 (median TFx 6.8e-3, [2.9e-6 to 6.6e-2]).

Conclusions. After 3 weeks of NAT for eTNBC, ctDNA TFx decreased, with a 3900-fold change in responders and 18-fold change in non-responders. By W3, TFx for most pts with RCB 0/1 were below the 1 in 10,000 limit of detection for many currently available assays, emphasizing the need for sensitive tests to potentially guide therapy. Additional studies will determine if ctDNA-guided approaches in eTNBC can improve pt outcomes.
Table 1: Tumor Fraction and Tumor Fraction Fold Change by Response to Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>TFx</th>
<th>Responders (N=11)</th>
<th>Non-Responders (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Min, Max)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W0</td>
<td>7.0e-3 (2.4e-4, 9.0e-1)</td>
<td>3.0e-3 (7.8e-06, 4.3e-2)</td>
</tr>
<tr>
<td>W3</td>
<td>3.6e-6 (0, 1.1e-3)</td>
<td>2.0e-4 (0, 9.8e-3)</td>
</tr>
<tr>
<td>W12</td>
<td>0 (0, 1.2e-4)</td>
<td>2.4e-4 (0, 9.1e-3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TFx Fold Change</th>
<th>Median (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>From W0 to W3</td>
<td>3.9e-3 (3.2e-6, 6.6e-1)</td>
</tr>
<tr>
<td>From W0 to W12</td>
<td>1.0e-3 (7.5e-6, 7.8e-2)</td>
</tr>
</tbody>
</table>

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PD11-07 Association of TNBC-DX scores with outcomes in triple-negative breast cancer (TNBC) treated with neoadjuvant pembrolizumab and chemotherapy: a correlative analysis from NeoPACT and NeoSTOP trials

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Introduction: The TNBC-DX risk score includes the 14-gene immunoglobulin (IGG) immune signature, tumor size, and nodal status and has shown prognostic value for survival in early-stage TNBC (B. Conte et al., ESMO Breast 2021). However, currently unknown are the value of the TNBC-DX risk score and IGG immune signature in 1) predicting pathologic complete response (pCR) following neoadjuvant therapy, and 2) predicting outcomes the context of neoadjuvant anti-PD1 treatment. Here, we assessed the IGG signature and the TNBC-DX risk score in patients with TNBC treated with neoadjuvant chemoimmunotherapy (NeoPACT; NCT03639948) and neoadjuvant chemotherapy without immunotherapy (NeoSTOP; NCT02413320). Methods: NeoPACT trial enrolled 120 patients with stage I-III TNBC who received carboplatin (AUC 6) + docetaxel (75 mg/m2) + pembrolizumab (200 mg) every 21 days x 6 cycles. NeoSTOP randomized 100 patients with stage I-III TNBC to two chemotherapy regimens; Arm B of NeoSTOP was included in this correlative study as the chemotherapy regimen was identical to NeoPACT. RNA isolated from pretreatment tumor tissue was subjected to next-generation sequencing. The 14-gene IGG immune signature and TNBC-DX risk score were calculated in silico as previously described. Evaluation of stromal tumor-infiltrating lymphocytes (sTILs) was performed as previously described. Markers were tested for prediction of pCR. Logistic regression analysis was used to examine the effect of multiple variables. Event-free survival (EFS) curves were assessed by the Kaplan-Meier method and groups compared by the log-rank test, followed by Cox regression analysis. Results: In this analysis, 112 patients were treated with chemoimmunotherapy on NeoPACT (node-positive = 38%, pCR rate = 58%). In the NeoPACT trial, the 14-gene IGG signature (as a continuous variable) was significantly associated with improved pCR (odds ratio [OR]=1.105, 95% CI 1.019-1.197, P=0.015 for every 0.2 increment). The pCR rates in IGG-high (≥ median) and IGG-low (< median) groups were 71% and 44%, respectively (OR=3.152, 95% CI 1.420-6.996, P=0.005). In terms of EFS, the 14-gene IGG signature was not prognostic (hazard ratio [HR]=0.507, 95% CI 0.148-1.735, p=0.269). In contrast, TNBC-DX risk score was strongly associated with EFS (HR=5.684, 95% CI 1.226-26.356, P=0.012), even when adjusted for sTILs and pCR status (HR=8.415, 95% CI 1.054-67.169, P=0.044). Estimated 3-year EFS rates in TNBC-DX high and low risk groups (above and below median) were 77% and 89%, respectively (P=0.012). In 43 NeoSTOP patients treated with neoadjuvant chemotherapy only (node-positive = 33%, pCR rate = 53%), no association of IGG signature with pCR or TNBC-DX score with EFS was observed. Finally, we observed a moderate correlation between IGG signature and sTILs in both trial datasets combined (r=0.642, P< 0.001). Conclusions: High expression of the 14-gene IGG immune signature in baseline pretreatment tumor samples in early-stage TNBC is significantly associated with pCR following pembrolizumab-based neoadjuvant chemotherapy. The combination of this signature with tumor burden as assessed by TNBC-DX is prognostic for long-term outcomes. Availability of biomarkers that can predict both pathological response and survival with chemoimmunotherapy can optimize this therapy, and evaluation of this biomarker in larger studies is warranted.

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PD11-08

PD11-08 Trastuzumab deruxtecan (T-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic hormone receptor-negative (HR−), HER2-low breast cancer: updated results from BEGONIA, a phase 1b/2 study

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Background: Patients with HR− advanced/metastatic breast cancer (a/mBC) with a low level of HER2 (immunohistochemistry [IHC] score 1+ or IHC 2+ and negative in situ hybridization [ISH]) have poor prognosis. Combining 1L chemotherapy with immune checkpoint inhibitors can modestly improve outcomes vs chemotherapy alone, but treatment benefit is largely seen in patients with PD-L1+ disease. BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study, evaluating safety and efficacy of D, an anti–PD-L1 antibody, combined with other novel therapies in 1L triple-
-low disease. T-DXd is a trastuzumab-topoisomerase I inhibitor antibody-drug conjugate that improves survival in previously treated HER2-low mBC (NCT03734029; Modi NEJM 2022). Here, we report updated results of the T-DXd + D combination from BEGONIA. Methods: Patients expressing tumor or immune cells. Primary endpoints were safety and tolerability. Secondary endpoints included investigator-assessed objective response rate (ORR; RECIST v1.1); progression-free survival [PFS]; and response duration. Patients included in the efficacy -treatment disease assessments, progressed, died, or withdrew from the study. Results: As of April 8, 2022, 56 patients received T-DXd + D (34 ongoing) and 46 were included in the efficacy analysis. Median (range) follow-up was 10.1 (0–22) months. Median age was 53.5 years, 71% had received prior treatment for early stage BC, and 64% had visceral metastases at baseline. Confirmed ORR was 26/46 (57%; 95% CI, 41–71) and unconfirmed ORR was 33/54 (61%; 95% CI, 47–74); 1/46 patients (2%) had complete and 25/46 (54%) had partial responses. Confirmed response occurred irrespective of PD-L1 expression (PD-L1 high ORR, 5/7 [71%]; PD-L1 low, 13/21 [62%]; PD-L1 missing, 8/18 [44%]). Median duration of response was not reached; however, 64% of patients remained in response at 12 month follow-up and 73% had an ongoing response at data cutoff. Median PFS was 12.6 months (95% CI, 8–not reached). Adverse events (AEs) were consistent with the agents' known safety, with treatment-related AEs occurring in 49 patients (88%), any Grade 3/4 AEs in 18 patients (32%), and any serious AEs in 10 patients (18%). The most common all-Grade AEs were nausea (41 [73%]), fatigue (26 [46%]), and vomiting (17 [30%]). Adjudicated treatment-related interstitial lung disease/pneumonitis occurred for 5 patients (9%), which were mostly Grade 1 or 2 and 1 case of Grade 5 associated with COVID pneumonia. Seven patients (13%) and 21 patients (38%) had T-DXd dose reduction and dose delay, respectively; 22 (39%) had D dose delay. Seven patients (13%) discontinued treatment due to AEs. Conclusions: For patients with HR−, HER2-low a/mBC, T-DXd in combination with D in the 1L setting shows manageable safety and promising efficacy including durable responses and an encouraging PFS. Although subgroups were small, responses were observed irrespective of PD-L1 expression. Analysis of additional translational data is ongoing. Funding: AstraZeneca/Daiichi Sankyo

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PD11-09
PD11-09 Datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): updated results from BEGONIA, a phase 1b/2 study

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Background: Patients with a/mTNBC have limited treatment options and a poor prognosis (objective response rate [ORR] of 37%, median duration of response 6.5 months, median overall survival 15.5 months for 1L chemotherapy [Rugo, et al. Ann Oncol. 2021 LBA16]). Combining checkpoint inhibitors with 1L chemotherapy modestly improves outcomes but only in PD-L1–positive a/mTNBC, emphasizing a critical unmet need for patients with PD-L1–negative disease and for further improving outcomes in PD-L1–positive disease. BEGONIA (NCT03742102) is an ongoing 2-part, open-label platform study, evaluating safety and efficacy of D, an anti–PD-L1 antibody, combined with other novel therapies in 1L a/mTNBC, including Dato-DXd, an antibody-drug conjugate consisting of a humanized anti-TROP2 antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. Early data from BEGONIA of D in combination with Dato-DXd showed promising responses. Here, we report updated results of Dato-DXd + D.

Methods: Patients with unresectable a/mTNBC eligible for 1L treatment were enrolled, regardless of PD-L1 or TROP2 status, and received intravenous Dato-DXd 6 mg/kg + D 1120 mg every 3 weeks until progression or unacceptable toxicity. PD-L1, assessed using the VENTANA PD-L1 (SP263) Assay, was defined as high if ≥ 5% of the tumor area was populated by PD-L1–expressing tumor or immune cells. Primary endpoints were safety and tolerability. Secondary endpoints included investigator-assessed ORR (RECIST v1.1) and duration of response. Patients included in the efficacy analysis had ≥ 2 on-treatment disease assessments, progressed, died, or withdrew from the study. Results: As of April 8, 2022, 47 patients received Dato-DXd + D (39 ongoing) and 33 of those were included in the efficacy analysis. Median (range) follow-up was 7.5 (0–11) months. Patient age was a median of 51 years, 57% received prior treatment for early stage TNBC, and 60% had visceral metastases at baseline. Confirmed ORR was 26/33 (79%; 95% CI, 61–91); 2/33 patients (6%) had a complete response and 24/33 (73%) had a partial response. Confirmed response was irrespective of PD-L1 expression (PD-L1 high ORR, 4/5 [80%]; PD-L1 low, 16/21 [76%]; PD-L1 missing, 6/7 [86%] patients). Median duration of response was not reached; 100% of patients with a complete or partial response remained in response at 6 month follow-up, and 96% had an ongoing response at data cutoff. Adverse events (AEs) were manageable and consistent with the known safety profiles of each agent, with treatment-related AEs occurring in 41 patients (87%), any Grade 3/4 AEs in 17 patients (36%), and any serious AEs in 7 patients (15%). The most common all-Grade AEs were gastrointestinal (nausea in 26 patients [55%] and stomatitis in 24 patients [51%]). A low rate of diarrhea was reported (6 patients [13%], all Grade 1 or 2); 4 patients had anemia and 1...
had neutropenia. There were no cases of interstitial lung disease/pneumonitis or thrombocytopenia. Nine patients (19%) and 11 patients (23%) underwent Dato-DXd dose reduction and delay, respectively; 14 (30%) had D dose delay. Treatment was discontinued due to an AE for 3 patients (6%). There were no deaths due to treatment-related AEs. Conclusions: In this updated analysis with additional patients and longer follow-up, the combination of Dato-DXd + D in 1L a/mTNBC demonstrated a manageable safety profile and compelling high response rates with promising durability. Although subgroups were small, responses occurred irrespective of PD-L1 expression. Further investigation of this treatment combination is warranted. Analysis of translational data is ongoing. Funding: AstraZeneca/Daiichi Sankyo

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Background: Despite recent FDA approval of immune checkpoint inhibitor pembrolizumab and drug-antibody conjugate in the treatment of mTNBC, the overall survival benefit of these patients remains modest. We conducted a phase 2 study to assess the efficacy and safety of
anti-PD-L1/CTLA-4 bispecific antibody KN046 in combination with nab-paclitaxel in mTNBC patients (pts) regardless of PD-L1 status. Preliminary results have been delivered in 2021 AACR[1], here we reported the final results of the progression-free survival (PFS) and overall survival (OS) analysis. Methods: This study enrolled pts with treatment-naïve locally advanced inoperable or metastatic TNBC. Eligible pts received nab-paclitaxel plus KN046 at two dose

duration of response (DoR), secondary included disease control rate (DCR), clinical benefit rate (CBR), PFS, 1-year/2-year OS rate and safety/tolerability. Results: As of May 9, 2022 (cut-off date), 27 pts were enrolled into DL1 (n=16) and DL2 (n=11). Median patient age in the study was 50 years (range, 33-70 years). At baseline, 52% and 48% of patients had ECOG PS of 0 and 1, respectively. By the cut-off date, there are 1 pts under treatment and 16pts alive. The median study follow-up time was 26.3 months (95% CI, 20.7 - 29.8). Based on the intent-to-treatment (ITT) population, the confirmed ORR was 33.3% (95% CI, 16.5% - 54.0%), DCR was 88.9% (95% CI, 70.8% - 97.7%), and CBR was 48.1% (95% CI, 28.7% - 68.1%), which remained stable compared with last reported in 2021 [1]. The DoR was 11.9 (95% CI, 5.6 - NR) months. The median PFS was 7.3 (95% CI, 3.7 - 13.7) months. The median OS is immature, the preliminary result is 27.7 (95% CI, 14.8 - NR) months, and the 2-year OS rate was 60.1% (95%CI, 37.2% - 76.9%). Among the 11 pts with PD-

positive and negative pts derived OS benefit from the combination treatment, with the 2-year OS rate of 57.14% (95%CI, 25.4% - 79.6%) and 62.5% (95%CI, 22.9% - 86.1%) respectively. Patients tolerated well to combination therapy in this trial. The most common reported treatment related adverse event (TRAEs) were ALT elevation (13 pts, 48%), AST elevation (12 pts, 44%),
elevation (5 pts, 15%). 13 pts (48%) experienced immune related adverse events (irAEs), and only 3 irAEs (11%) were grade 3. The incidence of SAE was 33%, with no TRAE leading to death.

Conclusions: The combination therapy of KN046 plus nab-paclitaxel has shown favorable clinical efficacy in mTNBC, especially in PD-L1 positive patients. By the cut-off date, the mOS is not mature and there is still more than half of pts alive, which demonstrated an encouraging 2-year OS rate. Pts in this trial tolerated well to the combination therapy and safety profile was manageable. Clinical trial information: NCT03872791 Reference 1. Cancer Res (2021) 81 (13_Supplement): 1660.

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Background: Immune checkpoint inhibitors (CPI) have shown efficacy against metastatic triple negative breast cancer (mTNBC), but only for PD-L1 positive tumors. It is not known if so-called
immunogenic chemotherapies may yield clinical relevant synergies with CPI. We addressed these issues, by conducting a trial evaluating atezolizumab (anti-PD-L1) in combination with doxorubicin, which has been reported to provoke immunogenic cell death, and low-dose metronomic cyclophosphamide, which has been reported to counter immunosuppressive cells. The pegylated liposomal form of doxorubicin (PLD) was selected to avoid steroids and allow for long term therapy in responders. To our knowledge, this is the first randomized trial reporting on the concomitant addition of CPI to antracyclines in mTNBC.

Methods: The trial enrolled patients with mTNBC and maximum one previous line of chemotherapy in the metastatic setting. Patients were randomized 2:3 into arm A (n=28), receiving chemotherapy alone, or arm B (n=40), receiving chemotherapy in combination with atezolizumab (840 mg every 2nd week). The chemotherapy consisted of PLD (20mg/m2 every 2nd week) + oral cyclophosphamide (cyclo; 50mg/day, 2/4 weeks) in both arms. The per protocol (PP) population was defined as patients receiving > 3 doses of atezolizumab and >2 doses of PLD. The primary efficacy endpoint was progression-free survival (PFS) in the PP population. The protocol power analysis focused on durable response, as measured by 15 months PFS. Safety, a co-primary endpoint, was evaluated in all patients that started therapy (Full Analysis Set; FAS). Secondary endpoints included PFS in FAS, objective response rate (ORR), clinical benefit rate (CBR), durable response rate (>6 months; DRR), overall survival (OS) and biomarkers. PD-L1 status was determined retrospectively by the Ventana SP142 assay, as tumor-infiltrating immune cells with cut-off ≥ 1%. Efficacy data are given in the PP population unless stated otherwise. Hazard ratios (HR) are given with 95% confidence intervals (CI). Results: A total of 68 patients started therapy (FAS), of which 59 were in the PP population and 57% had not received previous chemotherapy in the metastatic setting. PFS was significantly improved in arm B compared to arm A in both the PP population (HR 0.57; CI 0.33-0.99; p=0.0477) and in the FAS (HR 0.56; CI 0.33-0.95; p=0.0326). Median PFS was 4.3 months in arm B versus 3.5 months in arm A. The progression-free proportion after 15 months was 14.7% (CI 6.4-30.1%) in arm B versus 0% in arm A. The ORR was 30.6%/21.7%, CBR was 52.8%/43.5% and DRR was 13.9%/4.3% in arm B/A. The PFS advantage was observed for both PD-L1+ (n=27; HR 0.58) and PD-L1- subjects (n=31; HR 0.66). All five patients without progression after 15 months belonged to arm B, and three out of these patients were PD-L1 negative. Serious adverse events occurred for 48% in arm B and 29% in arm A (FAS). The most common immune related adverse events of any grade in arm B/A were hypothyroidism (10.0%/7.1 %), pneumonitis (10.0%/3.6%), hyperthyroidism (5.0%/7.1%) and rash (7.5%/3.6%). Further biomarker analyses and assessments of immunological changes during therapy are ongoing. Conclusions: The addition of atezolizumab to PLD and low-dose metronomic cyclophosphamide significantly improved PFS. A benefit was indicated also in patients with PD-L1 negative disease. The combination regimen was well tolerated with no new safety signals. Results from the ongoing analyses of consecutive tumor and blood samples will be important to assess the hypothesized immunological effects of the chemotherapy and to investigate biomarkers associated with the response to the combined treatment.

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Introduction: A significant proportion of aTNBC patients carry homologous recombination defects associated with platinum sensitivity. Olaparib is an approved PARP inhibitor (PARPi) for germline BRCA (gBRCA) associated early and metastatic breast cancer as well as maintenance therapy in platinum-sensitive ovarian cancer irrespective of gBRCA status. PARPi enhances immune response via cGAS/STING activation and is synergistic with anti-PD-1 blockade in preclinical models without overlapping toxicities. Here, the efficacy of maintenance olaparib (O) +/- durvalumab (D) in aTNBC patients following clinical benefit from platinum chemotherapy is investigated (NCT03167619). Methods: Eligible pts had aTNBC with investigator-assessed clinical benefit (SD, PR, CR) after a minimum of 3 q3-weekly or 6 q1-weekly cycles of platinum-based chemotherapy in the 1st or 2nd line treatment setting. Patients were randomized 1:1 to receive O 300 mg BID daily or O 300mg BID daily + D 1.5g IV q4 wks. The study was a non-comparator trial; randomization aimed to reduce bias. Tumors were evaluated by RECIST1.1 at baseline and q8 wks. Known gBRCA carriers were limited to 10. The primary endpoint was progression-free survival (PFS). Secondary endpoints were disease control rate (DCR), clinical benefit rate (CBR), and overall survival (OS). Results: From 2/4/2019-12/24/2020, 45 pts were randomized (23 pts in O arm; 22 in O+D arm). 82.2%
received platinum as 1st line therapy and 82% received a platinum-doublet. As of data cutoff (6/30/2021), median follow-up of 9.8m (7.2-15.1), the median PFS was 3.95m (p= 0.0023; 95% CI 2.55-6.13) with O monotherapy. The median PFS was 6.1 mos (p= <.0001; 95% CI 3.68-61.5%) and 36.4% (17.2%-59.3%) in the O and O+D arms, respectively. DCR was 52.2% (30.6%, 73.2%) and 68.2% (45.1%, 86.1%) in the O and O + D arms, respectively. Currently, 7 pts (15.6%) remain on study treatment, only 2 have gBRCA alterations. No new safety signals were reported. Correlative analysis including germline/somatic BRCA, HRR genes, BRCA methylation, TMB and PDL-1 in association with clinical outcomes will be presented. Conclusions: A subset of non-gBRCA altered aTNBC pts who derived clinical benefit from platinum-based chemotherapy had a durable disease control with a chemotherapy-free maintenance strategy of olaparib +/- durvalumab.

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Discussion 1 + Q&A: PD12-05, PD12-07, PD12-08 & PD12-09

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Discussion 2 + Q&A: PD12-01, PD12-06, PD12-04 & PD12-02

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Poster Spotlight Discussion 12: Obesity and Breast Cancer

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PD12-01

PD12-01 Impact of obesity and post-diagnosis weight change on survival in women with breast cancer diagnosed at Smilow Cancer Hospital from 2013-2019

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Background: The association between obesity and breast cancer risk is well documented, but fewer studies have explored the impact of post diagnosis weight changes on survival especially in more contemporary contexts. The existing evidence has mainly focused on weight gain, been limited by small sample sizes and has evaluated prospective cohorts with restrictive eligibility criteria rather than population-based samples. Our study uniquely contributes to the literature by using a population-based approach and recent clinically measured weight data from the electronic health record (EHR) to explore the impact of weight change following a breast cancer diagnosis on survival. Methods: EHR weight measurements were extracted for women diagnosed with stages I-IV breast cancer at CT’s Smilow Cancer Hospital and Care Network between 2013-2019 (N=6,934). During the follow-up period through April 26, 2020 (mean=3.2
years, standard deviation=1.8), there were 497 deaths. We used multivariable Cox regression models, adjusting for age at diagnosis, race/ethnicity, chemotherapy, radiation therapy, ER/PR subtype, to estimate the association between body mass index (BMI) at diagnosis and all-cause mortality from time since first post-diagnosis clinic visit (within 6 months of diagnosis). Percent weight change at 1-year post-diagnosis was categorized as a 5-level variable (weight stable – change within 5% of weight at diagnosis, moderate weight loss – 5% to < 10% change, large weight loss – ≥10% change, moderate weight gain – 5% to < 10% change, and large weight gain – ≥10% change) and evaluated in relation to all-cause mortality. A non-linear relationship between percent weight change at 1-year post-diagnosis and mortality was evaluated by comparing linear and cubic spline models. Results: Among these 6,934 breast cancer cases, the mean age was 61±13 years, BMI at diagnosis was 29±7 kg/m2 and weight change from diagnosis to 1-year post-diagnosis was -0.47±5.4 kg. Being underweight (BMI< 18.5) or having class II obesity (BMI>35) at diagnosis were statistically significantly independently associated with higher all-cause mortality compared with normal BMI (Hazard Ratio [HR]=1.43, 95% Confidence Interval [CI]=1.11-1.85 and HR=3.32, 95% CI=1.90-5.80, respectively). At 1-year post-diagnosis, 64% of women remained weight stable since diagnosis, 12% gained moderate body weight, 5% had large weight gain, 12% lost moderate weight and 7% experienced a large weight loss. Compared with the weight stable group, there was a positive, non-significant association between moderate weight gain at 1-year post-diagnosis and overall mortality (HR=1.24, 95% CI=0.84-1.81). Greater than 10% weight loss at 1-year post-diagnosis was statistically significantly associated with higher mortality (HR=2.87, 95% CI=2.13-3.87). The test for curvature suggested a non-linear relationship between percent weight change at 1-year and mortality (p< 0.001). Conclusion: In this contemporary, population-based study of women with breast cancer from one large academic medical center, underweight and obesity at diagnosis were associated with poorer survival. Weight loss during the first-year post-diagnosis was also strongly associated with an increased risk of mortality. To further inform weight management strategies and future interventions for breast cancer survivors, we need to better understand changes in body composition in the post-diagnosis period.

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PD12-02 Obesity is associated with poor breast cancer prognosis, particularly among women with low socioeconomic position

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Purpose: To examine the association between obesity and breast cancer outcomes and to describe socioeconomic position (SEP) in patients enrolled in the Malmö Diet and Cancer Study (MDCS) according to anthropometric measures. Patients and methods: The MDCS is a prospective cohort study that enrolled 17,035 female individuals in Malmö, Sweden from 1991 to 1996. The primary objective of the MDCS was to investigate associations between dietary patterns and cancer risk. Body mass index (BMI) and waist circumferences were measured upon enrollment, in the MDCS cohort. We identified all female MDCS participants with incident invasive breast cancer diagnosed between 1991 and 2014. The primary endpoint was breast cancer recurrence, defined as the time from breast cancer diagnosis until the earliest occurrence of invasive loco-regional recurrence or distant metastases. Follow-up time began at breast cancer diagnosis and continued until the first of breast cancer recurrence, death, emigration, or end of follow-up (June 8, 2020). BMI and waist circumference were categorized according to the World Health Organization guidelines as healthy weight (18.5-24.9 kg/m2 or waist < 81 cm), overweight (25.0-29.9 kg/m2 or waist 81-85 cm), and obese (≥ 30.0 kg/m2 or waist > 85 cm). Consistent with the Swedish socioeconomic classification, we categorized labor status into two groups—manual labor and non-manual labor. We categorized socioeconomic position (SEP) as low if patients had unskilled manual labor with < 2 years post-high school education, low-middle if skilled manual labor with > 2 years of post-high school education, high-middle if assistant non-manual labor with < 3 years of post-high school education, and high if non-manual labor with > 3 years of post-high school education. We fit Cox regression models to compute crude and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CI) of breast cancer recurrence as well as all-cause mortality according to BMI and waist circumference. To evaluate effect measure modification, we stratified the Cox models by labor
status, SEP, and smoking. Results: Among 1,099 breast cancer patients, 263 breast cancer recurrences were diagnosed over 12,810 person-years with a median follow-up of 11.1 years (IQR = 6.6 -16.2). The cohort consisted of 556 patients with healthy weight, 384 patients with overweight, and 159 patients with obesity. The median age at breast cancer diagnosis was 66.3 years (IQR: 61.2 -72.8), and patients with obesity were older than patients with healthy weight (69.2 vs 64.9 years). In multivariable analyses, having obesity according to BMI was associated with increased rate of recurrence (HR= 1.44 [95% CI: 1.00-2.07]) and all-cause mortality (HR= 1.50 [95% CI: 1.13-1.98]) in comparison to having healthy weight. Similarly, having obesity according to waist circumference was associated with higher risk of recurrence (HR= 1.31 [95% CI: 0.98-1.77]) and all-cause mortality (HR= 1.72 [95% CI: 1.39-2.13]) in comparison to having healthy weight. When evaluating effect measure modification, we observed that obesity was associated with breast cancer recurrence in obese non-smoking women (HR= 1.66 [95% CI: 1.01-2.73]), in obese women with manual labor (HR= 2.45 [95% CI: 1.22-4.93]), and obese women with low SEP (HR= 2.55 [95% CI: 1.08-6.02]). We observed little evidence of an association between obesity and breast cancer recurrence among smokers (HR= 1.12 [95% CI: 0.43-2.92]), among patients with non-manual labor (HR= 0.94 [95% CI: 0.44-2.00]), or among patients with high SEP (HR= 1.47 [95% CI: 0.58-3.75]).

Conclusion: Obesity defined by pre-diagnostic levels of BMI and waist circumference was associated with an increased risk of recurrence and all-cause mortality among breast cancer patients. The association between obesity and breast cancer recurrence seems dependent on patient characteristics such as labor status, socioeconomic position, and smoking.

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PD12-03 WITHDRAWN
Background
Breast cancer (BC) is the most common cancer among women and the second most common cause of cancer-related mortality among women. Much attention has been paid to factors that increase the risk of developing BC. Among these are weight, typically defined by body mass index (BMI), and race. Elevated BMI has not only been shown to increase the risk of BC in some patients but has also been associated with increased rates of hormone receptor (HR) positive BC, particularly among postmenopausal patients. In premenopausal patients, an inverse relationship has been established between obesity and BC. In fact, a 2008 meta-analysis of obesity and malignancy evaluated almost 8,000 cases of premenopausal BC and showed a BC risk reduction of 8% for every 5 kg/m². However, this study was not inclusive of African American (AA) patients. AA women are more likely to be obese than any other racial group in the US. They are also at higher risk of aggressive breast cancers, and at an earlier age. We sought to evaluate the relative risk of breast cancer diagnosis among obese vs nonobese patients of different races, as well as the rate of HR positivity in patients diagnosed with BC.

Methods
BMI, age, and self-declared race were collected from the electronic health record for all female patients presenting to our health system located in Louisiana and Mississippi between 2012 and 2022. This same data was collected for female patients who were diagnosed with BC in the same time period (n=9123), as well as HR positivity vs HR negativity. Patients less than 50 years old were considered premenopausal, and patients greater than 50 years old were considered postmenopausal. BMI greater than 30 was used to define obesity. The relative risk of BC was calculated for demographic groups according to premenopausal or postmenopausal status, White or Black/African American race, and BMI less than or greater than 30. The relative risk of HR positive BC was calculated among the same demographic groups.
Discussion
Data collected across the largest health system in Louisiana and Mississippi shows that a higher BMI is linked to an increased risk of BC, regardless of age or race. This was seen across both stratifications and was statistically significant except in postmenopausal AA women. This is contrary to what is frequently published in the literature that premenopausal obesity is protective against BC. Additionally, this data demonstrates that there is not a link between obesity and HR+ BC. This data did show that obesity in younger white patients may be protective against HR+ BC, which is aligned with prior research.

Conclusion
The association between obesity and BC incidence has been well-described in the literature, primarily in the postmenopausal setting. This large, retrospective analysis confirms that association, but also shows a strong association in premenopausal patients. Unlike other studies, this review did not show an association between obesity and HR positivity, and additionally did not show significant differences between AA patients and White patients. This provides needed insight into the inequities faced by AA women with BC. Further studies should be done to evaluate the association of socioeconomic status with BC subtypes.

Breast cancer cases (5/1/2012-5/1/2022) among women by BMI, age group, and race

<table>
<thead>
<tr>
<th>Breast Cancer Age</th>
<th>Race</th>
<th>Number of cases (n=9123)</th>
<th>Standardized Risk Estimates</th>
<th>Risk Ratio (95% CL RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>African-American</td>
<td>672</td>
<td>0.0203</td>
<td>0.00140</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>White</td>
<td>978</td>
<td>0.0226</td>
<td>0.00147</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>African-American</td>
<td>2469</td>
<td>0.01166</td>
<td>0.01199</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>White</td>
<td>5005</td>
<td>0.01114</td>
<td>0.00885</td>
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</tbody>
</table>

*statistically significantly different

Hormone receptor positivity (5/1/2012-5/1/2022) among women with breast cancer by BMI, age group, and race

<table>
<thead>
<tr>
<th>Hormone Receptor positive</th>
<th>Age</th>
<th>Race</th>
<th>Number of cases (n=7116)</th>
<th>Standardized Risk Estimates</th>
<th>Risk Ratio (95% CL RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>African-American</td>
<td>440</td>
<td>0.03779</td>
<td>0.06853</td>
<td>0.90(0.83 - 1.00)</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>White</td>
<td>746</td>
<td>0.72992</td>
<td>0.78756</td>
<td>0.90(0.80 - 0.99)*</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>African-American</td>
<td>2174</td>
<td>0.74442</td>
<td>0.71182</td>
<td>1.0(0.87 - 1.17)</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>White</td>
<td>4233</td>
<td>0.86556</td>
<td>0.83427</td>
<td>1.02(1.00 - 1.05)</td>
</tr>
</tbody>
</table>

*statistically significantly different

Disclosure(s):
Victoria Chung, DO: No financial relationships to disclose
Ruby Maini, MD: No financial relationships to disclose
Rabia Cattie, MD: OncLive: Speaker and discussant (Ongoing)
Susan Olet, PhD: No financial relationships to disclose
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Background: Obesity is an important risk factor for breast cancer and women with metabolic syndrome may be at the highest risk. Infiltration of CD8 T-cells into fat is an early event in obesity. Type I cytokines secreted by CD8 T-cells upregulate costimulatory molecules on enlarged adipocytes. The adipocytes, now antigen presenting cells, further stimulate Type I T-cell activation. The resulting T-cells compete for glucose and fatty acids which leads to metabolic dysfunction in both the adipose tissue and the T-cells themselves. The T-cells are not able to maintain tumor immune surveillance and secretion of adipokines promotes malignant transformation. Immunologic memory prevents inflammation from resolving even if an individual becomes normal weight. Strategies to increase Type II (anti-inflammatory) T-cells in inflamed adipose could have clinical benefit. Methods: We developed a method of CD4 epitope identification that includes functional screening for Th1 or Th2 epitopes. We use a multi-algorithm approach to ensure responsiveness across diverse HLA alleles. We identified Th2 selective epitopes associated with high IL-10 secretion for 6 adipocyte associated antigens that become overexpressed in inflamed adipocytes (IGF-IR, HIF-1a, DUSP1, FABP4, PAI-1 and ATGL). The epitopes were highly homologous between mouse and man (median 100% (range-82-100%). When the epitopes were used to immunize mice, all antigens generated a significant IL-10 response compared to control (p< 0.05). We questioned whether our “adipocyte directed” vaccine (ADVac) could prevent the development of breast cancer in obese mice. Results: First, C57BL/6 mice were fed a high fat high sucrose (HFHS) diet or normal chow. When mice became obese, vaccination with ADVac or adjuvant alone (Alum) was initiated. Four weeks after the final vaccine, visceral adipose tissue showed significantly fewer CD8 T-cells in the obese mice immunized with ADVac as compared to the control, p=0.0011. The decrease in CD8 T-cells was specific for adipose tissue as no change was observed in matched spleen. There was a significant increase in T-regulatory cells in the adipose tissue of mice immunized with ADVac as compared to control, p=0.031. Two weeks after the final vaccine, a glucose tolerance test (GTT) and insulin tolerance (ITT) showed blood glucose concentrations were significantly lower at all time points for the ADVac-immunized obese mice as compared to the control obese mice (p< 0.01 for all). TgMMTV-neu develop aggressive breast cancer when made obese. Ten-week old TgMMTV-neu mice were fed a HFHS diet for 4 weeks, then randomized into 2 cohorts when obese, one cohort receiving the adjuvant only (Alum) and one receiving ADVac. Mice were sacrificed at 31 weeks of age when all controls had developed
tumor. ITT showed the glucose levels in the blood were significantly lower in the ADVac group as compared to control (p< 0.0001). Fewer CD8 T-cells were observed in mammary adipose tissue of AdVac immunized mice compared to control (p=0.001). There was significantly less leptin detected in the serum of ADVac vaccinated mice compared to Alum immunized, p=0.024. The median age of tumor development was 25 weeks in controls and 29 weeks in the immunized group (p=0.009). Sixty percent (9/15) of the vaccinated mice were tumor free at study termination, whereas 100% of the control mice had developed tumor. Conclusions: ADVac represents the first vaccine to lower breast cancer risk in obesity. Vaccination corrected metabolic dysfunction as evidenced by reversal of diabetes and prevented breast cancer in the majority of obese ADVac immunized mice. Further studies are ongoing evaluating the systemic distribution of ADVac specific T-cells and the safety of the approach.

Disclosure(s):
Mary Disis, MD: Aston Sci: Contracted Research (Ongoing); Bavarian Nordisk: Contracted Research (Ongoing); Epthany: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing); Precigen: Contracted Research (Ongoing); University of Washington: Receipt of Intellectual Property Rights / Patent Holder (Ongoing); Veanna: Contracted Research (Ongoing)
Lauren Corulli, MS: Pfizer: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Terminated, May 12, 2022); Sage Therapeutics: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Terminated, November 20, 2020); ViewRay: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Terminated, August 10, 2020)
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Denise Cecil, PhD: No financial relationships to disclose
Mammographic breast density is a well-established and strong risk factor for breast cancer. Widespread use of digital mammography has opened new potential for assessment of density changes over time. The underlying premise is that changes in breast tissue due to evolving structures that support cancer development should translate to quantifiable differences between the two breasts over time. To address this hypothesis, we draw on extensive digital mammography data and bring repeated measures over up to 10 years to evaluate the association between change in mammographic breast density and risk of breast cancer.

Women were recruited from November 2008 to April 2012 through the mammography service at the Joanne Knight Breast Health Center at Washington University in St Louis. Baseline questionnaire risk factors and screening mammograms were collected from 12,153 women. Of these, 1,672 were excluded for prior history of any cancer (except non-melanoma skin) or diagnosis of breast cancer within 6 months of registration for the study, for a total of 10,481 women. Follow-up is through linking to electronic health records, tumor registry and death register. Routine screening mammograms are collected every 1 to 2 years. Follow-up of cohort participants through December 2020 was: 78% seen in 2019 or 2020; a further 4.4% seen most recently in 2018 and a further 2.4% in 2017 giving over 80% active follow-up for women seen within the last 36 months. The median number of mammograms is 5 (min = 1, max = 10; sd = 2.43). The average person-years of follow-up through most recent contact is 9.2 person-years. We have excluded women who are diagnosed within the first 6 month of baseline mammogram date in all analyses, leaving 259 cases and 695 controls with a total number of 8,966 craniocaudal (CC) view mammograms for analysis. For these 954 women, the mean number of years between mammograms is 1.3 (10th percentile: 1.0, 90th percentile: 2.0). For the cases, the mean number of years from last mammogram date to diagnosis date was 2.0 years (10th percentile: 1.0, 90th percentile: 3.9) after excluding mammograms that are within 6 months of diagnosis.

The percentage volumetric density (MD) within each digital CC-view mammogram is estimated with an automated pixel-thresholding algorithm ADAPT implemented within the Division of Public Health at WashU. The skin around the breast is automatically removed using a boundary detection algorithm prior to estimating the dense areas. The percent density (MD) is then estimated using the dense area divided by the total breast area which normalizes the difference in breast size across women. The correlation between average MD generated from our automated algorithm with Volpara is 0.82. Initial analyses use linear mixed effects with average density between breasts (fitted with R package lmer). We performed test of assumptions for all linear mixed effects models, including the normality of residuals, linearity, and homogeneity of residual variance. Assessing the averaging density between 2 breasts
controlling for age, BMI, histology confirmed benign breast disease, family history, parity, and alcohol, MD decreases significantly over follow-up (time in years) (P < 0.01). At baseline, postmenopausal women had lower density than premenopausal women after controlling for the same set of risk factors. The average MD over all time points was significantly different for the case vs. control women (P < 0.01). For overweight women, the trajectory of MD over time was significantly different for the case vs. control women (P < 0.01). Drawing on over 10 years of follow-up we observe, for the first time, a dynamic effect for breast density such that divergence in density over time is related to risk for breast cancer.

Disclosure(s):
Graham A. Colditz, n/a: No financial relationships to disclose
Shu Jiang, n/a: No financial relationships to disclose
Background: Neoadjuvant systemic therapy is increasingly applied in breast cancer patients to improve surgical and oncological outcomes. There is only limited data from clinical practice on the relevance of body mass index (BMI) on the pathologic complete response (pCR) rate following neoadjuvant systemic treatment (NST). We aimed to retrospectively analyze the impact of BMI on pCR after NST for Dutch breast cancer patients.

Methods: Patients diagnosed with invasive breast cancer between 2019 and 2021 who were treated with NST followed by a surgical procedure, were selected from the Netherlands Cancer Registry (NCR). Patients were divided into three groups based on BMI: patients with underweight/normal weight (BMI< 25 kg/m²), patients with overweight (BMI 25-29.9 kg/m²) and patients with obesity (BMI>30 kg/m²). Patients with unknown BMI, ER/PR/HER2 or pCR status were excluded for analysis. The primary outcome was pCR after NST. The association between BMI and pCR was estimated using logistic regression models with the expression of odds ratios (ORs).

Results: After applying in- and exclusion criteria, 4430 patients were included for analysis, stratified into four molecular breast cancer subtypes; HR+/HER2- (n=2256), HR+/HER2- (n=722), HR-/HER2+ (n=405) and HR-/HER2- (n=1047). The predictors age, differentiation grade, histological type, clinical tumor (cT) and nodal (cN) stage and molecular breast cancer subtype were found significant for achieving pCR after NST. Multivariate regression analysis identified differentiation grade, cT and cN stage and molecular subtype as independent
predictors for pCR after NST. There was no association between pCR and (continuous or
categorical) BMI. Above mentioned analyses performed by stratification according to molecular
breast cancer subtype, also showed no statistically meaningful association between BMI and
pCR.

Conclusion: In this nationwide retrospective cohort study, evaluating 3340 patients with invasive
breast cancer, we found no evidence of BMI being a predictive factor for achieving pCR
following NST in neither the whole cohort, nor stratified according to molecular breast cancer
subtype.

Table 1. Multivariable regression analysis of the total cohort

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<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
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<td><strong>Age</strong></td>
<td>0.987</td>
<td>0.980 - 0.993</td>
<td>0.000</td>
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<tr>
<td><strong>Differentiation grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Ref</td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>II</td>
<td>1.967</td>
<td>1.128 - 3.431</td>
<td>0.017</td>
</tr>
<tr>
<td>III</td>
<td>3.730</td>
<td>2.133 - 6.522</td>
<td>0.000</td>
</tr>
<tr>
<td>Unknown</td>
<td>7.230</td>
<td>3.807 - 13.705</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>Ref</td>
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</tr>
<tr>
<td>Lobular</td>
<td>0.312</td>
<td>0.182 - 0.534</td>
<td>0.000</td>
</tr>
<tr>
<td>Other</td>
<td>0.652</td>
<td>0.474 - 0.897</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Clinical T stadium</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ref</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>0.525</td>
<td>0.759 - 1.131</td>
<td>0.453</td>
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<tr>
<td>3</td>
<td>0.586</td>
<td>0.430 - 0.799</td>
<td>0.001</td>
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<tr>
<td>4</td>
<td>0.556</td>
<td>0.358 - 0.863</td>
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<td><strong>Clinical N stadium</strong></td>
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<td>Ref</td>
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<tr>
<td>2</td>
<td>0.812</td>
<td>0.673 - 0.981</td>
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<td>3</td>
<td>0.665</td>
<td>0.408 - 1.084</td>
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</tr>
<tr>
<td>4</td>
<td>1.029</td>
<td>0.773 - 1.369</td>
<td>0.845</td>
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<td>HR-/Her2-</td>
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<tr>
<td><strong>Constant</strong></td>
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Disclosure(s):
Britt Jansen, MD: No financial relationships to disclose
Anke Gielen, MD: No financial relationships to disclose
Mariette Agteroff, MD, PhD: No financial relationships to disclose
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Emily Postma, MD, PhD: No financial relationships to disclose
PD12-08
PD12-08 Randomized trial of exercise and nutrition on pathological complete response among women with breast cancer receiving neoadjuvant chemotherapy: the Lifestyle, Exercise and Nutrition Early after Diagnosis (LEANer) Study

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Background: Neoadjuvant chemotherapy is available to women with locally advanced breast cancer where chemotherapy is given prior to surgery. By examining resected tissue following neoadjuvant chemotherapy pathological complete response (pCR) can be determined. pCR is a favorable prognostic factor associated with longer survival compared to residual disease after neoadjuvant chemotherapy. Physical activity and diet may improve some side effects during treatment, but less is known about their effect on chemotherapy completion and more specifically on pCR in the neoadjuvant setting. Utilizing data from a randomized trial of diet and physical activity with a primary endpoint of chemotherapy completion in women with newly diagnosed breast cancer initiating chemotherapy, we evaluated the effect of a lifestyle intervention on pCR among the subset of women in the trial who received neoadjuvant chemotherapy. Methods: The Lifestyle, Exercise and Nutrition Early after Diagnosis (LEANer) Study enrolled 173 women with Stage I-III breast cancer who were randomized to usual care (n = 86) or a yearlong, 16-session, in-person or telephone-administered diet and physical activity intervention (n = 87) delivered by registered dietitians. Among study participants, 73 women received neoadjuvant chemotherapy and of these, 72 (98.6%) had complete follow-up pCR data (intervention = 40; usual care = 32). pCR, dates, doses and reason for dose-adjustments/delays of chemotherapy were abstracted from electronic medical records and confirmed with treating oncologists. A Chi-square test was used to examine the effect of the intervention versus usual care on pCR. Results: The 72 women receiving neoadjuvant chemotherapy with complete follow-up pCR data in LEANer were 49.4±11.6 years old, had a body mass index of 30.0+6.7 kg/m2, and 37.0% and 49.3% had stage I or II breast cancer, respectively. Just over half (52.1%) of women had ER/PR positive cancers and 32.9% of tumors were HER2 positive, with no statistically significant differences in tumor type by study arm. 92.7% of the women randomized to intervention adhered to all of the counseling sessions during their neoadjuvant chemotherapy and had statistically significant improvements in mean physical activity (161 minute increase versus 40 minute increase, p-value = < 0.001) and fiber intake (0.21 gram/day increase versus -5.17 g/day decrease, p-value = 0.020), as well as median fruit and vegetable intake (0.6 serving/day increase versus -0.5 serving/day decrease, p-value = 0.041) compared to usual care. There was a benefit of the intervention on pCR compared to usual care (52.5% with pCR in the intervention arm versus 28.1% with pCR in the usual care arm, p-value = 0.037). The intervention effect on pCR did not appear to be impacted by chemotherapy completion (relative dose intensity of 92% in intervention versus 90% in usual care) or chemotherapy dose delays as these were similar in the two study arms. In mediation
analyses, results suggested that the changes in physical activity mediated, at least partially, the intervention effect on pCR. Conclusions: A primarily telephone-based diet and physical activity intervention led to improved pCR compared to usual care among the subset of women with breast cancer in the LEANer Study who received neoadjuvant chemotherapy. As pCR is an important prognostic factor for breast cancer, additional lifestyle interventions focusing on the neoadjuvant treatment setting with pCR as the primary outcome are necessary to confirm the potential benefits of lifestyle changes on pCR.

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Leah Ferrucci, PhD, MPH: No financial relationships to disclose
Tara B. Sanft, MD: No financial relationships to disclose
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Beth Jones, PhD, MPH: No financial relationships to disclose
Tish Knobf, PhD, RN, FAAN: No financial relationships to disclose
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Jennifer Ligibel, M.D.: No financial relationships to disclose
Melinda L. Irwin, PhD, MPH: No financial relationships to disclose
PD12-09

PD12-09 Serum Advanced Glycation End-Products are Associated with Breast Cancer Prognosis

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Country: United States

Background: Tumor characteristics such as grade, stage and receptor status are associated with breast cancer (BC) prognosis. Less is known about modifiable factors and BC prognosis. Advanced glycation end-products (AGEs) are reactive metabolites produced as a by-product of sugar metabolism, generated in conditions of increased oxidative stress. AGEs irreversibly accumulate in our tissues over time with pathogenic effects on genetic fidelity, protein function, cell signaling pathways, and chronic inflammatory diseases. The total body AGE pool is composed of endogenous AGEs and exogenous AGEs (consumed mainly through processed foods and those cooked at high temperatures). Serum AGE (sAGE) levels, a reflection of total body AGE, are higher in people with poor diet quality, lower levels of physical activity, and in women with BC compared to healthy controls. AGEs promote growth, migration and invasion in BC cell lines and activate prognostic inflammatory mediators such as interleukin-6 and C-reactive protein. Dietary AGEs have been associated with increased BC risk and increased mortality after BC diagnosis whereas lifestyle interventions can lower dietary and sAGE levels. The impact of sAGE levels, a better estimate of total body AGE than dietary AGE, on BC prognosis has not been previously evaluated. Methods: The Women’s Healthy Eating and Living (WHEL) study randomized 3088 BC patients stage I-III who completed their primary therapy to a high-vegetable, low-fat diet or control and followed for a median of 7.3 years. Main outcomes were invasive BC events (recurrence or new primary N=518), death due to BC (N=262) and deaths from any cause (N=315). sAGE was measured as the AGE metabolite
carboxymethyllysine (ug/ml) from WHEL fasting blood specimens at study entry. sAGE was logged and corrected for plate batch effect via linear regression and analyzed in continuous scale and in quintiles. The Kaplan-Meier method and Cox regression model were performed for risk impact of sAGE on overall survival (OS), recurrence free survival (RFS), breast cancer specific survival (BCSS) and distant metastasis free survival (DMFS). We additionally adjusted in Cox models for potential confounding variables (age, race, BMI, smoking, alcohol use, physical activity, tumor characteristics). Results: 2564 participants had sAGE available. After excluding samples for excessive variabilities, 2315 samples were analyzed. Raw corrected sAGE ranged from 0.0-48.15 ug/ml (median 7.39); logged and corrected range -5.04-1.67. sAGE was positively associated with BMI (p<.0001, rs 0.10) and negatively associated with physical activity (p< .001, rs -.06). sAGE was not significantly associated with tumor stage, grade, receptor status, or race or menopausal status. Comparing the highest quintile (logged and corrected range=0.33~1.67) to the lowest quintile (range=-5.04~0.30), sAGE was significantly associated with all survival outcomes (Table 1). As a continuous variable, AGE was

Conclusions: Higher sAGEs are associated with worse survival outcomes in BC and may represent a novel, lifestyle-linked, modifiable prognostic biomarker in BC. Interventions aimed at lowering sAGE levels should be tested for their impact on known prognostic biomarkers as well as clinical outcomes. Individualized cancer-specific lifestyle recommendations are a crucial but currently lacking component of personalized cancer medicine.

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Lindsay L. Peterson, MD, MSCR: No financial relationships to disclose
Yu Tao, MD: No financial relationships to disclose
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Graham A. Colditz, n/a: No financial relationships to disclose
Yikyung Park, ScD: No financial relationships to disclose
Jennifer Ligibel, M.D.: No financial relationships to disclose
David Turner, PhD: No financial relationships to disclose
GS3-01 EMERALD phase 3 trial of elacestrant versus standard of care endocrine therapy in patients with ER+/HER2- metastatic breast cancer: Updated results by duration of prior CDK4/6i in metastatic setting


* = co-first
** = presenting author


Background: In patients (pts) with ER+/HER2- metastatic breast cancer (MBC) following progression on prior endocrine and CDK4/6i therapy, the EMERALD trial demonstrated significantly prolonged progression-free survival (PFS) and a manageable safety profile for elacestrant versus standard of care endocrine therapy (SoC). Benefit was observed in all pts and in pts with ESR1 mutant MBC (ESR1-mut). EMERALD is the only oral SERD monotherapy pivotal trial where all pts were pretreated with CDK4/6i. Here, we examine the impact of duration of prior CDK4/6i on PFS.

Methods: EMERALD (NCT03778931) is a randomized, open-label, phase 3 trial that enrolled pts with ER+/HER2- MBC who previously had 1-2 lines of endocrine therapy, mandatory CDK4/6i, and ≤1 chemotherapy; prior treatment with fulvestrant was allowed. Patients were randomized 1:1 to elacestrant (400 mg orally daily) or SoC (investigator’s choice of aromatase inhibitor or fulvestrant). If randomized to the control arm, patients who received prior fulvestrant were to receive an aromatase inhibitor, and vice versa. If two CDK4/6i were used in the metastatic setting (n=40), the cumulative duration was calculated. Results: A total of 478 pts were randomized (228 with ESR1-mut) between Feb 2019 – Oct 2020 (n=239, elacestrant; n=239, SoC). Overall survival was not yet mature, as of September 2nd 2022. Updated PFS results show statistically significant results in favor of elacestrant, both in all pts and in pts with ESR1-mut. The duration of prior CDK4/6i in the metastatic setting was positively associated with PFS, the longer the duration of prior CDK4/6i in the metastatic setting (n=465), the longer the PFS on elacestrant versus SoC (Table 1).
Table 1: PFS estimates in the elacestrant and SoC arms based on different cut-off points for the duration of prior CDK4/6i. Updated safety data were consistent with previously reported results.

<table>
<thead>
<tr>
<th>Duration on CDK4/6i in the metastatic setting</th>
<th>≥6.0 months</th>
<th>≥12.0 months</th>
<th>≥18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Elacestrant (n=202) SoC (n=205)</td>
<td>Elacestrant (n=150) SoC (n=160)</td>
<td>Elacestrant (n=98) SoC (n=119)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>2.8 1.9</td>
<td>3.8 1.9</td>
<td>5.5 3.3</td>
</tr>
<tr>
<td>PFS rate</td>
<td>34.4% 19.9%</td>
<td>41.6% 21.7%</td>
<td>44.7% 25.1%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.69 (0.54-0.88)</td>
<td>0.61 (0.45-0.83)</td>
<td>0.70 (0.48-1.020)</td>
</tr>
<tr>
<td>ESR1-mut</td>
<td>(n=103) (n=102) (n=78) (n=81) (n=55) (n=56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>4.1 1.9</td>
<td>8.6 1.9</td>
<td>8.6 2.1</td>
</tr>
<tr>
<td>PFS rate</td>
<td>42.4% 19.2%</td>
<td>55.8% 22.7%</td>
<td>58.6% 27.1%</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.52 (0.36-0.74)</td>
<td>0.41 (0.26-0.63)</td>
<td>0.47 (0.20-0.79)</td>
</tr>
</tbody>
</table>

Most of the adverse events (AEs), including nausea, were grade 1 and 2, and only 3.4% and 0.9% of the pts discontinued trial therapy because of an AE on elacestrant and SoC, respectively. A low percentage of pts received an antiemetic; 8.0%, 3.7%, and 10.3%, on elacestrant, fulvestrant, and AI, respectively. No hematological safety signal was observed and none of the patients in either of the two treatment arms had sinus bradycardia.

**Conclusions:** EMERALD is the first phase 3 trial to demonstrate a significant PFS improvement versus SoC in all pts and in the subgroup with ESR1 mutations in pts with ER-positive/HER2-negative MBC with 1-2 prior lines of endocrine treatment ± one line of chemotherapy. Elacestrant demonstrated longer PFS versus SOC that was positively associated with the duration of prior treatment with CDK4/6i, which was more pronounced in pts with ESR1-mut MBC. In this 2nd and 3rd line setting, elacestrant was well tolerated with significantly longer PFS versus SoC, highlighting its potential role as a therapeutic option for pts with ER+/HER2- MBC.

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EMBARGOED GS3-02 Camizestrant, a next generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial
GS3-03 ARV-471, a PROTAC® estrogen receptor (ER) degrader in advanced ER-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer: phase 2 expansion (VERITAC) of a phase 1/2 study

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**Background:** ARV-471 is a selective, orally administered PROteolysis TARgeting Chimera (PROTAC®) protein degrader that targets wild-type and mutant ER. ARV-471 is being evaluated in patients with ER+/HER2- locally advanced or metastatic breast cancer in a first-in-human phase 1/2 study (NCT04072952). In the phase 1 dose escalation, ARV-471 monotherapy (dose range: 30–700 mg total daily dose) showed a manageable safety profile in patients who had previously received endocrine therapy and a cyclin-dependent kinase (CDK) 4/6 inhibitor. The clinical benefit rate (CBR; rate of confirmed complete or partial response or stable disease ≥24 weeks) was 40% (95% CI: 26–56) in 47 evaluable patients. The phase 2 expansion portion of the study (VERITAC) evaluated 2 doses of ARV-471. **Methods:** In VERITAC, ARV-471 monotherapy was administered at doses of 200 mg once daily (QD) or 500 mg QD to patients with ER+/HER2- locally advanced/metastatic breast cancer who had received ≥1 prior endocrine therapy for ≥6 months, ≥1 CDK4/6 inhibitor, and ≤1 chemotherapy regimen. The primary endpoint of CBR was evaluated in patients enrolled ≥24 weeks prior to the data cutoff. **Results:** As of June 6, 2022, 71 patients received ARV-471 (200 mg QD [n=35]; 500 mg QD [n=36]) in VERITAC. Across all treated patients, 69 (97.2%) were female and median age was 60 y (range: 41–86). Patients had received a median of 4 prior regimens in all settings (range: 1–10); 100% had prior CDK4/6 inhibitors, 78.9% had prior fulvestrant, and 73.2% had prior chemotherapy. ARV-471 was well tolerated at both doses, with most treatment-related adverse events (TRAEs) grade 1/2; the most common TRAEs were fatigue and nausea (Table). In all, 3 patients (1 in the 200 mg QD cohort and 2 in the 500 mg QD cohort) discontinued ARV-471 due to treatment-emergent adverse events (TEAEs); 3 patients had ARV-471 dose reductions due to TEAEs (all from 500 mg QD to 400 mg QD). CBR was 37.1% (95% CI: 21–55) in 35 evaluable patients treated at 200 mg QD and 38.9% (95% CI: 23–57) in 36 evaluable patients treated at 500 mg QD. CBR in evaluable patients with mutant ESR1 in the 200 mg QD (n=19) and 500 mg QD (n=22) cohorts was 47.4% (95% CI: 24–71) and 54.5% (95% CI: 32–76), respectively. **Conclusions:** In the phase 2 VERITAC expansion cohorts of patients with ER+/HER2- locally advanced/metastatic breast cancer and prior CDK4/6 inhibitor treatment, ARV-471 monotherapy showed evidence of clinical activity based on CBR, which was further enhanced in the subgroup with ESR1 mutations. The manageable AE profile observed in the phase 1 portion of the study was maintained during cohort expansion at doses of 200 mg QD and 500 mg QD. Additional analyses are ongoing.
Table. TRAEs reported in ≥10% of patients overall

<table>
<thead>
<tr>
<th></th>
<th>200 mg QD (n=35)</th>
<th>500 mg QD (n=36)</th>
<th>Total (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Any TRAE, no. of patients (%)</td>
<td>26 (74)</td>
<td>2 (6)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (40)</td>
<td>0</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (14)</td>
<td>0</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (11)</td>
<td>0</td>
<td>5 (14)</td>
</tr>
<tr>
<td>AST increased</td>
<td>4 (11)</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>6 (17)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

*aNo grade 3/4 TRAE occurred in >1 patient.
AST=aspartate aminotransferase

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EMBARGOED GS3-04 Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPitello-291 trial
GS3-06 Palbociclib After CDK4/6i and Endocrine Therapy (PACE): A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab for Endocrine Pre-treated ER+/HER2-Metastatic Breast Cancer

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Background CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have a well-established role in the management of hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). The benefit of continuing CDK4/6i beyond progression in combination
with a different ET has not been confirmed. Preclinical data suggest synergy between CDK4/6i and PD-L1 inhibition. The PACE trial prospectively evaluates whether continuation of the CKD4/6i palbociclib beyond progression on prior CDK4/6i and aromatase inhibitor (AI), with a change in ET to fulvestrant, improves outcomes beyond change to fulvestrant alone, as well as explores the activity of the palbociclib, fulvestrant, and avelumab triplet. Methods PACE is a multicenter randomized open-label investigator-initiated phase II trial, open at 11 U.S. sites. Eligible patients (pts) had HR+/HER2- evaluable MBC with prior progression on AI and any CDK4/6i after > 6 months (mo) of therapy in the MBC setting, or during/within 12 mo in the adjuvant setting, with no more than 1 prior line of chemotherapy for MBC. Pts were randomized 1:2:1 to fulvestrant alone (F); fulvestrant and palbociclib (F+P); or fulvestrant, palbociclib, avelumab (F+P+A), with tumor assessments every 8 weeks. Blood for circulating tumor DNA (ctDNA) analysis was collected at baseline, at times of tumor assessments, and at progression. The primary objective was to evaluate progression-free survival (PFS) with F+P vs F; secondary objectives included PFS with F+P+A vs F, objective response rate (ORR) in all arms, and safety. A sample size of 220 patients was planned to provide 80% power to detect of 220 pts were randomized from 9/2017-2/2022 (F: n=55, F+P: n=111, F+P+A: n=54); median age 57 years (range 25-83), 85% non-Hispanic (7.7% non-Hispanic black), 8.6% Hispanic, 6.4% unknown. 40% had de novo MBC, 60% had visceral disease, and 14% bone-only disease. 16% had 1 prior line of chemotherapy for MBC, 90% had received prior palbociclib, 4.5% ribociclib, 4.1% abemaciclib, 1.4% palbociclib and ribociclib. Pts entered the trial after a median 19 mo of prior CDK4/6i plus AI (interquartile range 12-31 mo). A total of 10 (5%) pts received protocol therapy as first line ET for MBC, 169 (77%) as second line, and 41 (17%) as beyond second line. 88% entered the trial directly after progression on CDK4/6i. After a median follow-up of 24 mo, 18 pts remained on protocol treatment. PFS was not improved with F+P vs F (median 4.6 vs 4.8 mo; HR=1.11, 90% CI 0.79-1.55; 2-sided p=0.62). Median PFS was 8.1 mo with F+P+A (HR=0.75 vs F, 90% CI 0.50-1.12; 2-sided p=0.23). ORR was 7.3% (90% CI 1.5-13.0) with F, 9.0% F+P (4.5-13.5%) and 13.0% F+P+A (5.4-20.5%). No new safety signals have been observed. Analysis of ctDNA panel sequencing encompassing 70 genes from 184 baseline samples, including correlation with known and hypothesized resistance genes, will be presented. Conclusions For ER+/HER2- breast cancer, combining palbociclib with fulvestrant beyond progression on prior CDK4/6i and AI did not significantly improve PFS compared with using fulvestrant alone. The observed longer PFS when a PD-L1 inhibitor was added to fulvestrant plus palbociclib is an intriguing signal in this ER+ population. Translational studies of blood and tumor tissue are ongoing and will be presented.

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GS3-07 Clonal evolution and mechanisms of acquired resistance to CDK4/6 inhibitors in ER-wild type and ER-mutant breast cancer

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Background Despite the remarkable activity of CDK4/6 inhibitors (CDK4/6i) in the treatment of estrogen receptor positive (ER+) metastatic breast cancer (BC), most patients eventually develop resistance to these drugs. The ctDNA analysis of the PALOMA-3 trial showed that the estrogen receptor (ER) mutation Y537S is a potential mechanism of acquired resistance to the combination of endocrine therapy (ET) with CDK4/6i. To date, the role of the ER mutations in the clonal evolution and the mechanisms of acquired resistance to CDK4/6i is unknown. Moreover, it is not known if the development of resistance to CDK4/6i in the presence or absence of ER mutations is due to the expansion of pre-existing resistant clones or to the de novo acquisition of resistance mechanisms. Methods To explore the clonal evolution and the mechanisms of resistance to CDK4/6i in ER-wild type (ER-WT) and ER-mutant (ER-Mut) BC, we transduced doxycycline (DOX)-inducible Y537S ER-Mut MCF7 cells with the ClonTracer library, a high-complexity DNA barcode library, and cultured the barcoded cells without DOX (MCF7), or with DOX to induce the expression of the Y537S ER mutation (MCF7-YS). To develop Palbociclib (Palbo)-resistant (PDR) and Abemaciclib (Abema)-resistant (ABR) cell models, the barcoded MCF7 and MCF7-YS cells were passaged in culture with increasing concentrations of Palbo and Abema until the acquisition of resistance. The clonal dynamics and the molecular characteristics of the PDR and ABR models were investigated by barcode sequencing, whole-exome sequencing (WES), bulk and single cell RNA sequencing (RNAseq) and protein analyses. Finally, using an ER-Mut barcoded mice model, we compared the in vitro clonal evolution of ER-Mut CDK4/6i-resistant cells with the in vivo clonal evolution of ER-Mut metastases. Results The analysis of the barcodes revealed that during the acquisition of resistance to either Palbo or Abema there is a strong clonal selection of pre-existing resistant clones. The PDR clones were different in the presence of the Y537S mutation versus WT-ER. In contrast, the clones enriched in the ABR cells were comparable between WT and mutant ER. Furthermore, the ER mutations led to decreased diversity of the enriched clones in the PDR but not in the ABR cells. Interestingly, the barcodes enriched in the PDR and ABR models did not overlap. Unsupervised analyses showed that the samples clustering based on the barcodes fractions and the mutations were similar, suggesting that the clonal selection was driven by cellular populations with specific mutational landscapes. All the ER-WT and ER-Mut resistant models had different transcriptional profiles and by single-cell RNAseq showed various degrees of intra-sample heterogeneity. At the protein level, the PDR and the ABR cells displayed downregulation of ER, Rb and p27 and upregulation of p21. In the ER-Mut conditions Cyclin D1 was upregulated in the PDR cells, while Cyclin E was upregulated in the ABR cells. Finally, the barcode sequencing of the mice metastases revealed that the clonal selection in ER-Mut metastases and in ER-Mut CDK4/6i-resistant cells is different. Conclusion Our study suggests that the development of resistance to CDK4/6i is due to the selection of pre-existing resistant clones. We also demonstrate that the expression of the Y537S ER mutation impacts the clonal
evolution and the mechanisms of acquired resistance to Palbo but not to Abema. Finally, we show that the clonal evolution and mechanisms are disparate in Palbo and Abema resistance. These results support the addition of a third drug to CDK4/6i and ET, early in treatment, to delay the selection of pre-existing resistant clones and prolong the response to treatment and highlight differences between Palbo and Abema.

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EMBARGOED GS3-09 Circulating Tumor Cells-driven choice of first line therapy for ER+ HER2- metastatic breast cancer: overall survival analysis of the randomized STIC CTC trial
Adjuvant endocrine therapy for premenopausal ER+ breast cancer had a relatively challenging initial pathway. The earliest trials testing adjuvant ovarian ablation in premenopausal breast cancer were hampered by the lack of ability to test for the relevant target, namely the estrogen receptor (ER). Therefore, trials testing adjuvant ovarian ablation and subsequently ovarian suppression with gonadotropin releasing hormone agonists (GnRHa) were diluted by the inclusion of women with estrogen receptor negative tumors. The subsequent demonstration of the effectiveness of adjuvant chemotherapy, initially with the CMF regimen, diverted some attention away from adjuvant endocrine therapy in premenopausal women, notwithstanding the fact that CMF, initially given for 12 months, resulted in permanent ovarian function suppression in many premenopausal women. Use of adjuvant CMF made it even more challenging to discern the added value of ovarian ablation or suppression. Oral adjuvant endocrine therapy with the selective estrogen receptor modulator tamoxifen became recommended for postmenopausal women, subsequently refined to only those with ER+ breast cancer, but the value of tamoxifen in premenopausal women was initially considered uncertain. Eventually, 5 years of adjuvant tamoxifen became a standard recommendation for premenopausal ER+ early breast cancer, although it took some time for evidence to emerge on the value of adding tamoxifen in women who received chemotherapy. The value of extending adjuvant endocrine therapy beyond 5 years was subsequently studied. More recent randomized premenopausal adjuvant endocrine therapy trials have focused on delineating the value of ovarian function suppression (OFS) added to tamoxifen or to an aromatase inhibitor. There are now a range of options for adjuvant endocrine therapy for premenopausal ER+ breast cancer, and identifying the clinical-pathologic features most appropriate for intensification of adjuvant endocrine therapy can assist with optimizing recommendations for an individual patient.

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Fasting and caloric restriction mimetics stimulate anticancer immunosurveillance

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Fasting and caloric restriction induce metabolic and neuroendocrine changes that have major anti-inflammatory and immunostimulatory effects. Some of these effects are mediated by a raise of ketone bodies (such as 3-hydroxybutyrate) and a decrease in circulating insulin-like growth factor-1 (IGF1), meaning that administration of 3-hydroxybutyrate and pharmacological inhibition of IGF1 receptor can mimic some of the beneficial effects of fasting on anticancer immunosurveillance. "Caloric restriction mimetics" (CRMs) are small molecules that induce autophagy through the same pathways that are activated by fasting, including the reduction of cytoplasmic protein acetylation. We have accumulated evidence that CRMs can stimulate anticancer immunosurveillance either as single agents (for the prevention of malignant disease) or in combination with chemotherapy and/or immune checkpoint blockade (for the treatment of established cancers). In preclinical experiments, fasting and CRMs have also been used for the prevention or treatment of hormone-induced breast cancer, and these effects are coupled to an increase in the T lymphocyte-mediated anticancer immune response. We have developed an in vitro screening assay to identify novel pharmacological agents that act as CRMs. Such neo-CRMs can be successfully employed to improve anticancer immunosurveillance in preclinical experiments.
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Microbiome and response to immunotherapy

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CDK4/6 inhibitor resistance: Biological mechanisms and novel approaches

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CDK4/6 inhibitors (CDK4/6i) in combination with antiestrogens have revolutionized the treatment of ER+ metastatic breast cancer (MBC), significantly prolonging survival. However, this combination is not curative in MBC, and resistance to CDK4/6i represents a major challenge. A diverse array of mechanisms of CDK4/6i resistance have been described, including deregulation of the G1/S cell cycle checkpoint (i.e. Rb, Cyclin E/CDK2, CDK6, INK4s), activation of growth factor signaling pathways (receptor tyrosine kinases, Ras/MAPK pathway, PI3K/AKT pathway), and contributions from the tumor microenvironment. A detailed understanding of these mechanisms is critical for overcoming CDK4/6i resistance. In this presentation, I will discuss recent advances in defining novel biomarkers that are causally associated with CDK4/6i resistance, therapeutic vulnerabilities linked to distinct mechanisms of resistance, and potential strategies to improve clinical responses to CDK4/6i in ER+ MBC.
Ki67 – a clinically relevant biomarker or just nice to have information?

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Ki67 is an immunohistochemical marker indicating the growth fraction of cycling cells from G1 to S-phase in tumor specimens. In breast cancer, Ki67 is a prognostic marker with high values indicating poor outcome. Over the last decades, obstacles for its wide-spread use in clinical practice included lack of methodological standardization and lack of specific cut-off values for clinical decision making, i.e. discrimination of luminal A vs. B early breast cancer (EBC), chemotherapy indication in HR+/HER2- EBC. However, recently, the International Ki67 working group has put forward consensus statements for a standardized methodology. In general, reproducibility of Ki67 values at extreme sides of the spectrum such as 10% or > 35% is much higher than in the intermediate range and quality assurance programs substantially improve laboratory performance. Moreover, clinical utility has also become apparent in two specific settings of HR+/HER2- EBC.

First, the monarchE trial evaluating adjuvant abemaciclib in node-positive high-risk disease used a Ki67 cut-off of 20% as a criterion for aggressive disease and as a sole inclusion criterion for patients with 1-3 lymph nodes (cohort2). While data for this cohort have not yet been reported, Ki67 was a strong prognostic factor in the overall trial population with patients with high Ki67 having worse outcome than those with Ki67 < 20%. Benefit from abemaciclib was independent of Ki67 index. Nevertheless, some health authorities included Ki67 in their abemaciclib label as the absolute benefit was greater in tumors with Ki67 > 20%.

Second, Ki67 response after a short (2-4 week) preoperative endocrine therapy allows endocrine response assessment by determining Ki67 in the surgical specimen. This information is widely used in drug development. Ki67 post 10% has been defined as endocrine response. In the POETIC trial, endocrine response was associated with improved outcome compared to tumors with Ki67 > 10% after 2-weeks of preoperative AI in postmenopausal patients. In the WSG ADAPT trial, patients with 0-3 lymph nodes, Recurrence Score 25 and endocrine response had excellent outcome with adjuvant endocrine therapy alone independent of menopausal status (5-year dDFS > 95%). In postmenopausal women, probability of endocrine response with an AI is around 80% whereas in premenopausal patients with tamoxifen it is only around 40%. Yet, in premenopausal women addition of GnRH substantially improves endocrine response probability reaching about 80% with GnRH and AI as recently shown by interim analysis of the WSG ADAPTcycle trial (about 2500 patients). Endocrine response probabilities
seen in the ADAPT trial (> 5000 patients) were validated in ADAPTcycle demonstrating clinical validity of this biomarker.

In conclusion, Ki67 is a clinically relevant biomarker that can be used for clinical decision making, particularly in HR+/HER2- EBC. As there is no single generally accepted Ki67 cut-off value to discriminate prognostically favorable from aggressive EBC, Ki67 needs to be used in the context of tumor burden and tumor biology. Currently, next to its use in allocating patients to adjuvant abemaciclib in countries where Ki67 index is included in the label, it provides clinically important information after short-term preoperative endocrine therapy regarding endocrine response in HR+/HER2 EBC. Given its easy and inexpensive determination method, its analytical validity within quality assurance programs, and its clinical usefulness, Ki67 needs to be integrated in our biomarker portfolio in EBC.

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Metaplastic breast cancer (MPC) is a less common subtype of breast cancer, representing approximately 0.2-0.5% of breast cancer diagnoses, which is often associated with poor outcomes. MPC is an overarching term for breast tumors which demonstrate differentiation toward epithelial or mesenchymal components, or a mixture of these. In the context of challenging subtypes of breast cancer, this educational discussion will review epidemiology and clinical course of these tumors. Molecular characteristics of MPC and how this might impact current, as well as possible future, management strategies will be discussed. Finally, opportunities for laboratory investigations and clinical trial approaches to further understand and better treat MPC will also be discussed.

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Inflammatory Breast Cancer (IBC) has an incidence of 1-5% among all breast cancers diagnosed within the USA, yet it accounts for a disproportionately high rate of mortality, leading to up to 10% of all breast cancer related deaths. Although IBC can present with any receptor status in terms of estrogen, progesterone, and human epidermal growth factor 2 (HER2), there is a higher proportion of HER2 positive cases compared to non-IBC. Given the distinct difference in outcome, it is important to differentiate IBC from more indolent locally advanced non-IBC with secondary inflammatory features. Despite ongoing efforts to identify molecular markers specific for IBC, the underlying tumor biology and genomic drivers of progression remain largely unknown. In this session we will review tumor-intrinsic signaling pathways, the role of the tumor microenvironment and clinical trials with combination therapies to inform future biomarkers of disease progression in IBC.

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Invasive lobular carcinoma (ILC) accounts for up to 15% of all invasive breast cancers. The general marker to identify lobular cancer is the loss or low expression of E-cadherin which is the result of genetic alterations of the \textit{E-cadherin} gene which accounts for about 95%. The majority of classical ILCs are of low grade and express both hormone receptors strongly and rarely any HER2. Those not expressing the hormone-receptors are categorised as apocrine breast cancers which is a small group.

Recently it has been shown that ILC is a breast cancer type which has unique genomic features. Desmedt and colleagues genomically profiled 430 ILCs, to characterize the genomic alterations present in these tumors compared to invasive ductal carcinoma (now cold unfortunately NST non-specific subtype). The most frequent altered gene was CDH1 which results in a mRNA or protein loss of the cell adhesion molecule E-cadherin. Amongst the genes found to be altered at a high frequency are ESR1 and PIK3CA/PTEN. Currently those have little or no clinical impact in early breast cancer there might be consequences for metastatic breast cancer.

The molecular alterations result in a less cohesive tissue connection and influence imaging as well as surgical procedures and in the end the prognosis in those patients.

The size and extend of ILC is often underestimated by imaging and clinical examination. MRI thought to be the optimal imaging turned out to have no influence on positive margins and is no longer considered standard for all ILCs.

Several data suggest that ILCs have an improved outcome the first 5 years after primary diagnosis but thereafter the survival curves in general lie below those for non lobular breast cancer. ILC has a distinct metastatic pattern and often metastasise into the GI tract and the ovaries and less frequently to the lung.

Breast conserving surgery as well as mastectomy can be used when indicated based on tumor size and patients preference. Because ILC more often presents at higher stage, mastectomy is more frequently performed. But even after neoadjuvant chemotherapy we could demonstrate, despite response even resulting in pCR, mastectomy was more frequently conducted in ILC patients compared to non-ILC. In this analysis 71% of the non-ILC did receive BCS compared to only 59% in ILC (p
Systemic therapy follows the general recommendations based on stage and histopathological profile.

Neoadjuvant chemotherapy results in significantly lower rates of pathological responses. All analyses showed response rate in single digit numbers (far below 10%) but the less classical ILCs with either grade 3 or hormone-receptor negativity have a higher chance of achieving a pCR. Those ILCs with grade 3 and hormone-receptor negativity (apocrine cancer) have a pCR rate comparable to invasive ductal carcinoma (IDC). It is not surprising that lobular breast cancer does not respond as well as IDC to neoadjuvant chemotherapy because their biological features are, as described above, more luminal A like (high hormone receptor positivity, low grade, low proliferation). Because many patients with ILC present with extended diseases, they might still benefit from neoadjuvant chemotherapy even if they do not achieve a pathologic complete response, downstaging is an option and would potentially lead to less mastectomies.

Because of the luminal A like type of the majority of ILCs endocrine therapy seems to be the treatment of choice. Some data even suggested a better outcome for ILC breast cancer when treated with an aromatase inhibitor compared to tamoxifen. But other data are controversial in this regard and did not confirm the data from BIG 1-98.

In conclusion the molecular profile of ILC seems to be distinct but does not result in different treatment paradigms. We should not underestimate the necessity of optimal treatment, including chemotherapy for invasive lobular breast cancer patients.

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Cancer risks in patients with high penetrance gene mutations

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Cancer risks in patients with moderate penetrance gene mutations

The genetic landscape of inherited breast cancer is broad, spanning from high and moderate penetrance pathogenic variants in breast cancer susceptibility genes, to polygenic risk associated with the cumulative impact of single nucleotide polymorphisms (SNPs). This educational session will review the landscape of inherited breast cancer. The discussion will then focus on breast cancer susceptibility genes associated with moderately elevated risks of breast cancer including PALB2, ATM, CHEK2 and others. Recent data informing quantitative and qualitative cancer risk estimates, management recommendations, therapeutic implications, and reproductive considerations will be reviewed. Emerging issues and treatment strategies under investigation will also be discussed.
Screening for high risk patients: does everyone need annual MRI with mammogram?

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Introduction:

To reduce mortality, all guidelines advice women with very high breast cancer (BC) risk, due to a pathogenic variant (PV) in genes like BRA1/2 or chest wall irradiation between age 10-30 yrs., annual screening with Magnetic Resonance Imaging (MRI) and 2 or 3D mammography (Mm).1-6 For MRI, starting age for this group is usually 25 years. However for Mm some guidelines advise annual from age 30 yrs.1,2, others 10 yr. younger than the youngest family member4,5, or for BRCA1 biennial from age 40 yrs.7

USA and Canadian but not European guidelines advice MRI screening also for women with a ≥20% lifetime breast cancer (BC) risk, while the European Eusobi guideline, unlike the US and Canadian, now advises to screen women with extremely dense breasts with MRI although not yearly.8

Considerations and evidence:

We need to balance the possible benefit with the disadvantages of screening, like false positive rate, possible overdiagnosis and cost. We therefore have to use the optimal frequency of screening, depending on the expected tumor growth rate, which varies with a woman's age and the cause of the increased risk.9

Two recent randomized trials one in women with familial risk the other for extremely dense breasts showed how much MRI advances BC detection compared to mammography, at which side effects.10,11

Observational and modelling studies show varying additional value of Mm to MRI-screening for different risk – and age groups.12-17

Conclusion: Screening for women at high risk can be better tailored to the age and risk-group.

References:


Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group.


6. National Institute for Health and Care Excellence (NICE). Familial breast cancer:


Women who inherit a pathogenic variant (mutation hereafter) in the BRCA1 or BRCA2 gene face extremely high lifetime risks of developing breast and ovarian (or fallopian tube) cancer. More than two decades since the discovery of these genes, and primary prevention with bilateral mastectomy and salpingo-oophorectomy remain the most effective options to manage cancer risk in this population. Understanding the impact of exogenous hormone use is important for both the clinical management of high-risk women and for furthering our knowledge of the pathogenesis of BRCA-associated disease. In this session, I will review the current epidemiologic data surrounding the role of exogenous (anti)hormone use on BRCA-cancer risk. Specifically, I will discuss the role of tamoxifen in preventing BRCA-associated breast cancer and I will describe whether use of oral contraceptives or hormone replacement therapy (HRT) increase the risk of breast cancer. Where possible, I will present data by gene mutation. Potential associations with the risk of ovarian cancer will also be referred to, given that managing BRCA-cancer risks is a balancing act. Finally, I will review how the epidemiologic information has contributed to the discovery of novel targets for the non-surgical prevention of BRCA1-associated breast cancer and gaps in the literature to be addressed in future research.
Circulating tumor DNA (ctDNA) is at the forefront of liquid biopsy technology. A key advantage of ctDNA is being able to achieve genomic profiling from a blood test rather than from a more invasive tissue biopsy, reducing risk and discomfort for patients as well as costs and logistical complexity. Increasing evidence supports ctDNA as a useful clinical tool in specific indications, for example in the detection of PIK3CA mutations to identify patients suitable for alpelisib plus fulvestrant. The expectation is that indications for routine ctDNA testing will expand as more data become available and ctDNA is embedded into clinical trials and paired with novel therapies.

Biological and technical factors both contribute to the feasibility of ctDNA expansion into the clinic. Representation of heterogeneity might be a key strength of ctDNA analysis over tumour biopsy analysis, as sampling the circulation compartment can in principle allow representation of a wider array of disease sites than a tumor sample acquired with a single needle.

However, the factors influencing how different metastases might contribute to the circulating compartment are poorly understood, presenting a challenge to clinical interpretation. Moreover, the limit of detection of ctDNA assays, the timing of treatment and stochastic effects can contribute to uncertainty, particularly in the interpretation of negative results. Recent work analyzing tumor mutational burden using ctDNA has highlighted these challenges as applied to biomarker development.

Circulating tumour DNA is likely to complement tissue biopsy in the future, and may substitute tumor biopsy in specific indications supported by the data. Ultimately, clinical utility for different ctDNA indications, as opposed to tissue biopsy, will need ongoing confirmation within clinical trials.
12/8/2022
5:00 PM - 6:15 PM
Ongoing Trials 3
A single-arm confirmatory study to evaluate the efficacy of non-surgical therapy for HER2 positive early breast cancer with clinical complete response after primary systemic therapy: (JCOG1806)

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Background: The surgical treatment is the standard therapy for early breast cancer (EBC) after primary systemic therapy (PST). In more than half of HER2 positive (HER2(+)) breast cancer, pathological complete response (pCR) is achieved by PST with HER2 inhibitors and chemotherapy. However, non-surgical therapy is not an option for EBC with cCR after PST because of little evidence. We planned a single-arm confirmatory study to evaluate the efficacy and safety of the non-surgical therapy for HER2(+) EBC with cCR after PST. Methods: The key eligibility criteria are as follows: 1) Histologically confirmed as invasive ductal carcinoma of the breast, HER2(+) 2) cT1-2, N0, M0 (UICC 8th). 3) No ipsilateral BC. 4) Women aged 20-74 years. 5) ECOG performance status 0 or 1. 6) Adequate hematologic and organ function. 7) Ejection fraction as cardiac function is over 50%. 8) Written informed consent. HER2 inhibitors...
(trastuzumab and pertuzumab) and cytotoxic drugs as PST are administered to all patients (pts). After completion of PST, cCR is diagnosed by breast imaging and physical examination. cCR is defined as 1) Not palpable breast mass by physical examination, 2) No enhanced breast mass by enhanced MRI, and 3) No breast mass by ultrasonography. 4) For hormonal receptor (+) EBC, needle biopsy after PST must be done to evaluate the pCR. After a diagnosis of cCR, conventional radiotherapy for whole breast and boost radiation for tumor bed is mandatory, followed by pertuzumab and trastuzumab every 3 weeks for 9 months. In non-cCR cases, surgical resection is performed and adjuvant therapy is not specified. The primary endpoint is a distant metastasis-free survival (DMFS) at 3 years, the secondary endpoints are DFS, OS, RFS, the proportion of local recurrence, and cosmetics outcome. Given that the threshold and expected DMFS at 3-year is 93% and 98% with a significance level of 2.5% (one-sided) and 80% power, 170 cCR cases are required. Assuming half of the HER2 pts reach cCR, 350 pts are required as the sample size started PST. Enrollment launched in January 2020, and 260 pts are enrolled as of July 12, 2022. This clinical trial has been registered at the Japan Registry of Clinical Trials as jRCTs031190129 and conducted by the Japan Clinical Oncology Group (JCOG) Breast Cancer Study Group under a public fund (National Cancer Center Research and Development Fund).

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WITHDRAWN
Phase I study of intratumoral administration of CF33-hNIS-antiPD-L1 (CHECKvacc) in patients with metastatic triple negative breast cancer

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Background: Despite recent FDA approvals of immune checkpoint inhibitor pembrolizumab and drug-antibody conjugate in the treatment of metastatic triple negative breast cancer (mTNBC), the overall survival benefit of these therapies remains modest. Oncolytic virotherapy (OV) utilizes genetically modified viruses to infect and kill cancer cells while sparing healthy cells. CF33-hNIS-anti-PD-L1 (CHECKvacc) is a novel chimeric orthopoxvirus with robust anti-cancer activity in TNBC xenografts. Cells infected with CHECKvacc were shown to express functional human sodium-iodide symporter (hNIS) and anti-PD-L1 proteins. hNIS gene transfer allows tracking of virus by 99mTc single-photon emission computed tomography (SPECT). Our preliminary animal studies demonstrated that tumor cells infected with CHECKvacc successfully secrete functional hNIS and anti-PD-L1. CHECKvacc administered by intratumoral injection appears safe and is generally well-tolerated. CHECKvacc detects and effectively kills TNBC at doses several magnitudes lower than other OVs in xenograft models. Methods: This study is a first-in-human phase I, single center, single arm clinical trial evaluating the safety and tolerability of CHECKvacc intratumoral injection in patients with mTNBC. Key eligibility criteria include patients with unresectable or metastatic TNBC; progressed on at least 2 prior chemotherapies including an immune checkpoint inhibitor-containing regimen; ECOG 0-1; RECIST 1.1 measurable disease; and at least one tumor amenable to repeated intratumoral injections. Eligible patients receive CHECKvacc intratumorally at one of 8 assigned dose levels (1 x 105 PFU, 3 x 105 PFU, 1 x 106 PFU, 3 x 106 PFU, 1 x 107 PFU, 3 x 107 PFU, 1 x 108 PFU, 3 x 108 PFU) on Days 1 and 15 of each 28-day cycle for a total of 3 cycles of treatment. The primary objective is to evaluate the safety and tolerability of CHECKvacc by CTCAE v5.0.
Secondary objectives are to determine optimal biological dose, recommended phase II dose (RP2D), and response rate by RECIST1.1. The first 3 subjects of dose level 1 were enrolled sequentially for safety monitoring. Once the initial 3 subjects were treated sequentially, the a dose level up to 8 subjects after a single DLT has been observed. Enrollment to the final RP2D may be expanded to include up to 12 patients for efficacy assessment. The estimated targeted accrual is 33 patients (minimum) to 78 patients (maximum). Correlative aims include assessing viral kinetics, viral plaque assay, 99mTc SPECT imaging for virus tracking, peripheral blood and tumor tissue for antiviral immune activation, and tumor microenvironment changes in association with response to therapy. Results: From October 2021 to June 2022, 6 patients were enrolled and received at least 1 dose of CHECKvacc injection at dose level 1 (1 x 10^5 pfu) and 2 (3 x 10^5 pfu). The intratumoral CHECKVacc injections were well tolerated. No DLTs were observed. No treatment emergent AEs (TEAEs) have been reported for the 6 patients so far. 99mTc SPECT imaging for virus tracking is on-going. Baseline and on treatment tumor biopsies were submitted for spatial immune profiling. Peripheral blood at baseline, on treatment and EOT were subjected for flow cytometry analysis. Conclusion: CF33hNIS-antiPD-L1 administered by intratumoral injection in patients with mTNBC is safe and well tolerated at the dose levels tested. Clinical trial information: NCT05081492

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A Phase 3 study evaluating ovarian suppression following three-month leuprolide acetate in combination with endocrine therapy in premenopausal subjects with HR+, HER2-negative breast cancer (OVELIA)

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Background: In US clinical practice, GnRH agonists are widely used to suppress ovarian function in pre/perimenopausal patients with breast cancer that is moderate-to high-risk for recurrence. Despite extensive use of leuprolide acetate (LA) for ovarian suppression, regulatory approval for this indication has not been established in the US. Additionally, existing three month formulations may not reliably provide ovarian suppression, as demonstrated by escapes in estradiol (E2). An extended-release LA product with a 3-month dosing period specifically developed for ovarian suppression in patients with breast cancer could fill this unmet need. TOL2506 is a 3-month, extended-release formulation of 30 mg of LA. This combination of active drug and in situ polymeric extended release technology is expected to deliver higher exposure to drug than the currently available 3-month (22.5 mg) formulations of LA marketed for advanced prostate cancer and potentially reduce escapes in E2 over the dosing period.

Methods: TOL2506A (OVELIA) is a phase 3, single arm, open-label study evaluating the effectiveness of TOL2506 to suppress ovarian function in premenopausal women with HR+, HER2-negative breast cancer. Approximately 250 subjects will be enrolled targeting 220 evaluable subjects, with 30% aged 40 years or younger. Subjects must be premenopausal women, age 18-49 (inclusive), with a diagnosis of Stage I, II, or III HR+, HER2-negative breast cancer (ER>1% and/or, PR>1%, HER2-negative per ASCO CAP guidelines), who are candidates for ovarian suppression with endocrine therapy. For subjects receiving chemotherapy, premenopausal status will be determined prior to initiating chemotherapy. Male subjects with HR+, HER2-negative breast cancer may also be eligible, but will be evaluated for safety analyses only. Eligible subjects will enter the 48 week Treatment Period in 2 groups: those receiving tamoxifen concurrently with TOL2506 or those who initiate therapy with an aromatase inhibitor (AI; letrozole, anastrozole, or exemestane) beginning 6 weeks after the first administration of TOL2506, if E2 < 20 pg/mL has been achieved. After Week 12, subjects will be allowed to switch from receiving an AI to receiving tamoxifen or from tamoxifen to AI at the Investigator's discretion. Subjects will receive 4 doses of TOL2506 every 12 weeks over the 48
90% of subjects with LH levels < 4 IU/L at Week 6. Secondary endpoints include suppression of LH, E2 (< 20 pg/mL for tamoxifen cohort and < 2.72 pg/mL for AI cohort) and absence of menses at weeks 6, 12, 24, 36, and 48. NCT04906395

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Adaptive Multi-Drug Treatment of Evolving Cancers (AMTEC): A Phase II, Open-Label, Study of Olaparib in Combination with either Durvalumab, Selumetinib or Capivasertib, or Ceralasertib Monotherapy in Patients with Metastatic TNBC

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BACKGROUND PARP inhibitors (PARPi) afford a rational therapeutic strategy in metastatic TNBC (mTNBC) due to the high incidence of dysregulated DNA damage repair mechanisms and high-level genomic instability that resemble tumors originating in germline BRCA-mutated carriers. However, PARPi monotherapy has limited efficacy in BRCA wild-type mTNBC; in BRCA mutant disease following initial response, compensatory mechanisms inevitably restore replication fork protection. AMTEC leverages pre- and on-therapy biopsies from a 4-week PARPi monotherapy run-in period for personalized biomarker-driven patient selection to interdict adaptive resistance to the PARPi. Data from our pilot study (NCT03544125) and from Arm 1 of AMTEC (olaparib + durvalumab) identified PI3K-AKT, RAS-MEK, and ATR/CHK1/WEE1 as targetable pathways contributing to PARPi adaptive resistance in individual participants. Clinically validated assays (DNA, RNA, and protein) enable the identification of cellular mechanisms of PARPi sensitivity and resistance in individual patients and further reveal combined drug treatments that could prevent emergence of PARPi resistance. METHODS AMTEC is a non-comparative, multi-arm, open-label, phase II study to assess the efficacy of combining olaparib (ola) with durvalumab (dur), or MEKi, selumetinib (sel), or AKTi, capivasertib (cap), or monotherapy with ATRi, ceralasertib, (cer mono) in mTNBC patients. Participants with biopsy proven mTNBC (ER< 10%, PR< 10%, and HER-2 non-amplified), AR< 80% are eligible. - Participants undergo a pre-treatment biopsy, then start a 28-day induction with ola (300 mg PO BID, D1-28). On C1D14, patients undergo a repeat, on-treatment biopsy. Clinically validated assays (DNA, RNA, protein) from both biopsies inform patient assignment to a specific ola combination arm starting on C2D1: - Arm 1 tumor immune
activated: ola + dur (1500 mg IV) - Arm 2 RAS-MEK-ERK pathway activation: ola + sel (BSA-based BID D1-28) - Arm 3 PI3K-AKT pathway activation: ola + cap (400 mg PO BID, 4 days on/3 days off) - Arm 4: If not eligible for Arms 1-3 (per biomarker selection criteria): Cer mono (240 mg PO BID D1-14)

Endpoints: The primary endpoint is objective response rate (ORR per RECIST 1.1). Secondary endpoints include safety and toxicity, clinical benefit rate, duration of response, and survival. Statistical Methods: - Arm 1 will enroll 28 patients to detect achieve a response. - Arms 2, 3, and 4, will each enroll 22 patients to detect an ORR difference achieve a response in each arm, respectively. For arms 2 and 3, if arm (N = 19 patients/arm). ENROLLMENT The study was activated on 1/7/2019. Arm 1 met pre-specified interim analysis criteria in 12/2020, and accrual to stage 2 began in 1/2021. Arms information: NCT03801369 Contact information: For more information or to refer a patient, email hobbev@ohsu.edu

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Background At the Penn State Cancer Institute (PSCI), there is currently a lack of patient education materials regarding self-management of cytotoxic chemotherapy related side effects, thus leading to use of disreputable sources (online searches) by cancer patients. A standardized brochure developed by our team aims to educate patients about commonly experienced chemotherapy related side effects. It also provides patients with tools to address these problems themselves, information on when to contact their medical oncologist, and brief guidance on when it is appropriate to visit the Emergency Department. We hypothesize that effective patient education through the brochure will improve patient related outcomes and quality of life. Moreover, empowering patients with such a trustworthy resource will decrease anxiety and distress related to their treatments. If this intervention is found to be impactful, it could be expanded to other cancer types within PSCI and eventually to other institutions across the country. Trial design • Recruitment and Screening: Chemotherapy naïve patients with breast cancer are recruited from our institution, screened, and enrolled on a rolling basis • Baseline Visit: Consent, receive the brochure, and complete the following questionnaires: the Patient Education Material Assessment Tool (PEMAT), Emotional Thermometer Scales (ETS), and Memorial Symptom Assessment Scale (MSAS) • PEMAT is utilized to evaluate if a teaching material is understandable and promotes action, which will help determine if the
brochure itself is an effective education tool. ETS is utilized to evaluate the mental health, specifically measuring distress, anxiety, depression, and anger. MSAS is a validated patient-rated instrument for evaluation of diverse group of symptoms commonly seen with chemotherapy. Follow Up Visits: Fill out the same 3 surveys again at their 6-week and 12-week visits. Patients will fill out the same questionnaires to assess changes over time, a surrogate for the effectiveness of the brochure. Surveys take about 12 minutes to complete on average.

Eligibility Criteria:
1. Adult with Breast cancer >18 years of age.
2. Chemotherapy naive, will either start cytotoxic chemotherapy in the next 6 weeks or have started cytotoxic chemotherapy in the past 6 weeks prior to enrollment.
3. May receive multiple forms of therapy such as immunotherapy, targeted treatment, endocrine therapy or radiation as long as they receive concurrent cytotoxic chemotherapy.
4. Ability to understand and read written English or Spanish without any functional difficulty.
5. ECOG performance status 0-3.
6. May be involved with other cancer trials being offered at the PSCI.

Specific Aims:
• Primary Outcome: Determine if effective patient education through a standardized brochure will improve patient-related outcomes and quality of life.
• Secondary Outcome: Drop-out rate after the baseline visit.

Statistical methods:
• Outcome variables from survey-based questionnaires will be measured at all three time points.
• Their distribution at time points will be summarized using numerical and graphical methods.
• Paired-sample tests will be used to compare the difference between visits’ data.
• Linear mixed-effect models for repeated measures will be used to examine the overall pattern by using data from all three time points.
• All tests will be two-sided with a significance level of 0.05.
• We do not plan to do adjustments for multiple testing.

Present accrual and target accrual:
• 24 total accrued, 14 completed.
• 60 target accrual.

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Real-World Data on First-line Treatment of HR-positive, HER2-negative, Metastatic Breast Cancer in Brazil (BRAVE Study / LACOG 0221)

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Background: It is estimated that 50 thousand patients live with metastatic breast cancer (MBC) in Brazil. A recent Brazilian registry (LACOG 0312) on MBC demonstrated a median overall survival (OS) by breast subtype of 15 months for triple negative, 23 months for HER2 positive, and 42 months for Luminal tumors, which are very similar to developed countries except the HER2 positive group which have limited access to targeted agents in the public health system. Recently, CDK 4/6 inhibitors were approved for the treatment of HR+ HER2-negative MBC with an improvement in progression-free survival (PFS) and ribociclib and abemaciclib demonstrating benefit in OS over endocrine therapy alone, establishing the standard of care in first-line setting for this BC subtype. In Brazil, disparities exist in the incorporation of novel anticancer agents between public and private health systems limiting treatment options for patients with HR+ HER2-negative MBC in the public system, which covers most of the population. The BRAVE study aims to describe the patient journey and current patterns of care for HR+ HER2-negative MBC to identify possible gaps and how health insurance type influences treatment patterns in Brazil. Trial Design: This is an observational, retrospective cohort study. All patients diagnosed with mBC (either de novo or recurrent) in the period of January 2018 to December 2020 at participating centers will be included. Data will be collected from medical records. No interventions are proposed. Enrollment of a total of 300 patients (150 patients from public health care system and 150 patients from private health care system) is
month 24; describe and compare the 1L treatment of HR-positive, HER2-negative mBC and PFS until month 24 according to the health care coverage (public vs. private); describe timelines from symptoms, histopathological diagnosis, molecular test, and treatment; describe the mBC pathological characterization; describe frequency of diagnostic tests to define breast cancer molecular subtypes; describe the subsequent line of treatment and corresponding PFS; describe overall survival (OS); evaluate PFS and OS according to visceral vs. non-visceral metastatic disease, primary endocrine resistance vs. acquired endocrine resistance, de novo versus recurrent disease, public vs. private health system and pre vs postmenopausal status. Statistical Methods: No a priori sample size calculation was performed. The expected sample size of 150 patients in each group allows description of the proportion of patients using CDK 4/6 inhibitors with two-sided 90% confidence interval ranging from 53.4% to 66.6% when the expected proportion is 60% in the private health system. Present Accrual and Target Accrual: A total of 12 sites of 14 planned were activated. The first patient was enrolled on February 8, 2022. As of June 24, 2022, a total of 122 patients were enrolled, 86 from public and 36 from private health system. The target accrual of 300 patients is expected to be completed by November 2022. Results are expected to be presented by April 2023. Funding: Novartis. Acknowledgements: SAS.

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A phase 1 trial of LOXO-783, a potent, highly mutant-selective, brain-penetrant allosteric PI3Kα H1047R inhibitor in PIK3CA H1047R-mutant advanced breast cancer (aBC) and other solid tumors (PIKASSO-01, trial in progress)

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Background: Phosphoinositide 3-

both wild-

tar -mediated toxicities, including hyperglycemia, skin rash, and diarrhea. LOXO-783 is an oral, potent and highly mutant-selective, brain-
h-inhibitor. Preclinically, LOXO-
other PI3K isoforms and induces single-agent tumor regressions in ER+, HER2-
H1047R-mutant BC models without causing hyperglycemia or increases in plasma insulin / C-
peptide. LOXO-783 also demonstrates brain penetration in vivo with dose-dependent tumor growth inhibition in brain metastasis models. This trial investigates LOXO-783 alone and in combination with other anticancer therapies in patients with PIK3CA H1047R-mutant aBC and
other solid tumors.

Trial Design: This global, first-in-human phase 1a/b study of LOXO-783 includes dose escalation of LOXO-783 monotherapy followed by dose expansion of LOXO-783 alone and in combination with other anticancer therapies (Table). Monotherapy dose escalation will be evaluated using a modified toxicity probability interval-2 (mTPI-2) design. In dose expansion (Parts A-E), each combination cohort will include a safety lead-in of 3-6 patients. Men and premenopausal women with ER+ aBC must receive concomitant treatment with a GnRH agonist. An optional pharmacodynamic (PD) biomarker sub-study will be conducted at select dose levels during dose escalation in patients with ER+, HER2- aBC with soft tissue disease amenable to safe repeat tumor biopsies.

Eligibility criteria: Eligible patients must have PIK3CA H1047R-mutant aBC or other solid tumors with measurable disease or non-measurable bone-only disease (aBC patients only). In dose escalation, patients may have received up to 5 prior regimens. In dose expansion, prior therapy requirements are outlined in the Table below. Key exclusion criteria include prior inhibitor(s) of PI3K/AKT/mTOR (except in dose escalation or in select patients with prior intolerance of these inhibitors), colorectal cancer, endometrial cancer with concurrent PI3K/AKT/mTOR and/or RAS/RAF alterations and diabetes mellitus (DM) requiring medication (except in Part C).

Study objectives: Recommended phase 2 dose (RP2D) determination; safety and tolerability assessment, PK and PD evaluation, objective response rate and clinical benefit rate assessment per RECIST v1.1. Recruitment is ongoing (PIKASSO-01, NCT05307705).

Table. Dose Expansion (Phase 1b)

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>Key Eligibility</th>
<th>Study Drugs (Cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part A: ER+, HER2- aBC</td>
<td>≤2 prior regimens for aBC * Prior CDK4/6 inhibitor (CDK4/6i) required</td>
<td>LOXO-783 + Fulvestrant (FUL) * LOXO-783 + Infinestrant (selective estrogen receptor degrader)</td>
</tr>
<tr>
<td>Part B: ER+, HER2- aBC</td>
<td>≤2 prior regimens for aBC</td>
<td>LOXO-783 + aromatase inhibitor + Abemaciclib * LOXO-783 + FUL + Abemaciclib * LOXO-783 + Infinestrant + Abemaciclib</td>
</tr>
<tr>
<td>Part C: ER+, HER2- aBC</td>
<td>≤3 prior regimens for aBC * Prior CDK4/6i required * Stable Type 2 DM (HbA1c ≤ 8% and not requiring insulin)</td>
<td>LOXO-783 + FUL</td>
</tr>
<tr>
<td>Part D: aBC</td>
<td>≤3 prior regimens for aBC</td>
<td>LOXO-783 + Pdtraxel</td>
</tr>
<tr>
<td>Part E: Solid tumors</td>
<td>≤3 prior regimens for aBC</td>
<td>LOXO-783</td>
</tr>
</tbody>
</table>

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Clinical Trial of Alpelisib and Tucatinib in Patients with PIK3CA-Mutant HER2-Positive Metastatic Breast Cancer

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Phosphatidylinositol 3-kinase (PI3K) pathway plays a key role in resistance to the drugs targeting human epidermal growth factor receptor 2 (HER2). Activating mutations in the gene encoding alpha catalytic subunit of PI3K (PIK3CA) are present in approximately 30% of HER2+ tumors. PIK3CA mutations are linked to drug resistance and decreased survival in patients with HER2+ breast cancer. To overcome this resistance mechanism, we designed a phase IB/II clinical trial to evaluate the combination of HER2 small molecule inhibitor tucatinib with PI3K inhibitor alpelisib in patients with HER2+ metastatic breast cancer (NCT05230810). This multicenter clinical trial is conducted through the Academic Breast Cancer Consortium (ABRCC), with the University of Colorado Cancer Center as the lead site. Target enrollment: 40 patients. This is a run-in phase IB / roll-over phase II study. Phase IB will follow Time-to-Event Bayesian Optimal Interval design and enroll from 9 to 19 patients to find the maximum tolerated doses (MTDs) of tucatinib and alpelisib. From 21 to 31 patients will be enrolled in phase II part, for a total of 40 patients in the final efficacy analysis. Main inclusion criteria: 1. Women and men 2. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 3. Presence of activating PIK3CA mutation in the tumor 4. Patients with HR-/HER2+ or HR+/HER2+ breast cancer may enroll; ovarian suppression is mandatory for premenopausal patients with HR+/HER2+ disease 5. HR+/HER2+ patients should be agreeable to concomitant treatment with fulvestrant 6. Prior treatment with at least two FDA-approved HER2-targeted agents 7. Measurable or evaluable disease. Bone only disease is allowed. 8. Subjects with untreated central nervous system (CNS) metastases not needing immediate local therapy, and subjects with previously treated stable or progressive brain metastases may enroll, provided that there is no indication for immediate re-treatment. For patients with treated CNS metastases: time from treatment of CNS disease until the first dose of study drugs should be as marrow function Main exclusion criteria: 1. Contraindications to undergo contrast brain MRI 2. Leptomeningeal disease 3. Poorly controlled seizures 4. Diabetes mellitus type I, or uncontrolled diabetes mellitus type II 5. Acute pancreatitis within 1 year of screening, or history of chronic pancreatitis 6. History of severe cutaneous hypersensitivity reactions 7. Toxicities of prior cancer therapies that have not resolved to grade 1 or less, except peripheral neuropathy, which must have resolved to grade 2 or less, and alopecia 8. Previous treatment with EGFR or HER2 tyrosine kinase inhibitors, or PI3K/mTOR/AKT inhibitors. 9. Systemic anti-cancer therapy, palliative radiation to extracranial sites, or surgery within 2 weeks of the first dose of study drugs 10. Active bacterial, fungal, or viral infections, hepatitis B, C, or HIV 11. Clinically significant cardio-vascular disease Primary objectives: • Phase IB: safety and tolerability of combination therapy • Phase II: efficacy by progression free survival Exploratory assessment of biomarkers will be performed in the liquid biopsy samples. Study contact: Elena Shagisultanova, MD, PhD, elena.shagisultanova@cuanschutz.edu

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TK IMPACT: Treatment Monitoring of Hormone Receptor Positive (HR+), HER2 Negative (HER2-) Metastatic Breast Cancer (MBC) Patients Receiving CDK 4/6 Inhibitors (CDK4/6i) with DiviTum® Thymidine Kinase 1 Activity

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Background: CDK 4/6i have altered the therapeutic landscape of HR+, HER2- MBC, improving progression free and overall survival (PFS and OS) compared to endocrine therapy (ET) alone. Despite durable responses to CDK 4/6i in a large majority of patients, treatment response monitoring in this population has historically included numerous serial blood-based and imaging studies at frequent time points. There is a growing global interest in utilizing novel non-invasive biomarker-driven disease monitoring assessments to improve patient outcomes and reduce health care costs. Thymidine kinase 1 (TK1), a key cell-cycle regulated enzyme important for nucleotide metabolism during DNA synthesis, is regulated by the E2F pathway, downstream of CDK 4/6. Studies have shown that DiviTum® TK1 activity (TKa) may serve as both a prognostic and predictive biomarker of CDK 4/6i treatment response (McCartney et al, Clin Canc Res, 2020; Malorni et al, Eur J Cancer, 2022; Bagegni et al, Breast Cancer Res, 2017). Early TKa suppression within 2 weeks (wk) post CDK 4/6i therapy initiation is associated with improved PFS, suggesting a subgroup of patients who may be able to de-escalate imaging frequency. Elevated TKa at baseline and post CDK 4/6i may identify patients with CDK 4/6i-resistant disease and disease progression (PD) requiring early therapy modification. TK IMPACT is a prospective, single-arm trial designed to assess the impact of incorporation of DiviTum® TKa on a physician’s decision regarding subsequent timing of routine disease monitoring modalities in patients with advanced HR+, HER2- MBC receiving ET plus CDK 4/6i (NCT04968964). Methods: Blood sample collections will be analyzed using DiviTum® TKa at baseline (bl), wk 2, -wk time period of study enrollment (+/- 36 months, whichever occurs first. Optional repeat TKa within 2-4 wks (+/-3 days) is permitted in case of rising TKa. Research blood (bl, wk 2, 12, 24, 48, and PD) and optional archival tumor tissue collection at diagnosis and PD will be obtained for correlatives. The investigator will record intended imaging modalities and timing prior to receipt of TKa, followed by documentation of any changes in imaging testing interval after receipt of TKa. Key eligibility criteria include postmenopausal women age ≥18 years with HR+, HER2- MBC, to initiate (Cohort 1) or are currently receiving (≤24 months, Cohort 2) any FDA approved first line ET plus CDK 4/6i with a life expectancy > 6 months. The primary endpoint is any physician-reported intended change in imaging testing interval post TKa by study cohort, within the first 48-wk period of study participation. Key secondary endpoints are concordance rate between TKa values and progression status at first on-study imaging and longitudinal TKa dynamics. Key exploratory endpoints include plasma and tumor tissue-based biomarkers of CDK 4/6i response and resistance. A total of 40 patients will be enrolled (n=20/Cohort). The expected change rate is 20% with a 95% Wilson confidence interval of 0.105~0.248 across all patients and if within each cohort, with a 95% Wilson confidence interval of 0.081~0.416 for N=20. N=40 allows the lower limit of the 95% CI > 10% and that of the N=20 in Cohort 1 to be ~10%, indicating some clinically meaningful influence of
TKa progression on patient management. The study is open to accrual and has presently enrolled 5 patients.

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SOLTI-1910: Predicting olaparib sensitivity in patients with unresectable locally advanced/metastatic HER2-negative breast cancer with BRCA1/2, PALB2, RAD51C/D mutations or HRD by the RAD51 test: RADIOLA TRIAL

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Background The OlympiAD trial evaluated the PARP inhibitor (PARPi) olaparib versus a non-platinum standard chemotherapy in HER2-negative metastatic breast cancer (MBC) patients with a germline BRCA1/2 (gBRCA) mutation. Olaparib resulted in improved progression-free survival (PFS) and doubled the response rate vs chemotherapy. Nevertheless, the response rate to PARPi is ≥60% in the gBRCA1/2 population with MBC (current approval), suggesting a limited positive predictive value of gBRCA1/2 status. Moreover, patients with other relevant Homologous Recombination Repair defects (HRD) such as PALB2 or RAD51C/D mutation carriers, or HRD epigenetic silencing, are not captured with a gBRCA analysis. We have previously shown that the functional HRD biomarker RAD51, tested in FFPE tumor samples using an optimized immunofluorescence-based assay, is associated with platinum response in early TNBC and PARPi response in preclinical BC models. We hypothesize that the RAD51 test would help to expand the clinical benefit of PARPi by predicting response to olaparib in MBC with germline/somatic BRCA1/2, PALB2 or RAD51C/D mutation and beyond. Study design RADIOLA is an open-label, single-arm, multicentre phase II study evaluating treatment lines in two cohorts: cohort 1 (N=41) with known germline/somatic BRCA1/2, PALB2 or RAD51C/D mutation; cohort 2 (N=25) with functional HRD, namely RAD51-low score -type/unknown mutation status at study entry. All patients will receive olaparib 300mg po BID until progression or unacceptable toxicity. Primary objective will assess, in terms of overall response rate (ORR), the capacity of the RAD51 score to predict olaparib efficacy in cohort 1. Secondary objectives include PFS, clinical benefit rate, duration of response, safety in both cohorts and ORR in cohort 2. Recruitment Recruitment (11 sites) started in March 2022. As of July 2022, 7 patients have been enrolled in Spain. Funding This study is financially supported by AstraZeneca.
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The PREDICT Registry Australia: A prospective registry to evaluate the clinical utility of a 7-gene predictive biosignature on treatment decisions in patients with ductal carcinoma in situ

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Background: For women with ductal carcinoma in situ (DCIS) treated with breast conserving surgery (BCS), the benefit of adjuvant radiation therapy (RT) remains controversial. Since there is level 1 evidence supporting the role of RT in reducing the risk of local recurrence, current guidelines generally recommend RT for all women having BCS even though the absolute benefit is variable. In response to the need for prognostic and predictive tools to better assess risk and RT benefit, a 7-gene predictive biosignature (DCISionRT, PreludeDx, Laguna Hills, CA) was developed. The test provides a validated score (DS) for assessing 10-year risk of pathologic biomarkers. The primary objective of the PREDICT registries is to understand the decision impact such a tool has on treatment decisions.

Prospective Clinical Trial Design: This is a multicenter, prospective, observational registry for women diagnosed with DCIS in Australia. After DCIS diagnosis, sites will send the most representative tissue block or sections mounted on charged slides to the PreludeDx lab for biosignature testing. Treating physicians will complete a treatment recommendation survey before and after receiving the biosignature test results. Test results, treatment recommendations, patient preferences and clinicopathologic features will be stored in a de-identified registry for participating institutions from a variety of geographic regions across Australia. Women will then be followed for up to 10 years with completion of a follow-up form. The study has been approved by the North Shore Local Health District Human Research Ethics Committee, St Leonards, NSW, Australia. Universal Trial Number (UTN): U1111-1266-0439; ANZCTR: ACTRN12621000695808; ClinicalTrials.gov: NCT04916808. Eligibility Criteria: The study includes females age 26 or older who are candidates for BCS and eligible for RT and/or systemic treatment. Subjects must not have been previously treated for DCIS or have previous or current invasive or micro-invasive breast cancer.

Specific Aims: The primary endpoints are changes in treatment recommendations for surgical, radiation and hormonal therapy. Secondary endpoints are identification of key drivers for treatment recommendations, including age, size, grade, necrosis, hormone receptor status, patient preference and biosignature status.

Statistical Methods: Changes in pre- and post-DCISionRT treatment recommendations will be analyzed using McNemar's test (alpha level = 0.05). Multivariate logistic regression will be used to determine odds ratios of clinicopathologic factors leading to pre- and post-test treatment recommendations. Pre-test covariates include patient age, tumor size, palpability, margin status, hormone receptor status, nuclear grade, tumor necrosis, family history of breast cancer, race, ethnicity and patient preference, as well as physician specialty (surgeons vs. radiation oncologists) and post-test covariates will also include the DCISionRT Decision Score (DS). Differences in recurrence-free and overall survival will be assessed by Kaplan-Meier survival analysis using the log-rank test and/or the Cox Proportional Hazards model. Statistical analyses will be carried out using R (https://www.r-project.org) or SAS. An early interim analysis currently underway. Present and Planned Accrual: We are planning to enroll up to 1,500 women from up to 100 sites across Australia. A similar registry has recently completed enrollment of 2,500 women from 68 sites in the US.

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Immunological predictors of nodal response in breast cancer patients undergoing neoadjuvant therapy

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Immunological predictors of nodal response in breast cancer patients undergoing neoadjuvant therapy Maria Luisa Gasparri1, Ilary Ruscito2, Filippo Bellati2, Fabio Corsi3, Rosa Di Micco4, Oreste D. Gentilini4, Thorsten Kuehn5, Andrea Papadia1, Donatella Caserta2, Lorenzo Rossi6, Arianna Calcinotto7 1 Department of Gynecology and Obstetrics, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Lugano, Switzerland 2 Department of Medical and Surgical Science and Translational Medicine, Sapienza University of Rome, Azienda Ospedaliera
Background: Almost 20% of breast cancer patients present at diagnosis with clinically positive nodes. Most of these patients undergo neoadjuvant therapy in order to de-escalate the axillary surgery in case of response (sentinel lymph node biopsy, targeted axillary dissection or targeted axillary dissection, instead of an axillary lymphadenectomy). The conversion from positive to negative nodes after neoadjuvant therapy is expected in approximately the 60% of the cases, depending by tumor subtypes. Several models have been proposed with the goal of identifying predictors of nodal response prior to neoadjuvant treatment. The immune system plays a pivotal role in cancer invasion and progression. Its role in treatment response is currently under investigation in several settings. Primary endpoint: to identify a preoperative immune profiling of breast cancer patients with nodal involvement at diagnosis and to correlate the immune changes after neoadjuvant therapy with the nodal response (macrometastases, micrometastasis, isolated tumor cells, complete response). Trial design: It is an international prospective cohort study including breast cancer patients undergoing standard neoadjuvant therapy, who present initially with biopsy-proven axillary lymph node metastasis. Ten immune markers will be analyzed using immunohistochemistry and tissue microarray in primary tumor and nodal tissue samples (tumor associated neutrophils, CD4 lymphocytes, CD8 lymphocytes, T regulatory cells, Macrophages, Follicular dendritic cells(DC), plasmacytoid DC, interdigitant DC, mature DC, Lysosomal associated membrane protein 3). The tissue analysis will be performed on the biopsy collected at diagnosis (prior to neoadjuvant therapy) and during the axillary surgery (after neoadjuvant therapy). Target accrual/sample size: 210 patients Statistical analysis: To compare the distribution of immune cells according to the state of lymph node metastasis, Student’s t test will be performed. Pearson’s chi-square test will be used to evaluate the correlation between immune profile and nodal response, based on clinic-pathological features. Odds ratios (ORs) and 95% confidence intervals (CIs) will be calculated using logistic regression analysis. Multivariable analysis will be performed using the multivariable logistic regression model. Logistic regression models will be used to identify the clinical, pathologic and immunological variables associated with the nodal response. P-values less than 0.05 will be considered significant. Analyses will be performed using Microsoft IBM SPSS® version 20.0 for Mac. Current status: Recruitment has not started yet. Contact information: marialuisa.gasparri@eoc.ch

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First in Human Study of AG01 a chimerized monoclonal antibody to Progranulin/Glycoprotein 88 (GP88)

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Progranulin (PGRN/GP88) is an 88 kDa glycoprotein characterized by seven and a half double cysteine rich repeats in the granulin-epithelin family. PGRN/GP88 is an autocrine biological driver of tumorigenesis, survival & drug resistance in several cancers including breast, ovarian, multiple myeloma, prostate cancers, non-small cell lung carcinoma (NSCLCA) & digestive cancers. PGRN/GP88 tissue expression is an independent prognostic factor of recurrence while elevated serum PGRN/GP88 level in metastatic breast, lung & prostate cancer patients is associated with poor outcomes such as progression & shortened survival. An anti-human PGRN/GP88 monoclonal antibody inhibiting PGRN/GP88 action has been developed & expressed as recombinant antibody in CHO cells. Activities including pharmacology, manufacturing, formulation & GLP toxicology studies have been carried out. The IND application has been cleared by the Food and Drug Administration to proceed with the first-in-human AG01 clinical study in adult patients (pts) with advanced solid tumors. We present an ongoing First in Human Phase 1A (dose escalation, 1+(3+3) & IB (expansion cohorts) study of AG01 in pts advanced solid tumor malignancies (1A) with 4 expansion cohorts (1B) in pts with advanced Triple Negative Breast Cancer (TNBC), Hormone Resistant ER+/Her2- BC, advanced NSCLC & mesothelioma. Study Design: This is an open-label, dose escalation study of AG01 antibody administered intravenously (IV) over 90 minutes every 14 days +/- 1 day (1A), followed by 4 predefined expansion cohorts, which will be treated at the RP2D determined in the phase 1A of this study. In the 1A part, initially accelerated titration design will be utilized to guide dose progression & estimation of the maximum tolerated dose (MTD and/or maximum administered dose (MAD). In the 1A portion of the study pts with advanced relapsed/refractory solid tumor malignancies who failed 1 or more standard of care (SOC) therapies (tx) or for whom no SOC tx exists will be accrued. The primary objective of the 1A part is to determine the MTD and/or MAD of AG01. Secondary objectives are to determine the RP2D, assess the safety/tolerability, the pharmacokinetics (PKs) & immunogenicity of AG01 & the preliminary anti-tumor activity of AG01 via RECIST 1.1. The exploratory objectives are to determine PGRN/GP88 expression in tumor tissue and PGRN/GP88 blood levels using A&G’s ELISA test. In the 1B Cohort Expansion phase, 4 separate cohorts of pts with PGRN/GP88 tissue expression of 1+, 2+, 3+ by IHC will be enrolled. Cohort 1- TNBC: ER and/or PR < 1% by IHC, HER2 < 3+ by IHC and/or FISH negative, pts must have failed 1 or more SOC tx for metastatic BC. Cohort 2- Hormone-resistant BC: ER and/or PR >1%, HER2 < 3+ by IHC and/or FISH negative, failed 1 or more prior hormonal tx (HT) or HT/CD4/6 kinase inhibitor tx or other targeted tx. Cohort 3- NSCLCA: metastatic/recurrent NSCLCA failed 2 or more SOC tx. Cohort 4 -Mesothelioma- failed 1 or more SOC tx for metastatic/recurrent mesothelioma or not a candidate for SOC tx. The primary objective of 1B part is to evaluate the antitumor efficacy of AG01 by overall response rate (ORR) defined as completed response (CR), partial response (PR), stable disease >=24 weeks (SD) (CR+PR+ SD) based on RECIST v1.1 in the 4 cohorts with each cohort assessed separately for response. Secondary objectives are to evaluate progression free survival (PFS), duration of response (DOR) & overall survival (OS) of pts in cohorts 1-4, & to evaluate the ORR, DOR & PFS based on GP88 tissue expression, to further characterize the PKs & the safety/tolerability of AG01. Exploratory objectives in 1B part will assess AG01 effect on circulating PGRN/GP88 levels in plasma or other potential biomarkers in the 4 cohorts. The estimated study sample is approximately 77 pts; 17 pts for the 1A part & 60 pts for 1B part. The study is open to accrual at the UMGCCC. Supported by NCI grants R44CA224718 and R44CA162629

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A longitudinal investigation of sociocultural and behavioral influences on symptom management, biological response, and functioning among Chinese American and White female breast cancer survivors

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Background: Socioeconomically disadvantaged and immigrant cancer survivors account for a significant and growing proportion of the breast cancer population in the US. Research on symptom burden and control among Chinese American (CA) breast cancer survivors (BCS) is scarce. Among all BCS, over 55% report treatment-related symptoms (e.g., fatigue and pain) and psychological stress (e.g., fear of recurrence). In our preliminary cross-sectional study, we found similar rates (~58%) but showed that CA (especially low-acculturated) BCS were particularly likely to report fatigue, pain, and poorer physical functioning relative to non-Hispanic White (NHW) BCS. We understand very little about whether CA and NHW BCS have different ways of managing symptoms, improving quality of life and decreasing risk for functional decline. We therefore propose a study to examine how CA and NHW BCS, two culturally distinct groups with divergent social resources, adapt to breast cancer. Study design: This longitudinal, prospective study will investigate sociocultural influences on individual coping behaviors and how they in turn affect racial differences in inflammation markers, symptom severity, and functional outcomes in breast cancer. This study will enroll 260 CA and 260 NHW female BCS to examine multifactorial pathways to breast cancer survivorship outcomes. The CA cases will be age- and stage-matched to the NHW cases. Utilizing a multilevel biobehavioral framework, we will investigate the dynamics of biological, sociocultural, and behavioral (diet and exercise) influences on symptom severity, physiologic status, and functional outcomes. Participants will complete telephone survey interviews and provide blood samples at baseline and 6- and 12-month follow-up. Pro-inflammatory cytokines (e.g., IL-1β, IL-1α, IL-6, IL-8, IL-10, TNFα, TNFγ, and CRP) and cortisol will be analyzed. In-depth individual interviews with a subset of participants will be conducted to investigate causal factors in order to develop individually and culturally appropriate interventions to improve future clinical care for targeted breast cancer survivor populations. This study is supported by NIH R01CA248413. Eligibility criteria: Eligible participants are CA and NHW women (age >= 18) who are diagnosed with invasive breast cancer (stage I, II, or III), are 1-5 years post diagnosis, and have completed primary treatment (e.g., surgery, radiation, chemotherapy, and/or targeted therapy). Patients currently on adjuvant endocrine therapy are allowed. Specific aims: Aim 1: Examine whether CA BCS’ symptom, functional, and physiologic outcomes (e.g., cytokines and cortisol), and trajectory of these outcomes differ from NHW BCS at baseline, 6- and 12-month follow-up, controlling for covariates. Aim 2: Examine to what extent social resources mediate BCS’ individual behavior (e.g., medical communication, diet, and physical activity) and to what extent such pathways explain outcome differences (Aim 1) among BCS. Aim 3: Examine whether race and acculturation moderate the mediational pathways. Statistical methods: Multiple general linear mixed models will be performed to examine racial differences in the trajectory of symptom and biobehavioral outcomes across time, controlling for covariates (Aim 1). To examine mediation and moderation effects (Aims 2 and 3), we will use a cross-lagged path analysis model to simultaneously describe reciprocal relationships, or directional influences, between variables over time. Present accrual and target accrual: A total of 520 participants (260 CA and 260 NHW) will be enrolled at NYU Perlmutter Cancer Center, Columbia University Irving Medical Center, Georgetown University Medical Center, and Texas A&M University community networks. Contact information: Judy Huei-yu Wang, PhD: jw235@gunet.georgetown.edu or 202-687-6306 Maryann Kwa, MD: maryann.kwa@nyulangone.org or 212-731-6364

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TBCRC-053: P-RAD: A Randomized Study of Preoperative Chemotherapy, Pembrolizumab and No, Low or High Dose RADiation in Node-Positive, HER2-Negative Breast Cancer

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Background: The introduction of immune checkpoint inhibitors (ICI) to standard neoadjuvant chemotherapy regimens has been shown to significantly improve outcomes in patients with triple negative breast cancer and is being investigated for high-risk hormone receptor-positive (HR+)/human epidermal growth factor-2 negative (HER2-) breast cancer. Preclinical evidence suggests radiation therapy (RT) can stimulate intra-tumoral T cell infiltration and enhance the expression and immune detection of tumor-specific neoantigens. This phase II pilot randomized study (NCT04443348) aims to evaluate the safety and efficacy of two different doses of preoperative primary tumor RT boost when combined with neoadjuvant pembrolizumab, then followed by standard neoadjuvant chemotherapy. Dual co-primary endpoints include determining the pathologic complete response (pCR) rate in the non-irradiated and pathologically confirmed metastatic axillary lymph node(s) in each treatment arm and quantifying tumor-infiltrating T lymphocytes in on-treatment (C1D14) tumor biopsies. We hypothesize that high-dose RT will increase the proportion of tumors with high T cell infiltration (i.e., top quartile) from 25% to 55%. Secondary endpoints include measuring residual cancer burden, evaluating tolerability of the regimen, and assessing quality of life. Exploratory endpoints include evaluation of treatment-associated changes in the tumor immune microenvironment, circulating immune cell analyses, and circulating tumor DNA kinetics.

Methods: The study plans to enroll 128 participants with either triple negative (n=80) or high-risk HR+/HER2- (n=48) breast cancer who will be randomized to receive no, low (9 Gy), or high (24 Gy) dose of preoperative RT boost, after which 24 participants of either breast cancer subtype will be enrolled to an exploratory high dose proton therapy boost cohort. The eligibility criteria include patients who have biopsy-proven, axillary lymph node-positive breast cancer that is either triple negative (defined as ER< 10%, PR< 10%, and HER2-negative) or high-risk HR+/HER2- (grade III or having a high-risk genomic assay score). Study treatment is given in 6-week cycles, with 400 mg Pembrolizumab given on day 1 of each cycle. For those participants randomized to receive a preoperative RT boost, treatment is delivered in 3 fractions (3x3 Gy or 3x8 Gy) over consecutive business days, where one of the fractions is given on the same day as C1D1 Pembrolizumab. Standard neoadjuvant chemotherapy begins on C1D15 with paclitaxel (plus carboplatin for triple negative) administered weekly for 12 weeks, and then starting on C3D15, dose-dense doxorubicin/cyclophosphamide is administered every 2 weeks for 8 weeks. Following neoadjuvant treatment, participants will receive standard breast surgery (including removal of the pathologically confirmed metastatic lymph node) followed by adjuvant pembrolizumab, radiation therapy, and standard-of-care systemic therapy as clinically indicated. Tissue samples from the primary tumor and biopsy-proven lymph node are taken at baseline, C1D14, and at the time of surgery. There are eleven blood collection timepoints throughout the neoadjuvant and adjuvant settings. Participants will be followed for 2 years after surgery to assess safety and durability of responses. Results: This study has accrued 12 participants to date, including 10 with triple negative breast cancer and 2 with high-risk HR+/HER2- breast cancer. Formal results for this study are forthcoming, as the trial is actively accruing at 6 institutions, with plans to open at 3 more within the year. For persons with a specific interest in this trial, please contact Joseph Connolly, Multi-Center Coordinator, at jconnolly28@mgh.harvard.edu.

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A Phase II Study Evaluating the Combination of Radiotherapy with Chemotherapy and Pembrolizumab in Patients with PD-L1-Positive Metastatic Triple-Negative Breast Cancer

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Background: Metastatic triple-negative breast cancer (TNBC) is aggressive and lacks targeted therapies. The KEYNOTE-355 trial demonstrated that immunotherapy could bring efficacy to the TNBC population. In this trial, the addition of pembrolizumab (PD-1 inhibitor) to chemotherapy (nab-paclitaxel, paclitaxel, or carboplatin/gemcitabine) prolonged median 1-year progression free survival (PFS) (12.0% to 39.0%) when compared to chemotherapy (CT) alone in patients with PD-L1-positive (combined positive score (CP) ≥ 10) metastatic TNBC. Despite these encouraging results, patients with metastatic TNBC treated with the KEYNOTE-355 regimen developed delay in disease progression only for months. Studies have demonstrated that the addition of radiotherapy (RT) to immunotherapy and / or CT can result in a more robust immune response by releasing tumor antigens and promoting a local T cell response. Importantly, localized RT with immunotherapy has been shown to cause abscopal effect, a robust immune activation and tumor shrinkage at distant sites of metastasis. Based on these findings, RT in combination with immunotherapy and CT represents a potential avenue to prolong immune response in metastatic TNBC. The purpose of this study is to test this hypothesis and investigate the benefit of combining RT with pembrolizumab/chemotherapy in patients with metastatic PD-L1-positive TNBC. Methods: This two-stage, single-arm phase II study will assess the efficacy of RT in combination with CT plus pembrolizumab in PD-L1-positive unresectable or metastatic TNBC patients aged ≥18 years. Patients must have received < 1 prior lines of systemic therapy in the metastatic setting or adjuvant/neoadjuvant setting if metastatic recurrence was within 12 months of treatment. Patients must have a PD-L1 positive CPS ≥ 10 and must not have had a prior PD-1/PD-L1 inhibitor within 6 months. Patients will receive ablative RT 8 Gy per fraction for a total of 3 fractions (24 Gy) completed within 2 weeks prior to systemic therapy. RT will be directed at 1-4 sites of metastatic disease at the discretion of the treating radiation oncologist. Systemic therapy will then be given within seven days with either a taxane [nab-paclitaxel 100 mg/m2 or paclitaxel 90 mg/m2 intravenous weekly for 4 - 6 cycles] or carboplatin at area under the curve (AUC) 2 and gemcitabine 1000 mg/m3 weekly every 21 days if not taxane eligible. Pembrolizumab will be given at 200 mg every 3 weeks. Imaging will be repeated every 8-9 weeks to assess response based on RECIST 1.1. The primary endpoint of the study will be 1-year PFS which will be determined by comparing the 1-year PFS rate to historical controls. The study is powered to reject a 1-year PFS rate of 39% when the true value is 60%. Seventeen subjects will be enrolled in the first stage followed by an additional twelve subjects in the second stage if the trial is not stopped due to futility. Baseline tumor tissue will be collected for all patient and serial tumor biopsies will be performed at cycle 2 day 1 and at the end of study in patients with accessible disease (8 patients in Stage I and 5 patients in Stage II). Serial blood draws for immune assays and ctDNA will be performed in all patients.

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The ARETTA Trial Experience: Radiotherapy Quality Assurance in an International Breast Cancer Trial

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Background: The ARETTA trial is a Phase II feasibility study that tests the efficacy of Taxotere + Herceptin subcutaneous (SC) X 4 cycles in the neoadjuvant setting and one year of Herceptin SC as adjuvant therapy for HER2 positive breast cancer among Nigerian women. This study is being used to test an emerging platform for future biomarker based multi-institutional oncology clinical trials in Nigeria and across Sub-Saharan Africa. Radiotherapy is an integral part of multimodality breast cancer care. However, there are fewer than ten radiotherapy centers in Nigeria and limited experience in delivering radiotherapy within the context of a clinical trial. We describe the processes incorporated within the ARETTA trial to ensure protocol compliance and radiotherapy quality and to enhance patient safety. Methods: To centralize treatment, patients from the five participating sites throughout Nigeria were all referred to the Department of Radiotherapy, Lagos University Teaching Hospital (LUTH) to receive radiotherapy. A Radiation compliance and enhance patient safety. This consisted of preparatory educational lectures on breast radiotherapy contours, treatment planning and plan assessment. Subsequently, pretreatment review of contours was conducted by two radiation oncologists with expertise in breast cancer. Feedback on contours was provided via Zoom conference and email correspondence and weekly ARETTA trial meetings were used to track patient progress and adverse effects. An audit was conducted after treating 24 patients (half of the target enrollment). Patients were registered after lumpectomy or mastectomy and treated as follows: Hypofractionated radiation to the breast alone, breast and regional nodes, chest wall alone, or chest wall and regional nodes. The regional nodes will consist of the supraclavicular fossa, axilla and internal mammary nodal basin. The prescribed dose is 42.56 Gy in 16 daily 2.66 Gy fractions. Boost dose for the lumpectomy cavity or close/positive margins post-mastectomy is 10 Gy in 5 fractions of 2 Gy for cumulative total doses of 52.56 Gy. If there is suspected gross disease, these regions are treated with a boost dose of 18 Gy in 9 fractions of 2 Gy for a total dose of 60.56 Gy in 25 fractions. Treatment is given 5 days a week for 3-4 weeks. In the case...
of a departmental holiday, RT may be given 4 days a week. In case of medical illness or RT side effect(s), treatment breaks are allowed as needed per standard practice. Results The average surgery to RT start interval was 82 days (range 73 – 161 days). The average duration of RT was 23.1 days (range 18-35 days) and all patients who began RT completed their course of treatment. Radiation oncologists were able to independently and accurately contour targets after attending preparatory lectures and intensive review of the first ten patients. While breast and chestwall target coverage met protocol stipulations, deviations of mean heart dose and internal mammary chain target goals were noted. No Grade 3 or 4 side effects were noted. Enhanced protocol compliance. Additional educational efforts focused on dosimetric planning and plan assessment are needed to enhance adherence to organ constraints and target goals as stipulated in the protocol.

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The ability to monitor response to therapy and disease progression in metastatic breast cancer (MBC) patients is a major step in patient management. Imaging is the method of choice for the assessment of disease status and the monitoring of disease progression. However, this approach remains expensive, expose patients to radiation and thus is mainly performed every 2-3 months. During this time interval, the disease may progress significantly on ineffective treatment and the patient may present treatment related toxicities due to the inability to detect progression at earlier times. Circulating levels of tumor associated biomarkers such as CA15-3 and CEA are often determined to track disease status of MBC. However, even though they can provide information about disease progression, they do not always provide a reliable measure of response to therapy. The monitoring of disease status and progression through the measurement of drivers of disease should provide an alternative and complementary approach
to existing strategies in order to better to monitor the disease status and enable proactive management of MBC patients. Progranulin also called Glycoprotein 88kDa (PGRN/GP88) is an autocrine growth factor overexpressed in breast cancer. Biological studies have established GP88 as a critical player in breast tumorigenesis. GP88 overexpression is associated with the malignant phenotype, estrogen independence, increased proliferation, survival, and drug resistance. High PGRN/GP88 tumor expression measured by immunohistochemistry in invasive ductal carcinoma is an independent prognostic marker associated with increased risk of recurrence and mortality. Clinical studies have demonstrated that GP88 circulating levels as measured by enzyme immunoassay are elevated in breast cancer patients, compared to healthy individuals. In MBC patients, circulating GP88 levels correlate with overall survival. These facts are supportive of the hypothesis that the measurement of circulating GP88 levels in MBC patients can serve as an additional biomarker to monitor MBC disease status and be predictive to outcome. A prospective study was established is to identify whether there is a statistically significant change in serum GP88 levels associated with time to progression of breast cancer as measured by RECIST 1.1 criteria in MBC patients. With the assumptions that patients will provide a baseline and four follow up visits and that 20% of the visits record a disease progression, taking the plausible and clinically relevant performance to be 75% sensitivity and 46% false positive, a sample of ninety patients would give 85% power. Under IRB approved protocols at the University of Maryland Greenebaum Comprehensive Cancer Center and at two Baltimore Medstar Health Facilities, a total of 103 female breast cancer patients with measurable or evaluable metastatic disease will be consented and enrolled. The patients have been re-staged within 4 weeks and will continue or begin new therapy. Currently, we have enrolled sixty-five subjects at the three facilities. In addition to standard laboratory assessment and radiographic imaging/staging every 2-3 months on study, blood samples will be collected from each patient. The samples are stored at -70C until evaluated for GP88 using a GP88 enzyme linked immunoassay. We will analyze the GP88 serum level in correlation with survival and with disease status determined as responder, stable or progressing based on the RECIST criteria. This study is supported by grant R44CA210817 from the National Cancer Institute to Ginette Serrero Principal Investigator.

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Electronic Health Record Patient Portal (MyChart) Research Study Recruiting Methods and Results: the WISDOM Study

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BACKGROUND: The WISDOM (Women Informed to Screen Depending on Measures of risk) Study is a population-based, pragmatic trial comparing annual mammogram screening to risk-based breast cancer screening in women ages 40-74 with no history of breast cancer or DCIS. WISDOM’s enrollment process includes registration, consent, and completion of study surveys over a secure, cloud-based electronic patient reported information platform. One of the most valuable methods of study recruitment has been invitations through institutional electronic medical record (EMR) patient portals. Patient portals are used broadly today and allow patients to communicate with their care teams, pay medical bills, and access their full electronic health record. Over the last 4 years, EMR patient portals have been more widely used for research recruitment. Here we examine the recruitment results and methods used by five WISDOM sites.

METHODS: UCLA, UCSF, UCI, UCSD, and Sanford Health medical centers have employed patient portal study recruitment via MyChart for the WISDOM study. Each site sent WISDOM recruitment messages to patient MyChart inboxes who met study criteria (females between ages 40-74). Although research messaging receipt is defaulted to opt-in, all sites provide patients with a method to opt-out. Except for at Sanford and UCSF, recruiting messages included all necessary information for study registration, including a direct link to the study website for registration. The following highlights differences in recruitment processes used by each site through June 2022. Study recruitment via MyChart is ongoing at some of the sites.

• UCLA sent institution-wide messages in 3 rounds. For rounds 2 and 3, new MyChart patients and those who did not previously open a recruiting message were re-invited.

• Sanford and UCSF sent institution-wide messages that allowed patients to either choose to learn more about the study or opt out. Contact information for interested patients was provided to WISDOM Study coordinators (WSCs), who emailed each patient the study website and registration steps. Sanford re-invited those who did not initially respond whereas UCSF did not track and re-invite those who did not respond.

• UCSD partnered with study physicians to send research recruitment messages from their Chiefs of Medicine and Family Medicine. These messages were sent to patients in 3 rounds. For rounds 2 and 3, only patients who had not registered for WISDOM were re-invited.

• UCI piloted MyChart recruitment with individual messages sent to study-eligible patients of 3 primary care physicians from the WSC. Recruiting messages were sent to patients in 3 rounds. The recruiting messages included the ability for patients to opt out of further contact from the study. Patients who did not respond were contact by phone by the WSC.

RESULTS: For each site, the following registration and consent rates were observed:

- UCLA: 2.3% registration rate; 1.9% consent rate (7,257)
- Sanford: 4.1% registration rate; 3.5% consent rate (5,844)
- UCSF: 3.2% registration rate; 2.6% consent rate (2,501)
- UCSD: 6.6% registration rate; 4.6% consent rate (1,789)
- UCI: 6.1% registration rate; 1.7% consent rate (11)

CONCLUSION: Using EMR patient portals like MyChart for research recruitment has proven successful for WISDOM. UCSF and Sanford MyChart workflows resulted in better consent conversion rates compared to direct in-basket messages at UCLA without personal follow-up. However, accessing UCLA’s large patient population size has led them to have the highest number of MyChart enrolled study participants. Having medical practices send research recruitment messages using MyChart to their patients, as UCSD piloted, showed the highest rate of enrollment. MyChart is
quickly becoming a popular method to recruit for research, but there are still variations in medical center policies around the use of MyChart for researchers, which can create challenges for certain research institutions to effectively use this platform for research outreach.

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Clinical validation of “TriNetra™-Breast” test for breast cancer screening in a prospective, observational, case-cohort study

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Introduction
The Standard of Care for early detection of breast cancer in asymptomatic women is screening mammography, which has limitations such as radiation exposure and lower sensitivity to detect cancer in women with high breast density or invasive carcinomas. TriNetra™-Breast is a blood test for the detection of breast cancer associated circulating tumor cells in blood. Previously, this test has been used in a study for breast cancer detection in India, where it has shown a sensitivity of 92.5%. It has since been granted the United States Food and Drug Administration (USFDA) Breakthrough Device Designation, attesting its potential to provide for improved detection of breast cancer. This prospective, observational, case-cohort study will confirm the clinical performance characteristics of the technology in the US population.

Patients and Methods
The primary endpoint of this study will be to determine the sensitivity and specificity of the test for breast cancer screening, using mammography and years, with no prior diagnosis of any cancer and undergoing screening mammography for breast cancer will be eligible for participation in this study. 700 women, representing the diverse ethnic US population, will be enrolled. Cohort A will have 500 women with BI-RADS score of 1, 2, or 3. Among these 500 participants, the age categories of 40-49 years, 50-74 years and >74 years will have 100, 300 and 100 women respectively. Cohort B will have 100 women with suspicion of DCIS (without a suspicion of simultaneous invasive carcinoma) and 50 women each with BI-RADS score of 4 or 5. These study population numbers will ensure optimal representation of in-situ carcinoma, malignant and benign cases. Blood samples will be collected from the enrolled women for TriNetra™-Breast, within sixty (60) days of the screening mammogram. If biopsy is indicated, sample collection will be required prior to the procedure. The lab investigators will be blinded to the clinical information of all participants, including mammography and histopathology results, while the participants and clinical investigators will be blinded to the TriNetra™-Breast test results. The results of TriNetra™-Breast will be compared with the results of mammography and/or histopathology for performance estimation.
of the test. Study participants will be followed for clinical outcomes for maximum duration of 2 years.

Disclosure(s):

**Ulka Vaishampayan, MD**: AAA: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); Alkermes: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); Aveo: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); Bayer: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); BMS: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing), honoraria (Ongoing); Exelixis: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); Merck: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing), honoraria (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing); Sanofi: Consulting Fees (e.g., advisory boards) (Ongoing), honoraria (Ongoing)

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The PRAIM study: A prospective multicenter observational study of an integrated Artificial Intelligence system with live monitoring

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Background. Several retrospective studies have illustrated the potential clinical benefit of artificial intelligence (AI) systems for breast cancer screening. Some systems optimize normal mammography examination triaging, while others aim to improve cancer detection. However, no AI system has shown specificity high enough to replace human radiologists, suggesting that AI should play a different role in the breast screening pathway. The decision-referral approach is a promising alternative that has demonstrated the most potential to improve radiologist screening sensitivity and specificity while reducing workload. This collaborative human-AI approach combines AI pre-screening to triage normal examinations and post-screening to prevent missed cancers. The actual performance of decision-referral, including the interaction with human radiologists, can ideally be evaluated in a prospective real-world setting.

Trial design. The PRAIM (PRospective, multicenter observational study of an integrated AI system with live monitoring to support breast cancer screening) study (German Trial Register: DRKS00027322) is a prospective controlled observational non-inferiority study to compare the use of CE-marked screening software including AI support (Vara) via the decision-referral approach, with standard screening for women participating in the German breast cancer screening program. Ethics approval was obtained from the University of Lübeck Research Ethics Committee (22-043). Examinations assessed by readers using Vara are compared to examinations without Vara (control). Eligibility criteria and target accrual. Women ages 50 to 69 years old undergoing biennial breast cancer screening within the national screening program are eligible for inclusion. We expect the inclusion of approximately 400,000 women within the inclusion period of 1.5 years.

Statistical methods. The primary outcome is the screen-detected
cancer rate, defined as biopsy-confirmed cancer diagnoses per 1000 screening examinations. For each screening site, rates over the prospective observation period are calculated for examinations read with AI and without. To control for systematically different screen-detected cancer rates across screening sites, a historical 5-year rate is computed for each site and subtracted from the corresponding prospective rates. Non-inferiority of the screen-detected cancer rate for the AI group compared to the control group is evaluated with a weighted, mixed-effects linear regression model. AI is considered as non-inferior if the lower bound of the two-sided 95% confidence interval for the estimated difference in screen-detected cancer rates of AI and non-AI group is not below -10%, which corresponds to a deviation of -0.6 screen-detected cancers per 1000 examinations.

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Personalized Breast Cancer Screening in a Population-based Study: Women Informed to Screen Depending On Measures of risk (WISDOM)

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Background: Women Informed to Screen Depending on Measures of risk (WISDOM) is a preference-tolerant, pragmatic study comparing annual mammography to risk-based breast screening. WISDOM aims to assess if risk-based screening, compared to annual screening, is as safe, less morbid, enables prevention, and is more accepted by women. Though open nationally, by 2018 recruitment of Black/African American women was low, therefore we developed a strategy to correct this disparity.

Methods: Women 40-74 years old living in the US with no history of breast cancer or DCIS, and no previous double mastectomy are eligible. Participants can either elect randomization or self-select a study arm (annual vs. risk-based). Consent is obtained through an online electronic-signature platform. Participants in the risk-based arm undergo panel-based mutation testing (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2). Their 5-year risk is calculated using the Breast Cancer Screening Consortium (BCSC) score combined with a Polygenic Risk Score (220 single nucleotide polymorphisms (SNPs)). The SNPs and mutations are assessed by saliva-based genetic testing. Five-year risk thresholds are used to determine starting age, stopping age, and frequency of screening, as well as modality. To strengthen generalizability, in 2020 WISDOM opened new recruitment sites and spearheaded new partnerships and an education and engagement campaign to enroll more women of color.

Results: Of the 64,095 participants registered for WISDOM, over 49,611 (77%) provided consent and 41,910 (84%) have fully enrolled. 61% of fully enrolled participants selected to be randomized and 39% selected their study arm. To date, 83% of enrolled participants have received a WISDOM screening recommendation. Of the 21,572 participants in the risk-based arm, over 17,392 (80.6%) completed a saliva kit and received a genetic testing report. Median participant age is 56 years. WISDOM has improved its racial and ethnic diversity through intentional recruitment methods including expansion of enrollment centers, Veterans Affairs (VA) email outreach, and partnerships with community organizations. Prior to these efforts (from 2016-2019), the WISDOM study population was over 80% White non-Hispanic and has now decreased to 74% in 2020 and 73% in 2021. Rates of Black/African American (AA) participants increased from 1.7% prior to 2020 to 4.2% in 2020, 8.1% in 2021, and 11.3% in Q2 2022, a 10-fold increase.

Across all time, 76.9% of participants identified as White, 4.6% African American, 4.6% Asian, and 3.1% identified as multiracial. 9.2% self-reported Hispanic ethnicity. Through 13 eligible VA facilities, 2,875 veterans enrolled in WISDOM and 23% identify as Black/African American. At our expansion sites, 23% UChicago, 21% University of Alabama Birmingham, and 14% Louisiana State University participants identify as Black/African American across all-time. 17% of participants enrolled at our Florida site (Femwell/ToplineMD) identify as Hispanic. At our newest site, DHR Health (Rio Grande Valley Texas), 48% of study participants identify as Hispanic. Conclusions: Engagement of VA centers, community partnerships, and opening new expansion sites in diverse communities have increased racial and ethnic diversity in WISDOM, thereby strengthening our scientific knowledge of breast cancer risk for all women. Passive recruitment efforts with VA facilities have contributed to valuable improvements to the diversity of our research studies. Results of the WISDOM Study will enable us to evaluate whether personalized screening improves healthcare value by identifying those at highest risk and offering more frequent screening and prevention options, while safely reducing screening for those a lower cost, increasing healthcare value and improving outcomes.

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Phase II Study of Screening Brain MRIs in Stage IV Breast Cancer

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Background: As systemic therapy improves, there has been an increasing number of breast cancer patients who develop brain metastasis. Screening of asymptomatic stage IV breast cancer patients with brain MRIs is not currently recommended by the National Comprehensive
Cancer Network (NCCN) Guidelines. Retrospective reports suggest breast cancer patients are more likely to present with more advanced central nervous system disease at the time of brain metastasis diagnosis compared to melanoma and non-small cell lung cancer (NSCLC) patients. This may be in part due to routine screening recommendations in melanoma and NSCLC. Early detection and treatment of brain metastases may improve outcomes for breast cancer patients. Trial Design: The study is designed as a single arm, nonrandomized phase II study, with the goal of investigating the role of screening brain MRIs in neurologically asymptomatic patients with metastatic breast cancer. Breast cancer patients will be allocated based on receptor subtypes into triple negative (TN), HER2+, and hormone receptor (HR+)/HER2- breast cancer. Following study enrollment, patients will undergo a screening brain MRI. Patients will undergo a second brain MRI at first systemic progression or at 6 months whichever event occurs sooner. Eligibility: Asymptomatic, stage IV breast cancer patients that have progressed past first line therapy in the metastatic setting with an ECOG ≤ 6 months are eligible. Specific Aims: The primary objective is to determine the incidence of asymptomatic brain metastasis in metastatic breast cancer by subtype. Secondary objectives include determining the incidence of asymptomatic leptomeningeal disease, the number and size of brain metastases at diagnosis, the number of patients requiring whole brain radiation therapy vs. stereotactic radiation following diagnosis and overall survival and brain metastasis specific survival following brain metastasis diagnosis in metastatic breast cancer by subtype. Statistical Methods: A total of 30, 30, and 40 TN, HER2+, and HR+/HER2-, breast cancer patients will be enrolled, respectively. Using an incidence rate of 17%, the 95% CI by subtype will be (0.06,0.351), (0.06,0.351), and (0.07,0.322). Patient Accrual: This study is open with 30 patients enrolled at the time of submission. A total of 100 patients will be enrolled. Contact Information: Kamran A. Ahmed MD, Moffitt Cancer Center, email: kamran.ahmed@moffitt.org, Clinical trial information: NCT05115474. Funding: Florida Breast Cancer Foundation.

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Background: Post-mastectomy pain syndrome (PMPS) affects up to 60% of women undergoing mastectomy. Standard perioperative multimodal analgesia remains only moderately effective in preventing PMPS, and many patients continue to rely on opioids for their chronic pain. In the context of the opioid overdose crisis, alternative interventions are urgently needed. Ketamine targets risks factors for PMPS including acute pain and negative mood, making it an ideal candidate for the prevention of PMPS. Trial Design: This is a multisite, three-arm, double-blind,
RCT to test the effectiveness of ketamine in reducing PMPS in women undergoing mastectomy for oncologic indication. Arm 1 consists of continuous perioperative ketamine infusion that begins during surgery and continues for 2 hours in the post-anesthesia care unit (PACU). Arm 2 consists of a single-dose of ketamine in the PACU given over 50-60 minutes. Arm 3 consists of placebo. Standard surgical and postsurgical care remain unchanged across all arms. Eligibility criteria: Inclusion criteria are: women ≥18 years of age undergoing total mastectomy for oncologic indication +/- lymph node dissection and +/- immediate or delayed reconstruction with no distant metastases. Exclusion criteria include: (1) history of cognitive impairment (2) past ketamine or phencyclidine misuse or abuse, (3) schizophrenia or history of psychosis, (4) history of post-traumatic stress disorder, (5) known sensitivity or allergy to ketamine, (6) liver or renal sufficiency, (7) uncontrolled hypertension, chest pain, cardiac arrhythmia, stroke, head trauma, intracranial mass or hemorrhage, glaucoma, porphyria, uncontrolled thyroid disease, or other contraindication to ketamine, (8) lamotrigine alfentanil, physostigmine, or 4-aminopyridine use, (9) currently pregnant, (10) body mass index greater than 35, (11) non-English or non-Spanish speaker, (12) currently participating in another pain interventional trial, (13) patient has started or undergone hormone therapy for gender transition into male, or (14) patient is scheduled for bilateral (or greater) flap reconstruction. Specific Aims: The primary outcome is pain intensity on the Brief Pain Inventory short form scale at the surgical site three months after mastectomy. Secondary outcomes include pain severity and interference at the surgical site, incidence of PMPS, anxiety, and depression over 12 months after surgery. Tertiary outcomes include neuropathic symptoms, fatigue, sleep, physical function, and opioid use. Statistical Methods: We will test the differences in the primary outcome between 1) the continuous ketamine infusion and the control; and 2) the single-dose ketamine and the control, each at 0.025 significance level (adjusted for multiple comparisions using the Bonferroni correction), based on the two-sample t-tests (allowing unequal variances) if outcome variables are approximately normal, or Wilcoxon’s rank-sum tests otherwise. Accrual: The target accrual for this study is ~750. Recruitment began January 2022. Recruitment is expected to be complete by October 2025. As of July 14, 2022, 43 participants have been enrolled across all sites. If interested in the KALPAS Study, please contact kalpas@nyulangone.org, jing.wang@nyulangone.org, or lisa.doan@nyulangone.org This research is supported by the National Institutes of Health through the NIH HEAL Initiative under UH3CA261067. It is also supported by the NCATS Trial Innovation Network under award numbers U24TR001608 (CCC), U24TR001597 (DCC), U24TR001609 (SSC), U24TR001579 (RIC)

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SMALL: Open Surgery versus Minimally invasive vacuum-Assisted excision for smaLL screen-detected breast cancer – a UK phase III randomised multi-centre trial

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Background: Mammographic screening programmes reduce breast cancer mortality, but detect many small tumours with favourable biological features which may not progress during a woman’s lifetime. Screen-detected cancers are treated with standard surgery and adjuvant therapies, with associated morbidities. There is a need to reduce overtreatment of good prognosis tumours and numerous studies have evaluated the omission of radiotherapy in this context. However, there is little evidence to support surgical de-escalation, although percutaneous minimally invasive treatment approaches have been described. Vacuum-assisted excision (VAE) is in widespread use for management of benign lesions and lesions of uncertain malignant potential. SMALL (ISRCTN 12240119) is designed to determine the feasibility of using this approach for treatment of small invasive tumours detected within the UK NHS Breast Screening Programme (BSP). Methods: SMALL is a phase III multicentre randomised trial comparing standard surgery with VAE for screen-detected good prognosis cancers. The main eligibility criteria are age ≥47 years, unifocal grade 1 tumours with maximum diameter 15mm, which are strongly ER/PR+ve and HER2-ve, with negative clinical/radiological axillary staging. Patients are randomised 2:1 in favour of VAE or surgery; with no axillary surgery in the VAE arm. Completeness of excision is assessed radiologically, and if excision is incomplete, patients undergo open surgery. Adjuvant radiotherapy and endocrine therapy are mandated in the VAE arm but may be omitted following surgery. Co-primary end-points are: 1. Non-inferiority comparison of the requirement for a second procedure following excision 2. Single arm analysis of local recurrence (LR) at 5 years following VAE Recruitment of 800 patients will permit demonstration of 10% non-inferiority of VAE for requirement of a second procedure. This ensures sufficient patients for single arm analysis of LR rates, where expected LR free survival is 99% at 5 years, with an undesirable survival probability after VAE of 97%. To ensure that the trial as a whole only has 5% alpha, the significance level for each co-primary outcome is set at 2.5% with 90% power. The Data Monitoring Committee will monitor LR events to ensure these do not exceed 3% per year. Secondary outcome measures include time to ipsilateral recurrence, overall survival, complications, quality of life and health economic analysis. A novel feature of SMALL is the integration of optimise recruitment to the study. Recruitment challenges are identified by analysing recruiter/patient interviews and audio-recordings of trial discussions, and by review of trial screening logs, eligibility and recruitment data and study documentation. Solutions to address these are developed collaboratively, including individual/group recruiter feedback and recruitment tips documents. Results: SMALL opened in December 2019, but recruitment halted in 2020 for 5 months due to COVID-19. At 7st July 2022, 142 patients had been randomised from 26 centres, with a randomisation rate of approximately 45%, and a per site recruitment rate of 0.4-0.5 patients/month, approaching the feasibility recruitment target of 144 patients. Drawing from preliminary QRI findings and insights from patient representatives, a recruitment tips document has been circulated (on providing balanced information about treatments, encouraging recruiters to engage with patient preferences, and explaining randomisation). Individual recruiter feedback has commenced, with wider feedback delivered across sites via recruitment training workshops. Conclusion: Despite pandemic-related challenges, SMALL has an excellent recruitment rate to date and is expected to have a global impact on treatment of
breast cancer within mammographic screening programmes. SMALL is funded by the UK NIHR HTA programme, award 17/42/32

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Refusal of Breast Surgery in Breast Cancer Patients With cCR After Neoadjuvant Systemic Therapy and Vacuum-assisted Biopsy (VAB) and SLNB Confirmed pCR. An interim report of the prospective non-randomized trial. NCT04293796.

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Introduction The aim of the study was to prove efficacy and safety of de-escalation of traditional breast surgery in BC patients who develop cCR after neoadjuvant systemic therapy. Refusal of surgery was offered to exceptional responders after vacuum-assisted tumor bed biopsy and sentinel lymph node biopsy confirmed absence of residual disease (pCR). Materials and methods A single-center prospective study was run in the NMRC n.a. N.N. Petrov. Starting from -2N0-1M0 (stage Ia-IIb) triple-negative and HER2-positive (both ER+ and ER-) unifocal tumours without DCIS in core-biopsy specimen enrolled in
the study. Primary lesions were marked with a single clip in the centre. In cases with nodal involvement (cN1) the affected lymph nodes were also clipped. Patients with triple-negative breast cancer received 4 cycles of AC q21d followed by 12 cycles of weekly paclitaxel and carboplatin AUC 2.0. HER2-positive patients received 4 cycles of AC followed by 4 cycles of docetaxel combined with trastuzumab and pertuzumab q21d. Breast US, mammography and SPECT were used at baseline and at response evaluation. Vacuum-assisted biopsy was performed with 7G needle and US-guidance in the OR simultaneously with the SLNB. VAB protocol included retrieval of the tumor clip as first stage. Subsequently surrounding tissues were sampled, and markers were placed to guide radiotherapy. In case residual tumor was found patients received standard breast-conserving surgery. In case the sentinel lymph nodes were found to be positive, standard level II axillary clearance was performed. HER2-positive patients with pCR confirmed by VAB and SLNB received adjuvant trastuzumab up to one year. HER2-positive patients with residual breast or nodal involvement received trastuzumab emtansine up to one year. In case ER+, all patients received appropriate endocrine-therapy. In case of residual in-breast or nodal involvement patients with triple-negative breast cancer received standard capecitabine. Results The interim analysis included 25 patients in both groups. The median follow-up of disease-free survival for patients is 12 months. In the triple-negative group 12 patients achieved cCR. All patients went on to receive VAB and SLNB. After VAB and SLNB pCR was confirmed 11 patients (91.7%). 1 patient had invasive residual tumor with less than 5% cellularity. FNR in this group was 8.3% (1/12). Patient with invasive residual tumor received standard breast-conserving surgery. All the patients in the TNBC group were also found to be (sn)ypN0. In the HER2-positive group cCR was achieved 13 patients. All patients went on to receive VAB and SLNB. After VAB and SLNB pCR was confirmed 10 patients (77%). 3 patients had invasive residual tumor with less than 5% cellularity. FNR in this group was 23% (3/13). Patients with invasive residual tumor received standard breast-conserving surgery. All HER2-positive patients were found to be (sn)ypN0. One patient with HER2-positive subtype experienced a local recurrence in the postoperative zone 16 months after surgery. Initially, this patient achieved cCR and undergone VAB with SLNB. On final pathomorphologic examination isolated focuses of DCIS were found (ypTisN0). Standard breast-conserving surgery was performed and histologically only DCIS was found. This patient received 1-year of Trastuzumab and standard radiotherapy with boost. After the histologic confirmation of local recurrence patient underwent nipple-sparing mastectomy with reconstruction and nowadays she is receiving therapy with trastuzumab emtansine (T-DM1). Conclusion All visualization modalities fail to provide reliable information on the true rate of pCR. Contemporary systemic therapy regimens after accurate selection of patients, following the inclusion criteria, allows to achieve pCR in 75-90%, thereby reducing the risk of FNR after VAB. The trial continues to enroll patients and further follow-up is needed.

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Background Postoperative seroma formations are one of the most common and serious complications after implant-based breast reconstruction and can lead to implant and thus breast loss. The cause hasn’t yet been clarified. Hypothesis generating and thus as a basis for this multicenter study is the suspicion of a connection between immunological-inflammatory processes that promote the development of a seroma. First promising results of the pilot phase (SerMa pilot) have been published and gave the first impulse for this study. Trial design The SerMa (EUBREAST 5) study is a prospective, multicenter, interventional, international study including patients with primary breast cancer and a skin-/nipple-sparing mastectomy combined with an implant-based reconstruction method. Control groups were chosen to work out common group-specific differences. Intra- or directly preoperatively collected blood as well as intraoperatively collected local smear using swabs are preserved specimens. Follow-up includes visits after 2 and 6 weeks as well as after 6 months. In case of a seroma formation fluid aspirations are preserved for laboratory analyses. Eligibility criteria: The study population contains patients with primary diagnosis of breast cancer scheduled for skin-/nipple-sparing mastectomy and implant-based breast reconstruction. The three control groups are: one with simple mastectomy without breast reconstruction as well as healthy persons with implant insert but without breast cancer after bilateral risk reducing mastectomy or last in case of purely cosmetic implant placement. Specific aims: The main objective of the study is to identify a
patient subgroup with an increased risk of seroma development for future precision elucidation regarding the prevention of postoperative complications such as implant and thus breast loss. FACS-/Bioplex and microbiome analyses will be applied for the detection of certain immune markers, microbiomes and microbiome diversity using preoperative blood samples, intraoperative local smear collection and in case of later seroma formations also postoperative seroma aspirations. Secondary endpoints include the comparison of these factors and elaborate differences between study and control groups. Furthermore clinico-pathological factors as well as different surgical methods are compared. Statistical methods: A statistical plan for this analysis was specifically developed (Power analyses with Wilcoxon-Mann-Whitney test) and leads to a number of 300 participants per group. Target accrual: Planned start:

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A pilot study of robot-assisted nipple-sparing mastectomy followed by immediate breast reconstruction using da Vinci SP ® single-port system

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Introduction- Robotic mastectomy is a novel breast surgery approach accessed from a concealable anterior axillary incision showing better cosmetic outcomes with a scarless front view. The oncological safety awaits further follow-up from clinical trials or registered studies to mature. Compared to older da Vinci systems with multiple arms, the new SP system is single-armed, equipped with flexible instruments and a camera that may avoid instrument collision and dead spots in the surgical field. This trial (NCT05448963) is not only the leading SP mastectomy trial in Asia but also the first one that incorporates autologous flap reconstruction.

Methods-
-Objectives: To determine the performance, technical algorithm, safety data, and patient-reported outcomes in single-port-accessed nipple-sparing mastectomy using da Vinci SP® system. 
-Study design: This study is a pilot clinical study conducted in a single-arm, non-randomized design with a goal to recruit 30 participants. The da Vinci SP ® surgical robot is applied in the nipple-sparing mastectomy and axillary lymph node dissection (if indicated) of each enrolled patient in Chang Gung Memorial Hospital Linkou Medical Center. The post-mastectomy reconstructive method may use autologous flaps or implants depending on the type of build, technical feasibility, and flap site availability of the patient. The eligibility criteria include: I. Meet at least one of the following indications of NSM for breast cancer: 1. Preoperative clinical tumor sizes less than 5 cm, with an adequate tumor-skin distance of at least 3mm and above, and without nipple-areolar involvement in at least 1cm around the nipple by image 2. Breast cancer up to stage IIIa (T3, N1-2) as the initial clinical stage showing adequate response to neoadjuvant therapy and meeting criteria 1. 3. Germline pathogenic/likely pathogenic BRCA1 or 2 mutation carriers (actionable mutations including pathogenic and likely pathogenic mutations) with a breast cancer diagnosis or requiring unilateral or bilateral prophylactic mastectomy as a risk reduction procedure II. Age equal to or above 20 years III. ECOG (Eastern Cooperative Oncology Group) performance score 0-1 IV. ASA anesthesia risk class 1~2, and with adequate organ functions
-Endpoint measures: 
-Primary endpoint: Ability to complete nipple-sparing mastectomy with da Vinci SP system in the per-protocol population. 
-Secondary endpoints: Safety measured by adverse events through 30-day post-operative follow up 
-Exploratory endpoints: Surgical time, blood loss, hospital stay, breast specimen weight, cancer resection margin, nipple-preservation rate morbidity and mortality rate within 30 days of operation, and reoperation within 30 days post-surgery
-Statistical analysis: Point estimation with a 95% confidence interval will be used to analyze the mean or proportion of key performance parameters. No interim analysis will be performed due to the limited number intended to recruit. 
-Trial status: Active recruitment

Conclusion: The single-port robotic system features single port access with multi-jointed instruments which is particularly designed for narrow surgical spaces such as mastectomy. The feasibility of applying da Vinci SP systems to
robotic nipple-sparing mastectomy and robotic axillary lymph node dissection will be demonstrated in this study.

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First-in-human global multi-center study of RLY-2608, a pan mutant and isoform selective PI3Kα inhibitor, as a single agent in advanced solid tumor patients and in combination with fulvestrant in patients with advanced breast cancer

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Background: Targeting constitutively active mutant kinases with selective small molecule inhibitors is a key therapeutic pillar of precision oncology. Phosphatidylinositol-4,5bisphosphate-3 kinase, catalytic subunit alpha (PIK3CA) mutations leading to oncogenic
activation of PI3Kα represent the largest opportunity for this approach in solid tumors. However, there is no selective inhibitor that targets mutant PI3Kα in the clinic. Toxicity related to non-selective inhibition of WT PI3Kα (hyperglycemia) and other PI3K isoforms limits the tolerability, dosing and efficacy of the orthosteric inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor. RLY-2608, a novel these limitations via mutant- and isoform-improved tolerability and antitumor activity. We initiated a first-in-human (FIH), study to evaluate the clinical activity of RLY-2608 as a single agent in advanced solid tumor patients (pts) with PI3KCA mutations and in combination with fulvestrant in pts with PIK3CA mutant, HR+, HER2-metastatic breast cancer (MBC). Methods: This is a global, multi-center, dose escalation/expansion study (NCT05216432) of RLY-2608 as a single agent in adults who have advanced solid tumors and are refractory, intolerant, or declined standard therapy and RLY-2608 in combination with fulvestrant in previously treated pts with HR+/HER2- MBC. Eligibility criteria include presence of PI3KCA mutation (blood or tumor) per local assessment, ECOG performance status 0-1, measurable or evaluable disease per RECIST 1.1 and no prior PI3K inhibitor (except combination group 2). RLY-2608 is administered on a continuous schedule with 4-week cycles. Adverse events (AEs) per CTCAE v5, PK, biomarkers (mutant ctDNAs and insulin pathway markers) and anti-tumor activity are assessed serially. Dose escalation employs a Bayesian Optimal Interval design to identify MTD and RP2D. Following dose escalation, pts will be treated with RLY-2608 at the MTD/RP2D in a monotherapy dose expansion with 5 groups (N=75, 15 each): 1. Clear cell ovarian carcinoma 2. Head and neck squamous cell carcinoma 3. Cervical cancer 4. Other solid tumors 5. PI3KCA double mutations. In addition, two expansion cohorts will enroll patients with HR+/HER2- MBC treated with RLY-2608 and fulvestrant combination (N = 30, 15 each); 1. No prior PI3K therapy 2. Intolerant to PI3K inhibitors. The primary endpoints are MTD/RP2D and AE profile for single agent and combination; key secondary endpoints are PI3KCA genotype in blood and tumor, PK, biomarkers, and overall response rate. US enrollment began December 2021 and ex-USA startup is under way.

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VELA: A first-in-human phase 1/2 study of BLU-222, a potent, selective cyclin-dependent kinase (CDK) 2 inhibitor in patients with cyclin E1 gene (CCNE1)-amplified or CDK4/6 inhibitor-resistant advanced solid tumors

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Background The regulation of cell growth and proliferation is dependent on cyclins and CDKs. The formation of the cyclin D-CDK4/6 complex increases the expression of cyclin E1 and E2. Cyclin E1 and E2 bind to and activate CDK2; this results in a cyclin E/CDK2 complex that assists with downstream expression of DNA synthesis machinery. The use of CDK4/6 inhibitors such as palbociclib or ribociclib is an effective treatment in patients with hormone receptor-positive (HR+), human epithelial growth factor receptor-2 negative (HER2-) breast cancer; however, resistance to treatment eventually occurs. Aberrant cyclin E/CDK2 activity has been identified as a potential resistance mechanism by which tumors can evade CDK4/6 inhibitors. BLU-222 is an oral, investigational, potent, and selective CDK2 inhibitor. In preclinical studies, BLU-222 treatment in combination with ribociclib led to durable tumor regression in both CDK4/6-resistant and sensitive models of HR+HER2- breast cancer.

Trial design VELA (NCT05252416) is an international, open-label, first-in-human phase 1/2 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BLU-222 in adult patients with CCNE1-amplified tumors or with HR+HER2- breast cancer with disease progression on CDK4/6 inhibitors. In phase 1 and 2, patients aged ≥18 years with an Eastern Cooperative Oncology Group performance status 0–2 are eligible. In phase 2, all patients must have ≥1 measurable target lesion per Response Evaluation Criteria in Solid Tumors version 1.1. Primary endpoints include assessing the safety of BLU-222 as a single agent or BLU-222 in combination with either carboplatin or ribociclib and/or fulvestrant (phase 1 and 2), identifying the maximum tolerated dose and/or recommended phase 2 dose (phase 1), and determining the objective response rate (phase 2). In the phase 1 dose-escalation part, patients with any advanced solid tumor with progression on standard of care (SOC) will receive BLU-222; -based therapy) or with CCNE1-amplified platinum-resistant/refractory ovarian cancer (OC) will receive BLU-222 and carboplatin; patients with HR+HER- breast cancer with progression on CDK4/6 inhibitors will receive BLU-222, ribociclib, and fulvestrant. In the phase 2 dose-expansion part, patients with CCNE1-amplified tumors including EC -resistant/refractory OC, or other advanced solid tumors (progression after SOC) will receive BLU-222 monotherapy; patients with CCNE1-amplified platinum-resistant/refractory OC will receive BLU-222 and carboplatin; and patients with CDK4/6 inhibitor-resistant HR+HER2- breast cancer will receive BLU-222 and fulvestrant with/without ribociclib. Pharmacokinetic parameters will be calculated using standard non-compartmental methods from the plasma concentration–time data. Tissue biopsies will be collected during cycle 1 to assess the phosphorylation of retinoblastoma 1 (Rb1) protein which will be used as a pharmacodynamic marker to assess target inhibition. Dose escalation is ongoing and approximately 50 sites are anticipated to enroll patients across North America, Europe, and the Asia/Pacific region.
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ReFocus: A Phase 1/2 Study of the Highly Selective FGFR2 Inhibitor, RLY-4008, in Patients with Advanced Solid Tumors Including Breast Cancer

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Background: Oncogenic alterations (gene amplification, mutation, and fusion/rearrangements) of fibroblast growth factor receptor 2 (FGFR2) are rare and occur at varying frequencies across solid tumor types and have become critical therapeutic targets in drug development. First generation FGFR pan-kinase inhibitors non-selectively inhibit FGFR1-4 and are associated with dose limiting toxicities and narrow therapeutic windows. Off-isoform toxicity (FGFR1-hyperphosphatemia; FGFR4-diarrhea) and on-target acquired resistance have led to limited efficacy, which is primarily seen in FGFR2-fusion+ intrahepatic cholangiocarcinoma. Therapies that selectively target FGFR2 remain an unmet need in advanced breast cancer as well as other solid tumor types. RLY-4008 is a novel, oral FGFR2 inhibitor designed to overcome the limitations of pan-FGFR inhibitors (FGFRi) by potently and selectively targeting primary oncogenic FGFR2 alterations and acquired resistance mutations. RLY-4008 is > 200-fold selective over FGFR1, > 80- and > 5000-fold selective over FGFR3 and FGFR4 respectively. Here we describe a phase 1/2 study to investigate the safety and antitumor activity in advanced FGFR2 altered cancers, including breast cancer. Methods: ReFocus is a phase 1/2 open label global study evaluating the safety and efficacy of RLY-4008 (NCT04526106) in adult patients with advanced unresectable and/or metastatic cancers harboring an FGFR2 alteration. Key eligibility criteria include: documented FGFR2 alteration in blood or tissue per local assessment, ECOG performance status of 0-1, disease that is refractory or not adequately responding to standard therapy, has no available standard therapy, or patient is intolerant of, or declined standard therapy (including pan-FGFRi), and measurable or evaluable disease per RECIST 1.1. FGFR2 alteration will be confirmed retrospectively by central laboratory assessment. Part 1 dose escalation employed the Bayesian Optimal Interval (BOIN) design to determine the MTD/RP2D of RLY-4008. Part 2 dose expansion is presently enrolling patients at the RP2D of RLY-4008 and includes 5 cohorts comprised of patients with: 1. FGFR2 fusion+ cholangiocarcinoma previously treated with an FGFRi; 2. FGFR2 fusion+ cholangiocarcinoma not previously treated with an FGFRi; 3. FGFR2 fusion+ solid tumors; 4. FGFR2 mutation+ solid tumors and 5. FGFR2 amplified solid tumors. Solid tumors in cohorts 3, 4 and 5 will have a focus in breast cancer. The primary endpoint is objective response rate (ORR); key secondary endpoints include: duration of response, safety and tolerability, correlation of FGFR2 genotype by central tissue assessment with antitumor response, characterization of PK profile, and quality of life. US enrollment began September 2020 and has expanded into Europe and Asia. Clinical trial information: NCT04526106.

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Neoadjuvant HER2-targeted Therapy +/- Immunotherapy with Pembrolizumab (neoHIP): An Open Label Randomized Phase II Trial

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Background: Immune checkpoint inhibition (ICI) is synergistic with HER2-directed therapy in pre-clinical models. Clinically, pembrolizumab (K)-mediated ICI plus HER2-directed therapy with trastuzumab (H) was safe and demonstrated modest activity in H-resistant HER2-positive (HER2+) metastatic breast cancer. Because ICI may confer more robust activity when administered earlier in the course of disease, H and K administered in the curative-intent, treatment-naïve setting may allow for de-escalation of cytotoxic chemotherapy; confer life-long, tumor-specific immunity; and ultimately, improve cure rates. Moreover, the synergy of H and K with paclitaxel (T) may overcome the need for dual HER2-blockade with H plus pertuzumab (P). In this randomized, multicenter, phase II, open-label, multi-center trial the efficacy and safety of neoadjuvant THP vs THP-K vs TH-

previously untreated, stage II-III, HER2+ breast cancer will be randomized and stratified by clinical nodal status (positive vs. negative) and hormone receptor status (positive vs. negative). In arm A, pts receive T at 80mg/m2 weekly for 12 weeks, H at 8mg/Kg (loading dose) and then 6mg/Kg every 3 weeks x 3 doses, P at 840 mg (loading dose) and then 420mg/Kg every 3 weeks x 3 doses (THP). In arm B, pts receive THP plus K at 200mg every 3 weeks x 4 doses (THP-K). In arm C, pts receive TH-K; however, in a preplanned interim analysis, arm C did not meet the pre-defined efficacy threshold and this arm was subsequently closed. Enrollment to arms A and B continue. Definitive surgery is 3-6 weeks after the last dose. After surgery, pts are treated per the treating physician’s discretion including radiotherapy per local clinical standard. Pts whose tumors are hormone-receptor positive will receive hormone therapy per local standard-of-care. The primary end point is pathologic complete response (pCR) rate in the breast and axilla (ypT0/Tis ypN0). Secondary end points include pCR rate by ypT0ypN0 and ypT0/Tis, residual cancer burden index, event free survival, breast conserving surgery rate, safety and overall survival. Exploratory correlative studies will characterize potential immune biomarkers predictive of efficacy and/or toxicity. Funding sources: BCRF, Merck NCT03747120

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Inetetamab combined with pyrotinib and Chemotherapy in Pretreated Patients with HER2-positive metastatic breast cancer, a single arm, multicenter phase II clinical trial

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Background: The HER2-targeted drugs selection after trastuzumab failure has become a challenging issue for HER2-positive metastatic breast cancer (MBC) patients. Inetetamab is a neotype of HER2-targeted monoclonal antibody with an engineered Fc segment that optimizes the antibody-dependent cell-mediated cytotoxicity (ADCC) effect, which was important for disease control. Moreover, HER2-targeted tyrosine kinase inhibitors, as pyrotinib, were found to further improve the ADCC effect of monoclonal antibodies in pre-clinical researches, indicating that the combination of pyrotinib and inetetamab could achieve complementarity and synergy effects in terms of short-term tumor killing effect and long-term immunotherapy benefits. Therefore, the combined treatment pattern of the two drugs has potential clinical benefits.

Methods: This is a prospective, multi-center, single-arm clinical study designed to evaluate the efficacy and safety of pretreated patients with HER2-positive MBC. We recruited patients with
Pathologically confirmed HER2-positive MBC who had received 1-3 prior regimens for metastatic disease, which must include trastuzumab. The enrolled patients received 6 cycles of Inetetamab combined with pyrotinib and chemotherapy, subsequent maintenance therapy should be considered according to tolerability. The chemotherapy drugs were decided by physicians’ choice, and could be microtubules, anthracyclines, or antimetabolites. The primary endpoint was objective response rate (ORR) after 6 cycles of treatment, secondary endpoints included progression-free survival (PFS), overall survival (OS), and clinical benefit rate (CBR) and adverse events (AEs). Results: 57 patients were enrolled from October 2020 to July 2022. And 45 patients were available for response evaluation. The ORR and DCR were 53.5 % (24 / 45) and 86.7 % (39 / 45), respectively after 6 cycles treatment. The median PFS was 7.3 months. The incidence of grade III-IV AEs was 15.8 %. The most common treatment-related AEs were diarrhea, anemia, neutropenia, leukopenia, hand and foot syndrome. No patient’s left ventricle ejection fraction (LVEF) decreased to < 50% or decreased by >15%. And no significant decline in quality of life score was reported. Conclusion: Inetetamab combined with pyrotinib and chemotherapy showed a promising efficacy and a good tolerance in patients with HER2-positive metastatic breast cancer, confirming the synergistic effect between the ADCC optimized monoclonal antibodies and TKIs, which brings more treatment options for HER2-positive metastatic breast cancer.

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Background: The PI3K/AKT/mTOR pathway is a rational target in the metastatic disease setting for hormone receptor positive breast cancer based on preclinical and clinical data demonstrating that pathway inhibition improves outcome (Baselga 2012, Andre 2019, Jones...
2019). Combining fulvestrant and AKT inhibition demonstrated efficacy in pts with HR+aBC (Howell 2022). Ipatasertib is a potent, highly selective, small-molecule inhibitor of three isoforms of serine/threonine kinase AKT. We hypothesize that Ipatasertib plus fulvestrant will improve PFS compared to fulvestrant in the second line setting post disease progression on aromatase inhibitor (AI) + CDK 4/6 inhibitor therapy. Methods: MA40 is a double blind, placebo-controlled trial in patients with hormone receptor positive, HER2-negative breast cancer with prior progression on AI plus CDK4/6 inhibitor therapy. Patients are randomized to fulvestrant/ ipatasertib 400 mg po days 1-21 every 28 day or fulvestrant/placebo. The primary objective is to compare Progression Free Survival (PFS) between arms (RECIST 1.1, investigator assessed). Secondary objectives include comparisons between arms: PIK3CA/AKT1/PTEN altered cohort and non-altered cohorts; PFS by Blinded Central Radiology Review (all enrolled patients, PIK3CA/AKT1/PTEN altered and non-altered cohorts), Response rate; Duration of Response; Clinical Benefit Rate; Overall Survival; Time to Commencement of Subsequent Line -C30, NCI PRO-CTCAE); Economic Evaluation, (healthcare utilization and health -5D-5L)). Statistical Design: Allocation 1:1 balanced for: PIK3CA/PTEN/AKT1 mutation status (ctDNA analysis using FoundationOne®Liquid Platform) (altered vs wildtype/unknown); prior treatment duration with CDK4/6 inhibitor (< 6 months vs > 6 months) and centre. Sample size is 250 to detect a benefit in PFS with the addition of ipatasertib. Eligibility Criteria: Histologically and/or cytologically confirmed ER positive and HER-2 negative breast cancer by local assessment that is advanced; postmenopausal status; clinical and/or radiographic progression during treatment with or within 28 days after discontinuation of first line of treatment with a CDK 4/6 inhibitor and an AI; only one prior line of chemotherapy in the advanced setting. Conduct to Date: Enrollment is ongoing. Supported by Hoffmann-La Roche Limited, CCS

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A Phase 3 study of gedatolisib plus fulvestrant with and without palbociclib in patients with HR+/HER2- advanced breast cancer previously treated with a CDK4/6 inhibitor plus a non-steroidal aromatase inhibitor (VIKTORIA-1)

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Background: Gedatolisib is a potent reversible dual inhibitor that selectively targets all Class I isoforms of phosphoinositide 3-kinase (PI3K) and mechanistic target of rapamycin (mTOR). Two separate pivotal clinical trials demonstrated that PI3K and mTOR inhibitors are active in combination with endocrine therapy and prolong progression-free survival (PFS) among patients with hormone receptor positive (HR+)/HER2-negative (HER2-) advanced breast cancer (ABC) who had previously received endocrine therapy (SOLAR-1, BOLERO-2). CDK4/6 inhibitor (CDK4/6i) therapy has been approved in the front-line setting. However, patients eventually experience disease progression on CDK4/6i based therapy. Available data indicates that resistance to CDK4/6i is a transient adaptive mechanism that may be reversed by adding inhibitors of the PI3K/mTOR pathway (PI3K/mTORi). Thus, combination of PI3K/mTORi and CDK4/6i in patients whose disease progressed on prior CDK4/6i could potentially both restore sensitivity to CDK4/6i and prevent adaptive activation of the PI3K/mTOR pathway. This hypothesis was evaluated in a Phase 1b study (Layman SABCS 2021). Subjects with HR+/HER2- ABC who were CDK4/6i pretreated received gedatolisib (180 mg IV weekly for 3 weeks, then one week off) in combination with standard doses of palbociclib and fulvestrant. Median PFS was 12.9 months, and overall response rate was 63%. Grade 3-4 adverse events (AE) were observed at a low rate, and toxicity was overall easily managed with available standards of care, and few patients discontinued treatment due to treatment-related adverse events (4%). The most common AE was stomatitis; hyperglycemia of any grade occurred in 26% of patients. This preliminary data, dosing schedule, and study population characteristics form the basis for the Phase 3 trial, VIKTORIA-1. Trial design: This Phase 3, open-label, randomized, multinational two-part clinical trial will evaluate the efficacy and safety of gedatolisib and fulvestrant with or without palbociclib in patients with HR+/HER2- ABC previously treated with any CDK4/6i in combination with non-steroidal aromatase inhibitor therapy. Those without tumor PIK3CA mutations will be assigned to Study 1 and those with PIK3CA mutations will be assigned to Study 2. Study 1 will include up to 351 subjects randomized in a 1:1:1 ratio to Arm A (gedatolisib, palbociclib, and fulvestrant), Arm B (gedatolisib plus fulvestrant), or Arm C (fulvestrant). For subjects in Arm C whose disease progresses, crossover to Arm A or B is allowed. Study 2 will include up to 350 subjects randomized in a 3:3:1 ratio to Arm D (gedatolisib, palbociclib, and fulvestrant), Arm E (alpelisib plus fulvestrant), or Arm F (gedatolisib plus fulvestrant). Key eligibility criteria include adults with confirmed metastatic or locally advanced breast cancer, any menopausal status for females, radiologically evaluable disease, and prior CDK4/6i treatment with non-steroidal AI. Prior therapy with SERD, including fulvestrant is allowed. Key exclusion criteria include prior treatment with a PI3K, protein kinase B (Akt), or mTOR inhibitor, prior treatment with chemotherapy for advanced disease, more than two lines of prior endocrine therapy, bone only disease with no soft tissue components, active CNS metastases, and type 1 diabetes or uncontrolled type 2 diabetes. The primary endpoint is PFS assessed by blinded independent central review (BICR) per RECIST v1.1. Secondary endpoints included overall survival (OS), safety and tolerability, ORR, duration of response, time to response, CBR, quality of life, and pharmacokinetics. This trial is open for enrollment.

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Subtyping-based platform guides precision medicine for heavily pretreated metastatic triple-negative breast cancer: a multicenter, phase 2, umbrella, FUTURE trial

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Background: Triple-negative breast cancer (TNBC) is a heterogeneous disease and lacks effective treatment. Our previous study classified TNBCs into four subtypes (luminal androgen receptor [LAR], immunomodulatory [IM], basal-like immune-suppressed [BLIS], mesenchymal-like [MES]) with distinct molecular features. We aimed to assess the efficacy and safety of molecular subtype-derived precision treatment in patients with heavily pretreated metastatic TNBC.

Methods: This open-label, phase 2, umbrella trial included patients from four centers in China. Participants were women (aged ≥18 years) with histologically confirmed metastatic TNBC with disease progression after multiple lines of standard chemotherapy. Patients were enrolled into seven parallel arms according to their molecular subtypes: LAR with or without ERBB2 somatic mutation/amplification assigned to arm A (pyrotinib with capecitabine) and arm B (androgen inhibitor included therapy); IM assigned to arm C (anti-PD-1 antibody with nab-paclitaxel); BLIS with or without BRCA1/2 germline mutation assigned to arms D (PARP inhibitor included therapy) and E (anti-VEGFR included therapy); MES without or with PI3K-AKT mutation assigned to arms F (anti-VEGFR included therapy) and G (everolimus with nab-paclitaxel). Bayesian predictive probability was adopted to monitor each arm, which can be terminated independently according to a prespecified futility or efficacy boundary. This trial is registered with ClinicalTrials.gov, NCT03805399.

Findings: Between October 18, 2018, and February 11, 2022, we enrolled 141 patients. All patients were heavily pretreated and resistant to six categories of the most common chemotherapeutic agents used in breast cancer treatment, with a median of 3 previous lines of therapies in the metastatic setting (Table 1 and 2). The median follow-up was 11.7-27.7 months. A confirmed objective response was achieved in 42 (29.8%, 95% CI 22.4-38.1) of the 141 patients. The median PFS was 3.4 months (95% CI 2.7-4.2), and the median OS was 10.7 months (95% CI 9.0-12.3) (Table 3). Arms A, C, E and G achieved efficacy boundaries, with 3 (75.0%) out of 4 patients in arm A, 20 (43.5%) out of 46 patients in arm C, 13 (28.3%) out of 46 patients in arm E, and 3 (33.3%) out of 9 patients in arm G achieving objective responses. Potential predictive biomarkers of efficacy in each arm were explored. Safety data were consistent with the known safety profiles of relevant drugs.

Interpretation: We demonstrate the feasibility and clinical utility of a subtyping-based, genomic sequencing-guided strategy which allows the majority of heavily pretreated metastatic TNBCs to benefit from precision treatment. Most arms exhibit promising efficacy and manageable
toxicities, providing subtyping schema to optimize personalized treatment.

Table 1. The FUTURE trial schema.

Patients are stratified into seven arms using the FUSCC 484-gene NGS panel testing and IHC subtyping. Abbreviations: mTNBC, metastatic triple-negative breast cancer; NGS, next-generation sequencing; IHC, immunohistochemistry; FUSCC, Fudan University Shanghai Cancer Center; LAR, luminal androgen receptor; IM, immunomodulatory; BLIS, basal-like immune-suppressed; MES, mesenchymal-like; n, number; AR, androgen receptor; PD-1, programmed cell death-1; PARPi, poly ADP-ribose polymerase inhibitor; VEGF, vascular endothelial growth factor; mTORi, mammalian target of rapamycin inhibitors.

Table 2. Patient characteristics in the FUTURE trial.
Table 3. Summary of treatment efficacy of TNBC in the FUTURE trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ER</th>
<th>PR</th>
<th>Tsur</th>
<th>RR</th>
<th>Tsur</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>55 (20.7%)</td>
<td>61 (6.5%)</td>
<td>61 (6.5%)</td>
<td>46.8%</td>
<td>61 (6.5%)</td>
<td>61 (6.5%)</td>
<td>46.8%</td>
</tr>
<tr>
<td>None</td>
<td>5 (2.1%)</td>
<td>3 (0.3%)</td>
<td>3 (0.3%)</td>
<td>100%</td>
<td>3 (0.3%)</td>
<td>3 (0.3%)</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>60 (25.6%)</td>
<td>64 (7.0%)</td>
<td>64 (7.0%)</td>
<td>46.8%</td>
<td>64 (7.0%)</td>
<td>64 (7.0%)</td>
<td>46.8%</td>
</tr>
</tbody>
</table>

Note: All values are percentage of patients responding to treatment.
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A Dose-escalation Study of the Safety and Pharmacology of DAN-222 in Subjects with Metastatic Breast Cancer NCT05261269

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Clinical Study:
This clinical study is designed to evaluate DAN-222 as a monotherapy and in combination with a PARP inhibitor which is expected to increase efficacy without significant increase in toxicity. DAN-222 is a novel therapeutic nanoparticle with a complimentary mechanism for combination with a PARP inhibitor anticipated for patients with HRD+ and HRD- tumors, and not restricted to BRCAm.

This is an ongoing phase 1/2 study to evaluate the safety and pharmacology of DAN-222 in patients with metastatic breast cancer and initial evaluation of efficacy. Here we report on the initial pharmacology. The results in the patients show the expected characteristics of the designed product, including consistency with preclinical models (e.g. T1/2= 28 hours), which is a feature of this platform given the non-enzymatic release mechanism of the payload that allows for improved translation from preclinical species to clinical patients as well low variability between patients (e.g. CV%=16.5).

Study Rationale:
DAN-222 is a topoisomerase-1 inhibitor (Camptothecin) nanoparticle therapeutic that has been optimized for tumor biodistribution and pharmacokinetics. DAN-222 has a broad therapeutic index in preclinical evaluation and the complementary mechanism of action with PARP inhibitors provides significantly enhanced efficacy while also sparing bone marrow. Importantly, the complementary enhanced efficacy is independent of tumor homologous repair deficiency (HRD) status, including BRCA status.

The efficacy of DAN-222 was evaluated alone and in combination with a PARP inhibitor (niraparib) in HRD+ breast cancer (MDA-MB-436) and HRD- ovarian cancer (OVCAR-3) xenograft models. Table 1 highlights the endpoints of the study as measured by partial response, complete response, tumor free survival and median tumor volume at end of study (Day 60). DAN-222 alone had PR effects and reduced median tumor volume compared to niraparib alone. The combination demonstrated enhancement of response as evidenced by an increase in partial response, a shift from partial to complete response, an increase in tumor-free survivors, and significant further reduction in median tumor volume.

Conclusion:
The clinical pharmacology will be presented and demonstrates the designed behavior of the
nanoparticle. A design feature of the nanoparticle is that the payload and linker are sequestered in the core, protecting them from circulatory components. Moreover, the covalent attachment of the payload allows for tunable release kinetics via a hydrolytic linker, preventing burst release and associated toxicities common to physical encapsulation-based nanoparticle systems (e.g., liposomes, micelles). The preliminary PK profile in patients supports the translatability across species and consistency of exposure across patients.

| Table 1: Efficacy of DAN-222 Alone or in Combination with Niraparib |
|-----------------------------|-----------------------------|
| HRD+                      | BRCAwt                      |
| **Treatment**              | Dose (mg/kg) | PR | CR | TFS | MTV Day 60 (mm³) | PR | CR | TFS | MTV Day 60 (mm³) |
| Niraparib                  | 50/40         | 0  | 0  | 0   | 1372           | 0  | 0  | 0   | 726             |
| DAN-222                    | 1             | 6  | 0  | 0   | 321            | 4  | 0  | 0   | 405             |
| DAN-222 + Niraparib        | 1, 50/40      | 5  | 3  | 2   | 18             | 1  | 6  | 4   | 4               |

HRD = homologous recombination deficiency, PR = partial response, CR = complete response, TFS = tumor-free survival, MTV = median tumor volume

Disclosure(s):

**Ashley P. Wright, n/a:** Dantari, 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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**Timothy Hagerty, n/a:** Dantari, Inc.: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing)
Background: Preclinical data showed that high levels of vascular endothelial growth factor (VEGF) may lead to aggressive behavior in breast tumors that overexpress HER2. AVEREL study demonstrated that bevacizumab in combination with trastuzumab and docetaxel as first-line treatment increased progression-free survival (PFS) in HER2 positive metastatic breast cancer (BC) patients (BTH vs TH: 16.5m vs 13.7m, HR=0.82, P=0.0775). It is necessary to exploring new effective and tolerable strategy of targeting both HER2 signaling and angiogenesis. PHENIX and PHOEBE studies proved pyrotinib (an irreversible pan-ErbB receptor tyrosine kinase inhibitor) plus capecitabine improved prognosis for patients with advanced HER2 positive BC. Anlotinib is a novel multi-target tyrosine kinase inhibitor that effectively inhibits VEGFR, FGFR, c-KIT, c-MET and RET. This study is aimed to evaluate safety, tolerability and efficacy of anlotinib combined with pyrotinib and capecitabine for HER2-Positive metastatic BC. Methods: This open-label study is designed to include patients with pathologically confirmed HER2-positive metastatic breast cancer that have progressed or relapsed after treatment with trastuzumab or inability to receive trastuzumab in West China Hospital, Sichuan University. Eligible patients have at least one measurable lesion according to RECIST v1.1; previously received taxanes regimen and had ≤2 line of chemotherapy for advanced disease; an ECOG performance status of 0-1; adequate organ function. In the “3+3” dose-exploring phase, pyrotinib and capecitabine are given at a fixed dose of 400mg qd and 1000 mg/m2 bid respectively. Anlotinib is initially given at a dose of 10mg/d (Level I). If the initial dose level could be tolerated, subsequent patients are assigned to the higher level (Level H) with anlotinib 12mg/d; otherwise, to Level L with anlotinib 8 mg/d. Primary endpoints of phase Ib are dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and efficacy. Phase II is an expansion cohort at the recommended phase II dose (RP2D). The primary endpoint for phase II is one-year PFS rate by investigator-assessed, and secondary endpoints include PFS, overall response rate (ORR), clinical benefit rate (CBR), duration of response (DoR), overall survival (OS) and quality of life. A sample size of 23 provided 80% power at 2-sided alpha = 0.20 to detect a minimum of 20% improvement (45% vs. 65%) in one-year PFS. The phase Ib portion of the trial is currently enrolling in China. Clinical trial information: ChiCTR2100045962. Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Disclosure(s):
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Xiaorong Zhong, n/a: No financial relationships to disclose
Jie Chen, n/a: No financial relationships to disclose
A randomized double-blind placebo controlled phase 3 trial on the effect of Salovum™ and SPC-Flakes™ on abemaciclib-induced gastrointestinal toxicity in early breast cancer – the ASF-BC study

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   City: Örebro
   Country: Sweden

Background: In patients with high-risk luminal breast cancer, the addition of CDK 4/6-inhibitor abemaciclib to adjuvant endocrine therapy for two years has been associated with improved disease-free survival and is now recommended as the preferred treatment strategy for this patient group. However, patients treated with abemaciclib frequently (82%) experience diarrhea which primarily occurs during the first three months from treatment initiation and seems to impact patients’ quality of life. No proactive strategy to reduce the occurrence of abemaciclib-induced diarrhea is proposed but patients are recommended to start with loperamide upon the occurrence of diarrhea to be combined with treatment interruption and dose adjustment as needed. Cholera induced diarrhea, as well as other forms of diarrhea-inducing agents, has been shown to elicit a stimulated, endogenous production of a protein, named "antisecretory factor", ASF, which acts by modulating secretion of water and ions but also counteracts inflammatory processes. ASF is commercialized as Salovum® and registered by the EU authorities as "Food for specific medical purposes". Another way to increase ASF and, thus, to achieve benefit, is to induce its production/conversion by ingestion of malted oat flakes (SPC-flakes®) which has been recommended or considered for several secretory pathological conditions. Salovum has been shown to rapidly, ie within hours to a few days, antagonize diarrheal diseases of various etiologies. It has also been used against high fluid passages and inflammation in Crohn disease, Colitis ulcerosa and carcinoids in adults. SPC-flakes have similar effects but need weeks of administration to emerge. Importantly, to raise body ASF, by Salovum or SPC-flakes, for the above indications has not been associated with adverse effects.

Methods: This is a randomized double-blind multicenter phase III study aiming to investigate a proactive strategy including Salovum and SPC flakes to prevent the occurrence of abemaciclib-induced diarrhea in patients with early breast cancer treated with abemaciclib. A total of 100 patients will be randomized, in a 1:1 manner, between 13 weeks with Salovum / SPC flakes (A) or placebo (B). The study will be conducted in up to ten different oncology departments in Sweden. Primary objective: Occurrence of any-grade (mild, moderate, severe) diarrhea according to the Systemic Treatment-Induced Diarrhea Assessment Tool (STIDAT; patient-reported outcome). Secondary objectives: Occurrence of any-grade diarrhea according to CTCAE v. 5.0, health-abemaciclib, adherence to planned abemaciclib treatment, adherence to and pharmacodynamic effect from study products, safety of investigational products, sick leave
duration, breast cancer recurrence. Investigational product, dosage and mode of administration:
Salovum/placebo egg powder high in antisecretory factor, 4 g. Four sachets, i.e. 16 g q 8 h for 5 -
7 days before start of abemaciclib. The appropriate amount of Salovum is mixed with 100 –
200 ml of suitable liquid, e.g., fruit juice, and ingested orally. SPC-flakes/placebo flat dose of 75
g/d divided in 2 – 4 doses started in parallel with Salovum/placebo to be continued during the
first 12 weeks of treatment with abemaciclib. End of study: All included patients will be followed
using questionnaires up to 12 weeks from initiation of abemaciclib. After 12 weeks, all the
patients will be followed through electronic medical records until the end of abemaciclib
treatment (up to two years) for collecting potential adverse events and information on sick
leave. Data from electronical medical records regarding recurrence and subsequent therapy will
be collected until breast cancer recurrence or up to 5 years from initiation of abemaciclib.

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The Amelia-1 Study: A phase 1b/2 trial of evexomostat (SDX-7320) plus fulvestrant (Faslodex®) and alpelisib (Piqray®) in patients with advanced breast cancer at risk for alpelisib (Piqray)-induced hyperglycemia

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Background: Breast cancer patients with mutation(s) in the PIK3CA gene have more aggressive disease and worse outcomes relative to patients without PIK3CA mutations. Alpelisib (Piqray), an inhibitor of PIK3CA, was approved for breast cancer patients with PIK3CA mutations. An on-target toxicity of alpelisib is hyperglycemia leading to hyperinsulinemia which may limit effectiveness of this drug. Patients with baseline metabolic dysfunction, insulin resistance, and/or elevated HbA1c are at greater risk of developing grade 3,4 hyperglycemia after receiving alpelisib (Piqray) than patients without metabolic dysfunction. Restoring insulin sensitivity and reducing systemic insulin levels improved the efficacy of alpelisib in preclinical models of breast cancer. Evexomostat is a polymer-drug conjugate of a novel small molecule methionine aminopeptidase 2 (MetAP2) inhibitor that in normal mice reduced alpelisib-induced hyperglycemia/hyperinsulinemia and in the MCF-7 model of HR+/PIK3CA-mutant breast cancer showed synergistic anti-tumor activity with alpelisib (Piqray). Evexomostat was well-tolerated in a phase 1 monotherapy safety study in late-stage cancer patients and improved insulin resistance in patients with elevated insulin at baseline, among other metabolic and angiogenic markers. Methods: This is a phase 1b/2, open-label, single-arm pilot study (NCT05455619) in postmenopausal women with PIK3CA-mutated, HR+, HER2- metastatic breast cancer with disease progression following treatment with endocrine therapy plus a CDK4/6 inhibitor who are at risk for hyperglycemia, with risk factors defined as HbA1c between 5.7 and 6.4% and/or
HOMA-IR ≥1.8. The primary objective is to determine the safety of evexomostat plus standard of care treatment alpelisib (Piqray) and fulvestrant (combined, the ‘triplet therapy’), to measure the severity and number of hyperglycemic events, and to assess clinical, anti-tumor benefit of the triplet therapy. The trial will begin with a dose-escalation cohort (n=6) at an evexomostat dose of 36 mg/m² (one dose below the monotherapy MTD of 49 mg/m²) in combination with alpelisib and fulvestrant given in accordance with their respective labels. Based on safety data from the first 6 patients (two cycles), the safety review committee may increase the evexomostat dose for the next cohort of six patients to 49 mg/m² or may decrease the evexomostat dose to 27 mg/m² and may adjust the dose of alpelisib if warranted. Once the MTD of the triplet therapy has been defined, additional enrollment will occur until a total of up to 20 patients have completed at least two cycles of triplet therapy at that dose. If warranted, an additional 20 patients may be enrolled to further characterize the safety profile and/or anti-tumor effect of the triplet therapy (total of up to 52 patients). This trial will open to accrual in August, 2022. Primary safety analysis consists of the type, frequency, and severity of treatment-emergent adverse events (TEAEs) per the NCI CTCAE, v5.0, the number of patients with grade 3 or 4 hyperglycemia during the first 2 cycles of therapy plus an estimate of the proportion and its exact upper one-sided 97.5% confidence bound will be analyzed. Efficacy analyses include calculation of the ORR, consisting of complete response (CR) and partial response (PR). The number of patients alive without disease progression six months from the weeks from C1D1 will be calculated. Overall survival data will be summarized as available or EORTC scoring manual. ECOG performance status and change from baseline will be summarized.

Disclosure(s):
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OPTIMA, a prospective randomized trial to validate the clinical utility and cost-effectiveness of gene expression test-directed chemotherapy decisions in high clinical risk early breast cancer.

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Background: Multi-parameter tumor gene expression assays (MPAs) are used to estimate individual patient risk and guide chemotherapy use in hormone-sensitive, HER2-negative early breast cancer. The TAILORx trial supports MPA use in a node-negative population. Evidence for MPA use in postmenopausal node-positive breast cancer has been provided by the RxPONDER trial interim analysis but this relies on the absence of superiority in an analysis where >50% of events were unrelated to breast cancer. There is much uncertainty about MPA use for premenopausal patients. OPTIMA (Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis) (ISRCTN42400492) is a prospective international randomized controlled trial designed to validate MPAs as predictors of chemotherapy sensitivity in a largely node-positive breast cancer population.

Methods: OPTIMA is a partially blinded study with an adaptive two-stage design. The trial recruits women and men age 40 or older with resected ER-positive, HER2-negative invasive breast cancer and up to 9 involved axillary lymph nodes. Randomization is to standard management (chemotherapy and endocrine therapy) or to MPA-directed treatment using the Prosigna (PAM50) test. Those with a Prosigna tumor Score (ROR_PT) >60 receive standard management whilst those with a low score (≤60) tumor are treated with endocrine therapy alone. Endocrine therapy for pre-menopausal women includes ovarian suppression for all participants unless they experience a chemotherapy-induced menopause. Adjuvant abemaciclib is permitted. The trial will be analyzed for (1) non-inferiority of recurrence according to randomization and (2) cost-effectiveness. The key secondary outcome is non-inferiority of recurrence for patients with low ROR_PT score tumors. The efficacy analyses will be performed Per Protocol using Invasive Breast Cancer Free Survival (IBCFS) as the primary outcome measure to limit the risk of a false non-inferiority conclusion. Recruitment of 4500 patients over 8 years will permit demonstration of up to 3% non-inferiority of test-directed treatment with at least 83% power, assuming 5-year IBCFS is 87% with standard management. An integrated qualitative recruitment study addresses challenges to consent and recruitment, building on experience from the feasibility study which found that a multidisciplinary approach is important for recruitment success. OPTIMA is strongly supported by a patient group which has helped design all patient documents and which is represented on the TMG.

Results: The OPTIMA main trial opened in January 2017 and has continued to recruit throughout the COVID-19 pandemic. Overall recruitment as of 1 July 2022 was 2814 (2593 from UK, 221 from Norway). Patient characteristics are well balanced between the trial arms. Currently 95% of randomized participants are eligible for inclusion in the PP analysis. 66% of the MPA-directed arm participants have been allocated to endocrine therapy only. The test failure rate is < 1%.

Conclusion: OPTIMA will provide robust unbiased evidence on test-directed chemotherapy safety for both postmenopausal and premenopausal women with 1-3 involved nodes as well as for patients with 4-9 involved nodes and for patients treated with abemaciclib.
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Trial Inquiries: OPTIMA@warwick.ac.uk

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<th>Characteristic</th>
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Patient characteristics

Disclosure(s):

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Prospective, Multi-Center, Artificial Intelligence Study for Early Prediction of Serious Events under Treatment Is Now Open for Recruitment in Breast Cancer - OMCAT Trial in Progress

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Background: Aim of the OMCAT trial (‘One Million CAncer Treatment months’, NCT04531995) is improvement of cancer patient care and safety by developing artificial intelligence (AI)-based, incident prediction algorithms. Incident detection allows early notification of treatment teams, enabling timely management changes or interventions. Ultimately the algorithms can also support improved health resource allocation. This trial in progress aims to provide learning databases in breast cancer comprising both electronic patient reported outcome (ePRO) data using the mobile medical device ‘CANKADO PRO-React’ and ground truth outcome data, which provide disease-specific events of interest (“incidents”) verified by the physician (e.g., during patient examinations). Methods: Incident prediction is posed as an application of stochastic time series analysis using AI and knowledge engineering technology. The learning process begins by fitting individualized and disease-specific stochastic process models to “incident-free” intervals extracted from the ePRO data series. Incidents produce detectable deviations from “ordinary” ePRO fluctuations. The algorithms are trained on CANKADO PRO-React data to produce real-time risk functions for predicting incidents on a clinically specified time horizon.
Results: Considering the heterogeneity and combinatorics of diseases, stages, therapies, and types of events considered in this study, ultimately the AI algorithms aim to discover about 360 distinct predictive relationships. The estimate of one million treatment months is derived from statistical power analysis of this target, considering estimated median documentation time of six months per patient and estimated 400-500 patients per predictive relationship. To date, 45 centers in Germany have expressed interest in participating. This participation level will enable proof of principle. Ethics votes are already available in most regions. Other centers are invited to participate in this trial. Conclusions: OMCAT opens a whole new path towards evidence-trained AI and a novel combination of patient observation and predictive care. The goals of OMCAT are ambitious and will therefore require many more supporters.

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12/8/2022
5:00 PM - 6:15 PM
Poster Session 5
Multiscale Deep Learning framework to capture systemic immune features in lymph nodes predictive of triple negative breast cancer outcome

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Systemic immune responses in lymph nodes (LN) convey significant prognostic value for breast cancer patients, which can inform disease progression and optimal treatment management. However, have, so far, not been assessed in large patient cohorts. We have previously shown that morphological alterations in axillary LNs, namely the formation of germinal centres (GCs) in cancer-free LNs, add prognostic value to tumour infiltrating lymphocytes (TILs) in triple-negative breast cancer patients (TNBC) for the development of distant metastasis. Extending manual assessment of LNs beyond the detection of cancer requires the integration of robust deep learning pipelines into the digital pathology workflow. Here, we propose a supervised multiscale deep learning framework named smuLymphNet to capture and quantify GCs and sinuses within LNs from digitised Haematoxylin and Eosin-stained (H&E) whole slide images (WSIs) and show good concordance compared with an inter-pathologist Dice coefficient of manual annotations from four pathologists. The smuLymphNet framework consists of (i) a detection algorithm to determine the boundaries of each LN section on the WSI, using an Otsu-based thresholding method and contouring algorithm; (ii) a supervised multiscale deep learning module for the segmentation of GCs and sinuses; and (iii) quantification of the number, size, and shape of the predicted features. We applied smuLymphNet to a total of 1,800 H&E-stained WSI of >4,000 cancer-free and involved LNs from a retrospectively collected breast cancer cohort collected at Guy’s Hospital (London, UK) from 177 patients (122 N+) enriched for the triple-negative phenotype. A subset of 114 WSI and five breast cancer LN WSIs from each Barts Hospital (London, UK) and Tianjin University Hospital (Tianjin, China) were used to train and evaluate the supervised deep learning module. For training Fully Convolutional Networks (FCNs), WSIs manually annotated for both GCs and sinuses formed a ground-truth set and three FCNs were implemented: (i) a standard U-Net architecture; (ii) a U-Net model with an attention gate mechanism; and (iii) a multiscale-U-Net network (MS U-Net) that encodes, in parallel, a feature representation of the image at multiple resolutions. The MS U-Net achieved the best performance with an average dice score of 0.86 for GCs and 0.74 for sinuses. In comparison, the average dice score amongst four pathologists assessing 24 LN WSI for GCs and sinuses was 0.67 and 0.61, respectively, demonstrating the robustness of the smuLymphNet framework. To establish associations between morphometric immune features and patients’ outcomes, we assessed smuLymphNet captured GCs and sinuses from 686 WSIs from 96 TNBC patients with extensive longitudinal outcome data. We found significant morphological differences in involved and cancer-free LNs between N0 and N+ patients, with the latter displaying larger GCs with more irregular shapes, especially in their involved LNs. Moreover, in alignment with our previously published studies, our multiscale smuLymphNet framework recapitulated and extended the prognostic value of the assessment of GC formation in TNBC N0 patients. We further revealed, for the first time, the prognostic significance of the intranodal lymphatic sinuses when measured in their totality in involved LNs, and the association of alterations in subcapsular sinus areas with superior distant metastasis-free survival in cancer-
free and involved LNs in TNBC N+ patients. In summary, smuLymphNet presents a robust multiscale deep learning framework to automatically detect, localise and quantify histopathological immune features in WSI of LNs. By applying smuLymphNet to LNs of TNBC patients from clinical trials, and thereby further evaluating its clinical utility, smuLymphNet could be implemented into the diagnostic digital pathology workflow and, as such, aid in informing on a patient’s disease trajectory.

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Background: Positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI) are useful imaging modalities for the preoperative nodal staging in breast cancer; however, clinical evidence demonstrating the diagnostic accuracy of the combination of PET/CT and MRI is limited. The purpose of this study is to establish a clinical prediction model based on PET/CT plus contrast-enhanced MRI for ALN metastasis, and explore the possibility of non-invasive patients' risk stratification using the PET/CT plus MRI model preoperatively. Methods: A total of 361 women (370 axillae; mean age, 56 years ± 12 [standard deviation]) who underwent surgery for primary invasive ductal carcinoma at a single institution between April 2017 and March 2020 were evaluated. Subjects were divided into two cohorts: a derivation cohort (n = 333) and a validation cohort (n = 37). In the derivation cohort, we constructed a prediction model with logistic regression to estimate the potential explanatory variables obtained by PET/CT, MRI, and preoperative core-needle biopsy. Using a simple integer risk score, patients were divided into low-risk and high-risk groups. We assessed the predictive ability of the PET/CT plus MRI model using the area under the curve (AUC), and internal validation was achieved by risk scoring system in the validation cohort. Results: The PET/CT plus MRI model included five predictor variables: maximum standardized uptake value of primary tumor and ALN, primary tumor size, ALN cortical thickness, and histological grade. The PET/CT plus MRI model had significantly improved AUC of 0.867 (p < 0.05) as compared to those of the PET/CT model (AUC = 0.821) and MRI model (AUC = 0.815). We assigned the
weighted scores to each retained variables in the PET/CT plus MRI model, and determined the optimal cut-off value of 7 (range, 0−17). In the derivation and validation cohorts, 55% and 65% of the patients were classified as low-risk by the risk scoring system, with negative predictive values of 97% and 100%, respectively. Conclusions: Our findings demonstrated a better diagnostic accuracy of the clinical prediction model utilizing both PET/CT and MRI than previous models based on either PET/CT or MRI, and the negative predictive value of 97% was not inferior to that of sentinel lymph node biopsy. Thus, the preoperative risk evaluation of axillary lymph node macrometastasis using our integrated model could be useful while considering individualized therapy for patients with invasive ductal breast cancer. Further validation should be performed for clinical applications.

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Evaluation of novel diagnostic kits using the semi-dry dot-blot method combined with an automatic reader for detecting metastases in sentinel lymph nodes of patients with breast cancer: a multi-center prospective study

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Background: The semi-dry dot-blot (SDB) method, a diagnostic procedure for detecting lymph node (LN) metastases using an anti-cytokeratin (CK) antibody, is based on the theory that epithelial components, such as CK, are not found in normal LNs. Thus, metastases are diagnosed according to the presence of CK in the lavage fluid of sectioned LNs. We prospectively evaluated novel SDB kits that use a newly developed anti-CK19 antibody and an automatic reader for diagnosing sentinel LN metastases in patients with breast cancer as a multi-center study. Methods: We obtained 924 sentinel LNs dissected from 405 patients with breast cancer between January 2021 and December 2021 at six institutes in Japan. We excluded patients who underwent neoadjuvant chemotherapy and neoadjuvant endocrine therapy. LNs were sectioned at 2-mm intervals and washed with phosphate-buffered saline. Cells suspended in the lavage fluid of sectioned LNs were centrifuged and lysed to extract protein. The extracted protein was applied to the SDB kit to diagnose LN metastasis using an automatic absorbance reader. Hematoxylin and eosin (H&E) stained and washed LNs were blindly examined by pathologists using intraoperative and permanent histological examination. Diagnoses based on SDB kit and automatic reader findings were compared with diagnoses made by permanent histological examination of paraffin-embedded H&E-stained sections of LNs. Primary endpoints were the sensitivity, specificity, and overall agreement of the SDB kit for distinguishing macrometastases from non-macrometastases. Results: Ninety-four of the 924 LNs were assessed as macrometastases, 40 as micrometastases, and 790 as isolated tumor cells by histological examination. Compared with patients with non-macrometastases, those with macrometastases had significantly younger age (p< 0.01), larger primary tumor (p< 0.01), higher nuclear grade (p=0.04), increased lymphatic invasion (p< 0.01), and increased venous invasion (p=0.01). Using a borderline CK19 absorbance of 11.9 milli-absorbance for detecting macrometastases with an area under the curve of 0.989, the sensitivity, specificity, and overall agreement of the SDB kit were 94.7%, 98.3%, and 97.9%, respectively. Moreover, the sensitivity, specificity, and overall agreement of the intraoperative histological examination compared with permanent histological examination for distinguishing macrometastases from non-macrometastases were 91.4%, 99.1%, and 98.3%, respectively. Furthermore, the kits and automatic reader yielded diagnoses within approximately 20 min at a cost of < 30 USD for the SDB kit and < 3,000 USD for the automatic reader. Conclusions: The kits with an automatic reader used in our study were accurate, quick, and cost-effective in diagnosing LN metastases without the loss of LN tissue and were particularly useful for distinguishing macrometastases. We plan to make the SDB kit and automatic reader commercially available worldwide soon.
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Contralateral Axillary Lymph Node Metastasis after Ipsilateral Breast Tumor Recurrence: Is it distant metastasis or locoregional progression?

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Background: Contralateral axillary lymph node metastasis (CAM) in breast cancer is currently classified as a stage IV disease but its prognosis is still controversial. Purpose: To determine outcomes in overall survival (OS) and disease-free survival (DFS) in patients with and without locoregional tumor recurrence who present with contralateral axillary lymph node metastasis (CAM). Methods: Patients with pathologically confirmed invasive breast cancer with metachronous CAM who received treatment between 1988 and 2017 were retrospectively reviewed. Patients with other distant metastases at the time of CAM diagnosis were excluded. The outcome of CAM in cases of IBTR and regional recurrence (RR) were compared to CAM not accompanied by locoregional tumor recurrence. Results: Thirty-eight patients with metachronous CAM were included in the study. Metachronous CAM occurred 55 months (interquartile range, 17-77 months) after surgical treatment of the primary tumor and median follow-up was 95 months (interquartile range, 49-117 months) from the initial operation date and 40 months (interquartile range, 15-54 months) from the diagnosis of CAM. At the time of initial CAM diagnosis, 11 patients had IBTR, 12 patients had RR, and 15 patients had no
locoregional recurrence. The estimated 5-year OS was 49.1% and 5-year DFS was 45.3%. Although statistically insignificant due to small sample size, when stratified by loco regional recurrence, the prognosis of CAM patients with IBTR appeared to be better than those without locoregional recurrence (5-year OS: 88.9% vs. 41.4%, HR 5.88, p = 0.09) whereas the prognosis of CAM patients with RR was worse than those without locoregional recurrence (5-year OS: 35.4% vs. 41.4%, HR 0.44, p = 0.20). Axillary lymph node dissection (ALND) improved median OS (83 vs. 36 months, p = 0.069) in all patients. When stratified, improvement in median OS was 13 vs 27 months (p = 0.094) in patients with RR, and 36 vs. 65 months (p = 0.061) in patients without locoregional recurrence. For patients accompanied by IBTR, ALND was performed in 8 out of 11 and only one patient died during the follow-up period. Conclusion: Our study indicates that the patients with CAM have superior survival outcome when compared to other stage IV patients, especially when CAM was accompanied by other loco regional recurrences. These data suggest that the CAM patients may benefit from active loco regional treatment.

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A Predictive Model for Axillary Pathologic Response after Neoadjuvant Chemotherapy for Clinically Node-Positive Breast Cancer

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Purpose: Neoadjuvant chemotherapy (NAC) has resulted in the eradication of axillary lymph node metastasis in approximately 40% of patients. Sentinel lymph node biopsy (SLNB) could be an alternative surgical procedure for these patients to avoid complications from axillary lymph node dissection (ALND). However, high false-negative rates of SLNB for clinically node-positive patients were reported in previous prospective trials. The aim of the present study was to evaluate clinicopathological factors and imaging characteristics by MRI and ultrasound (US) as predictors of axillary pathologic complete response (ypN0) after NAC, which enables to identify candidates for SLNB in patients with clinically node-positive disease. Patients and methods: We identified 177 patients with clinically node-positive breast cancer who received NAC from May 2009 to May 2021. All patients underwent MRI and US before and after NAC. Patients were judged to be node-positive when they have the cytologically-proven nodal disease by fine-needle aspiration (FNA) or suspicious lymph nodes by diagnostic imaging. Lymph nodes with the cortical thickness (>3.5mm), loss of fatty hilum, or round shape (short-axis/long-axis ratio > 0.5) were defined as suspicious lymph nodes. To develop a predictive model for ypN0, the association between ypN0 status and clinicopathological and imaging characteristics was assessed by multivariate logistic regression analysis. The area under the
receiver operating characteristic (ROC) curve was used to evaluate discrimination by the model. The model was further evaluated in the validation cohort with 20 patients who received NAC from March 2021 to December 2021. Results: The median age was 54.0 (range: 22-79) years and the mean tumor size was 3.97 ±2.29cm. Of 177 patients, 90 (50.8%) patients had luminal, 47 (26.6%) had HER2-positive, and 40 (22.6%) had triple-negative disease. Sequential anthracycline and taxane were administered for 157 (88.7%) patients, and 45 (95.7%) patients with HER2-positive-disease received concomitant anti-HER2 agents preoperatively. Overall, 77 (43.5%) patients achieved ypN0. Independent predictors of ypN0 status were clinical stage N1 (odds ratio [OR]: 9.17 vs. cN2-3, p=0.002), absence of lymphadenopathy after NAC (OR: 8.54, p< 0.001), breast complete response (CR) by MRI (OR: 5.96, p< 0.001), HER2 positivity (OR: 3.80, p=0.008), nuclear grade (NG) 3 (OR: 2.77 vs. NG1-2, P=0.020) and hormone receptor negativity (OR: 2.52, p=0.048). In a model using these predictors, the area under the ROC curve was 0.887 (95% confidence interval: 0.839-0.935, p< 0.001). The sensitivity, specificity, positive predictive value and negative predictive value of the model were 80.0%, 82.8%, 77.9% and 84.5%, respectively. In the validation cohort, the sensitivity, specificity, positive predictive value and negative predictive value were 66.7%, 90.9%, 85.7% and 76.9%, respectively. Among 84 patients who were predicted ypN0 by the model, SLNB was performed in 42 (50.0%) patients, and the identification rate of SLN was 95.2% (40/42). Overall, ALND was omitted in 38 (45.2%) patients and irradiation to regional lymph nodes was performed in 23 (60.5%) out of 38 patients. After a median follow-up of 53.9 months, 5-year recurrence-free survival was comparable between patients with or without ALND (78.0% vs. 94.4%, p=0.259). Conclusions: Our predictive model based on clinicopathological factors and imaging characteristics by MRI and US could help to identify good candidates for the omission of ALND after NAC in patients with clinically node-positive breast cancer.

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Single cell profile of tumor and immune cells in primary triple-negative breast cancer and different sites in the axillary lymph nodes

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Purpose: Little is known about the host-tumor interaction in the lymph node basin at a single cell level. This study examines single cell sequences in breast cancer nodal metastasis of a patient with triple negative breast cancer. Methods: The primary breast tumor, sentinel lymph node, an adjacent lymph node with metastatic involvement and a clinically normal-appearing lymph node were collected during operation. Single-cell sequencing was performed on all specimens. Results: 14,016 cells were clustered as 6 cell populations. Cancer cells demonstrated the molecular characteristics of TNBC basal B subtype and highly expressed genes in the MAPK signaling cascade. Tumor associated macrophages regulated antigen processing and presentation and other immune-related pathways to promote tumor invasion. CD8+ and CD4+ T lymphocytes concentrated more in sentinel lymph node and mainly stratified as two transcriptional states. The immune cell amount variation among primary tumor, sentinel and normal lymph nodes showed the similar tendency between the scRNA-seq profile of TNBC samples and a previous reported bulk RNA-seq profile of a breast cancer cohort including all four breast cancer subtype samples. Discussion: Single-cell sequencing analysis suggested that the sentinel lymph node was the initial meeting site of tumor infiltration and immune response, where partial T lymphocytes perform anti-tumor activity while other T cells exhibit an exhaustion state. We proposed a molecular explanation to the well-established clinical principle that the 5-year and 10-year survival outcomes were noninferior between SLND and ALND.

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Recruitment, clinical equipoise, patient acceptance and compliance in the UK-ANZ POSNOC trial

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Background: POSNOC is a UK-ANZ multicentre, non-inferiority, randomised trial comparing systemic therapy alone with systemic therapy plus Axillary Treatment (Axillary radiotherapy or recurrence within 5 years. This paper describes screening, recruitment and compliance data.

Methods: Sites were requested on a monthly basis to upload screening data and provide reasons for non-recruitment of eligible patients into the trial. Sites entered in the online database whether the patients were compliant with their randomisation allocation. Results: The study opened in July 2014 and completed target recruitment of 1900 women (24% of those screened) in July 2021, at 95 sites in the UK and 20 sites in Australia and New Zealand. The reason for non-enrolment was unknown in 1300 women. Of the remaining 4774 women with known reasons, who were screened but not randomised, the most common reasons for non-recruitment were due to either patients (n=2219, 46.5%) or their clinicians (n=782, 16.4%) favouring axillary treatment, or patients (n=490, 10.3%) or their clinicians (n=170, 3.6%) not wishing to have axillary treatment. Over the course of the study, there was an increase in the proportion of patients wanting axillary treatment and declining the trial (Mean % patients declined 2015 – 17.9%, 2021 – 39.1%). Mean number of participants recruited per site per month was 0.24 (SD 0.18) overall, 0.25 (SD 0.19) in the UK, and 0.19(SD 0.15) in ANZ. The mean was < 0.3 in 79 sites and >0.9 in only one site. Recruitment rate remained consistent throughout the study (mean 25.3 per month) except for during the first 6 months of recruitment (5.7) and during the COVID pandemic Apr-Sep 2020 (7.5). Of 89 (4.8%) participants non-compliant with allocation, n=45 (50.6%) received systemic therapy alone and n=44 (49.4%) received systemic therapy plus axillary treatment. There was no fluctuation in the direction of non-compliance during the study duration. There was increasing uptake of axillary radiotherapy to treat the axilla instead of ALND over the course of the study in patients receiving axillary treatment (Number who had ART of all who had axilla treatment2014-2017 - 248/454 (54.6 %); 2018-2021 – 315/449 (70.2%)). Conclusion: Recruitment and compliance with randomised allocation remained consistent over a seven-year period. POSNOC with in-built radiotherapy
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Steps toward noninvasive lymph node staging (NILS) in clinically node negative patients: Artificial neural network model to preoperatively predict lymphovascular invasion

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Background: Lymphovascular invasion (LVI) is one of the most important predictors for nodal status in breast cancer patients [1]. Multiple models have been published for prediction of preoperatively disease-free axillary using i.a. LVI [1-2]. However, LVI detection in preoperative core needle biopsy has been reported with a failure rate of 30% [3] and the analysis is not routinely performed in Sweden. Thus, a preoperative model of LVI status would be useful in prediction models for noninvasive lymph node staging (NILS). The purpose of this study was to develop an artificial neural network (ANN) model for LVI prediction using only clinicopathological variables that are routinely available in the preoperative setting. Methods: Data gathered prospectively during 2009-2012 in Lund, Sweden from 761 clinically node negative breast cancer patients were retrospectively extracted. Inclusion criteria were female sex, primary breast cancer and that each patient was scheduled for primary surgery. Patients with metastatic disease, bilateral cancer, tumor size greater than 50 mm, previous ipsilateral breast or axillary surgery, patients omitted of standard axillary staging procedure by SLNB or ALND, and those who had neoadjuvant treatment were excluded. LVI was assessed on surgical breast specimens and was defined as the presence of tumor cells within endothelium-lined vascular channels. Out of the 761 patients in the cohort, 613 patients were documented with LVI status. The LVI full case dataset was split 80/20 for training and validation. The remaining 148 patients were set aside for model testing. Since the test dataset did not contain information on LVI status, it was used to compare the predicted fraction of LVI positive patients to that of the development dataset. Only variables possible to obtain in the preoperative setting were included in the prediction models, comprising age, menopausal status, mode of detection (mammography screening or symptomatic representation), tumor size, multifocality (yes/no), histopathological type, histological grade, ki-67 percentage, estrogen receptor status, progesterone receptor status, and human epidermal growth factor receptor 2 status. An ensemble approach was used, where each ensemble constituted 30 ANNs that were trained and validated using 5-fold cross validation. For every ensemble model, different model parameters, such as L2-regularization and the number of hidden nodes, were tested. Model selection was based on validation AUC. Results: The study cohort included female clinically node negative breast cancer patients scheduled for primary surgery. Data from 613 patients (lymph node stages N0: 67.4%, N1: 26.9%, N2+: 5.7%) were used to develop the model, and
148 patients (N0: 56.8%, N1: 35.8%, N2+: 7.4%) constituted the internal test cohort. Fifteen percentage of the patients in the development dataset were LVI positive. The selected ensemble model achieved a validation AUC of 0.80 (CI 0.75-0.85). This model predicted an LVI positive rate of 16.2% in the test dataset. Conclusion: LVI was predicted with high accuracy using an ANN model based on routine preoperative clinicopathological variables. The result of validation AUC 0.80 (CI 0.75-0.85) indicates a potential for preoperative prediction of LVI, and the model can putatively be useful when applying preoperative nodal prediction models in patients without known LVI status. To confirm these results, verification in an external dataset is needed. Validation of the LVI-model in an independent dataset from the National Breast Cancer Registry will be performed, as well as an evaluation of the usefulness of the LVI-model as an imputation in a nodal prediction model. [1] Dihge, L. et al. BMC Cancer (2019). PMID: 31226956 [2] Bevilacqua, J. L. et al. J Clin Oncol. (2007). PMID: 17664461 [3] Harris, G. C. et al. Am J Surg Pathol. (2003). PMID: 12502923

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Evaluation of the efficacy of using fluorescence-associated indocyanine green in sentinel lymph node biopsies from breast cancer patients

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Introduction: Sentinel lymph node biopsy is the technique of choice for axillary staging in patients with breast cancer. Although it is already a widespread technique, its history is relatively recent. Three techniques are globally used to detect sentinel lymph nodes: the patent blue, described by Giuliano et al. (1994); the technetium-99 radiopharmaceutical with gamma probe, published by Krag et al. (1993); and the combination of these two techniques. Objective: This study aims to evaluate sentinel lymph node detection rate using the innovative fluorescence-associated indocyanine green technique in breast cancer patients, and to compare it with that of patent blue and with a combination of the two dyes. Method: A randomized trial was conducted on 99 patients who were equally divided into three arms, each one undergoing sentinel lymph node detection using either patent blue, indocyanine green, or a combination of the two dyes. The study was conducted at Hospital de Esperança, Presidente Prudente, SP, Brazil, in partnership with the Breast Department of Paulista School of Medicine, Federal University of São Paulo. Results: The accuracy rate in identifying sentinel lymph nodes was 78.8% with patent blue, 93.9% with indocyanine green, and 100% with patent blue + indocyanine green. Two sentinel nodes (48.5%) were mostly identified in the combined group; however, only one sentinel node was identified in the other groups. The mean time for sentinel lymph node identification was 20.6 minutes with the traditional dye, 8.6 minutes with indocyanine green, and 10 minutes with the combination of the two methods (p < 0.001). The mean surgical time was 69.4 minutes with patent blue, 55.1 minutes with indocyanine green, and 69.4 minutes with their combination (p < 0.001). Conclusion: Sentinel lymph node detection rate by fluorescence-associated indocyanine green was considered effective. The comparison
of sentinel lymph node detection rates between patent blue, indocyanine green, and a combination of patent blue + indocyanine green revealed statistically significant differences (p = 0.030), with the combined method being the most effective. Keywords: breast neoplasm, sentinel lymph node biopsy, fluorescence, indocyanine green

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WITHDRAWN
Utility of 18F-FDG PET/CT for the prediction of pathologic complete response in axilla to neoadjuvant chemotherapy in breast cancer

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Purpose: To evaluate the value of early FDG-PET (18F-Fluorodeoxyglucose-Positron Emission Tomography) metabolic criteria for prediction of pathologic complete response in axilla (pCRAx) after neoadjuvant chemotherapy (NAC) in breast cancer. Methods: Inclusion criteria were all T-stage breast cancers, non-metastatic, with initial lymph node involvement estimated by PET +/- lymph node biopsy, treated with NAC followed by surgery with axillary lymph node dissection (ALND), managed at the George-François Leclerc Cancer Center in Dijon, France, between 2009 and 2019. A PET was performed before and after the first course of chemotherapy (PET1 and PET2). pCRAx was defined as the absence of invasive cells in the nodes at the time of ALND (i.e. ypN0). The Sataloff classification was used as reference on each pathological report. Patients with a Sataloff NA classification (i.e. evidence of therapeutic effect, and no residual disease) and, if axillary involvement was proven at diagnosis, NB (i.e. no metastasis, no therapeutic effect) were considered as pCRAx. The PET metabolic criteria studied in the axilla were: - SUVmax (Standard Uptake Value) on PET1 and PET2 = fixation in the axillary voxel with the highest activity (kBq/mL) / (injected dose (kBq)/weight (g)) - ΔSUVmax (%) = metabolic response after the first course of NAC = 100 x (SUVmax1 - SUVmax2) / (SUVmax1). Univariate and multivariate analysis were performed to identify factors (clinical, pathologic, metabolic) that may be associated with pCRAx. Relationships between baseline TEP uptake and prognostic parameters were assessed using Receiver Operating Characteristic (ROC) curves. Results: Among 188 patients included, the rate of pathologically proven node involvement was 63.3% (n=119). The pCRAx rate was 45.7% (n=86/188) but varied according to tumor subtypes: 14.5% (n=9/62) of HR+/HER2-negative, 47.7% (n=21/44) of HR+/HER2-positive, 61.4% (n=27/44) of triple-negative (TN) and 76.3% (n=29/38) of HR-/HER2-positive. Factors significantly associated with pCRAx were by univariate analysis:
HER2-positive (HR+ and HR-) and TN subtypes (p< 0.001), SBR (Scarff-Bloom-Richardson) grade (p=0.01), breast pCR (ypT0/is) (p< 0.001), SUVmax2 (p=0.01) and ΔSUVmax (p< 0.001).

By multivariate analysis, it persisted the HR-/HER2-positive (p=0.02) and TN (p=0.02) subtypes optimal threshold to predict pCRAx (Area Under the Curve AUC = 0.73) with a sensitivity (Se) (AUC = 0.72; Se at 52%; Sp at 88%). In HR-/HER2-positive patients, SUVmax2 appeared to be max. A SUVmax2 value of 1.99 was the optimal threshold for predicting pCRAx (AUC = 0.72), yielding a Se of 66% and a Sp of 78%. None of the PET criteria predicted axillary response with sufficient accuracy for HR+ subtypes.

Conclusion: PET alone does not appear to be sufficient to predict pCRAx. It seems necessary to use other parameters, whether clinical, biological or imaging, to discriminate responders from non-responders to NAC in order to adapt the subsequent surgical management.

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Genomic Landscape of ER+/HER2- metastatic breast cancer as a function of prior treatment with a CDK4/6 inhibitor.

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Background CDK4/6 inhibitors (CDK4/6i), like palbociclib, ribociclib, and abemaciclib, along with antiestrogens, have revolutionized treatment for ER+/HER2- metastatic breast cancer (MBC). Although most patients initially respond, almost all eventually progress, and ER+ HER2-MBC remains incurable. There is an urgent need to understand the molecular processes that drive resistance in order to improve survival. The landscape of acquired somatic alterations causal to CDK4/6i resistance remains unknown. Here we report differences in mutational landscapes between ER+/HER2- MBC patients treated with and without CDK4/6i. Methods Deidentified data from 780 and 1073 ER+ HER2- MBC patients (solid tumor or ctDNA liquid biopsy sequencing respectively) with at least 6 months between diagnosis of Stage 4 disease and biopsy were analyzed. Patients were divided into either treated or untreated with CDK4/6i prior to biopsy. Sequencing was performed using the Tempus xT tumor assay (DNA sequencing of 595-648 genes at 500x coverage) and Tempus xF liquid biopsy (ctDNA sequencing of 105-523 genes). Gene alterations (consisting of pathogenic/likely pathogenic short variants and copy number alterations) were compared between groups by Chi-squared/Fisher’s Exact tests and p-values adjusted for false-discovery. Results We first analyzed sequencing data of both solid tumor and liquid ctDNA from ER+/HER2- MBC patients. ESR1 mutations were significantly more frequent in those that received CDK4/6i than those that did not (Solid tumor 33% vs 16%, p < 0.001, q = 0.001; Liquid biopsy 32% vs 16%, p < 0.001 and q < 0.001). We also saw more frequent mutations/amplifications in the following genes in
the CDK4/6i treated cohort vs. those that were not. These results trended towards significance in our solid tumor, but not in our liquid biopsy cohort: CCND1 (18% vs 11% p = 0.028 q = 0.3); FGF3 (17% vs 9.5% p = 0.010 q = 0.2); FGF4 (17% vs 11% p = 0.035 q = 0.3), GATA3 (17% vs 8.9% p = 0.008 q = 0.2), PTEN (12% vs 6.1% p = 0.030 q = 0.3) and FGF19 (8.2% vs 1.7% p = 0.002 q = 0.12). Interestingly, 96-98% of CCND1, FGF3, FGF4 and FGF19 alterations were copy number amplifications. Conversely, we saw a trend towards significance for more mutations in TP53 (37% vs 27% p = 0.008 and q = 0.2) in those that had not received a CDK4/6i than those that did. Conclusions Here we present the landscape of somatic alterations in ER+/HER2- MBC patients with and without prior CDK4/6i therapy from our large real world de-identified data set. Patients with prior CDK4/6i therapy harbored significantly more ESR1 somatic alterations, demonstrated in both solid tissue and liquid biopsies. In solid tissue biopsies, patients with prior CDK4/6i therapy harbored more CCND1, FGF3, FGF4, and GATA3 alterations and less TP53 alterations. These trends were not significant after adjustment for multiple testing. CCND1, FGF3, FGF4 and FGF19 alterations were copy number amplifications, which may be consistent with 11q13 amplification. Further studies will provide insights into how these trends translate towards our understanding of CDK4/6i related resistance mechanisms.

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**Combined biomarker analysis for prediction of pathological complete response (pCR) after 12 weeks of pembrolizumab + trastuzumab + pertuzumab in HER2-enriched early breast cancer: Keyriched-1 trial**

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Background In unselected HER2+ early breast cancer (EBC), de-escalated chemotherapy-free neoadjuvant therapy (NAT) with dual HER2-blockade induces pCR rates of only 20%-40%. In
order to achieve pCR rates by de-escalated therapy comparable to those achieved by chemotherapy-based regimens, patient selection and more effective chemotherapy-free regimens are thus key. KEYRICHED-1 (NCT03988036), a single-arm phase 2 study, is the first trial to investigate chemotherapy-free NAT with dual HER2 blockade and pembrolizumab in HER2-enriched HER2+ EBC. In a translational subproject, we analyzed gene signatures together with tumor cell proliferation and spatiotemporal immune cell profiling to identify predictive factors for pCR.

Methods

48 pre- and postmenopausal patients with newly diagnosed HER2 2+ (ISH positive) or 3+ EBC (stage I-III) and HER2-enriched (HER2-E) subtype by PAM50 were included in the study. All patients received 4 cycles of pembrolizumab (200 mg), trastuzumab biosimilar ABP 980 (loading dose (LD) 8 mg/kg bodyweight (BW), maintenance dose (MD) 6 mg/kg BW), and pertuzumab (LD 840 mg/kg BW, MD 420 mg/kg BW) q21d. Primary objective was pCR (centrally confirmed absence of invasive tumor in breast and lymph nodes: ypT0/is, ypN0). NanoString Breast Cancer 360 panel was performed in baseline week 3 biopsies (on treatment) were classified as early response. sTILs were analyzed at baseline (n=42) and week 3 (n=28). Ongoing analyses include whole exome sequencing and multiplexed immunohistochemistry for expression of PD1, PDL1, CD4, CD8, CD68, and CD20 levels in tumor and stroma at baseline and at week 3. Impact of standardized expression of single genes, signatures, and sTILs on pCR was evaluated with univariable and multivariate logistic regression analyses and summarized with odds ratios (OR) and 95% confidence intervals (95%CI). Results 42 patients with BC360 and sTILs data at baseline were included in the analysis. Median age was 55 years (range: 22-83), 11 patients (31%) had node-positive corresponding pCR rates were 57.1% (n=16) and 28.6% (n=4, p=0.108). At week 3 (on treatment), 16 patients had 30% sTILs (one patient out of 12, p=0.039). 37 patients had early response, 54.1% of them (n=20) had a pCR vs 0% in early non-responders (n=5, p=0.049). In univariate analysis, IDO1, ERBB2, IFNγ, cytotoxic cells, cytotoxicity, CD8 T-cells, TIGIT, and tumor inflammation signatures were statistically significantly associated with pCR (OR 2.3-3.6); ERBB2, IDO1, IFNγ and CD8 T-cells remained significant after adjusting for hormone receptor (HR) and central HER2 status (OR 2.2-4.3). 70 single genes were predictive for pCR; none of them remained significant after false discovery rate adjustment (25%). In multivariable analysis for baseline markers including signatures, sTILs, HR and central HER2 status, only ERBB2 (OR 8.7, 95%CI 1.9-39.0, p=0.0046) and cytotoxic cells signatures (OR 4.6, 95%CI 1.6-13.5, p=0.0059) were predictive for pCR. Results of whole exome sequencing, and multiplexed immunohistochemistry analysis of immune cell markers will be presented at the Symposium.

Conclusions Biomarker analysis in the unique KEYRICHED-1 cohort revealed that early response at week 3, ERBB2 and immune related signatures as well as on-therapy sTIL levels predict pCR after a chemotherapy-free combination of immunotherapy and dual HER2 blockade in HER2-enriched EBC. These results pave the way for validation in larger de-escalation trials investigating short, chemotherapy-free regimens in selected patients with HER2+ EBC. Funding for this research was provided by MSD Sharp & Dohme GmbH.

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Immune Signatures Display Subtype-Specific Activation in Breast Cancer

Background. The development of new anti-HER2 therapies for the treatment of HER2-positive breast cancer (BC) is changing the concept of HER2 dichotomization to select and treat this patient population. In addition, different immunotherapies tested in HER2-low BC are gaining continuous interest. However, a comprehensive characterization of HER2 BC subgroups and patients is required to identify the best treatment approach. Materials and Methods. Using 123 BC samples with gene expression and IHC/FISH determined HER2 status we determined cutoff values to identify HER2 positive, HER2 low, and HER2 ultralow cohorts. With the inclusion of hormone receptor (HR) status six clinically relevant cohorts were defined (HR+/HER2+, HR+/HER2-low, HR+/HER2-ultralow, and HR-/HER2+, HR-/HER2-low, HR-/HER2-low). An integrated database of 7,624 BC cases were assigned to the six subtypes. Prognosis determination was based on relapse-free survival (RFS), distant-metastasis-free survival (DMFS), and overall survival (OS). Clinical parameters evaluated include MKI67 expression, lymph node status and grade. All together 17 immune signatures resembling immune genes and related activated pathways were tested against the six molecular BC subgroups. Results. We defined a robust cutoff for HER2 expression levels to define six distinct HER2 BC molecular subgroups (>3034 for HER2 positivity and < 1780 for HER2 ultralow). Regardless the HR positivity, the overall distribution of HER2-low, and HER2-ultralow was 23% and 52%, respectively. In the HR+ subgroups the HER2-low showed a better prognosis as compared to the HER2-ultralow and HER2+ (RFS and DMFS P = 0.0048 and 0.0015, respectively) while there was no prognostic effect of HER2 expression in the HR- subgroups. Not surprisingly, an association with higher grade was demonstrated in all HR- as compared to the HR+ subgroups regardless of HER2 status. Overall, all HR- subgroups showed a higher involvement of immune genes as compared to the three HR+ subgroups. Of interest, HER2-low (HR+ and HR-) and HR-/HER2+ showed a significant overlap expression of immune signatures (71%). While the HR+/HER2-ultralow and HR+/HER2+ displayed minimal activation of immune pathways, the HR-/HER2-ultralow was the group most significantly associated with the activation of immune signaling including IFN signaling (67% percent of genes in the panel with altered expression), T cell active cytokines (34% of genes hit), and cytotoxic effector molecules (48% of genes hit). Conclusions. Our study supports a further molecular stratification of breast cancer based on HER2 status. The different tumor-immune background of these BC subgroups highlights that selected patient cohorts may derive benefit from targeted immunotherapy.

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Detection of high-risk patients resistant to CDK4/6 inhibitors with hormone receptor-positive HER2-negative breast cancer in Japan

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(Background) Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) improve the prognosis of hormone receptor-positive HER2-negative breast cancer (HR+/HER2- BC) by approximately 5 years. However, some patients show resistance to CDK4/6i and have poor prognosis. Thus, predicting resistance in patients is important. Although PAM50 is a strong tool for predicting late recurrence risk in HR+/HER2- BC by analyzing gene expression signatures, it is not always available. The non-luminal disease score (NOLUS), developed as an approximate formula for PAM50, is a pathology-based subtyping assay used to predict non-luminal disease using immunohistochemical analysis (Pascual et al. Front Oncol, 2021). (Materials & Methods) This multicenter, retrospective observational study was approved by the central ethics committee of Gifu University. From December 2017 to December 2021, real-world data of patients with metastatic HR+/HER2- BC who received CDK4/6i therapy were collected from 11 institutes in Japan. Data were obtained for patients who received CDK4/6i, such as palbociclib (PAL) or abemaciclib (ABE), as the first- or second-line endocrine therapy. The association between the efficacy of CDK4/6i and NOLUS was investigated by evaluating pathological and clinical data, including progression-free survival (PFS) and overall survival (OS). Pathological data, including the expression levels of ER, PgR, HER2, and Ki67, were evaluated according to the ASCO/CAP guidelines by experienced pathologists in each institute using either primary or metastatic tumors. PFS was defined as the period from the 1) starting date of combination therapy to progressive disease (PD); 2) the starting date of combination therapy to PD when CDK4/6i was interrupted due to adverse events or patients’ preference; and 3) the starting date of endocrine monotherapy to PD when CDK4/6i was added. NOLUS was calculated using the formula: NOLUS (0-100) = \[ -0.45 \times \text{ER}\% - 0.28 \times \text{PR}\% + 0.27 \times \text{Ki67}\% + 73 \] and the patients were divided into two groups, NOLUS(+) [≥ 51.38, non-luminal disease] and NOLUS(−) [< 51.38, luminal disease]. The expression rates (%) in NOLUS(+) and NOLUS(−) were, respectively, 28.2 ± 19.4 and 89.0 ± 11.3 for ER (p < 0.001); 6.3 ± 15.9 and 44.3 ± 37.9 for PgR (p < 0.001); and 42.5 ± 23.8 and 26.9 ± 19.1 for Ki67 (p < 0.001). The expressions of HER2 (score 0, 1, 2, and ISH-negative, 3) were 42.9%, 28.6%, 28.6%, and 0% for NOLUS(+); and 30.8%, 51.7%, 17.5%, and 0.4% for NOLUS(−) groups. PFSs for 6M and 1y were 71.4% and 30.5% for NOLUS(+), 85.2% and 66.6% for NOLUS(−) (HR, 3.15; 95%CI: 2.02-4.93; p < 0.001). OS for 6M and 1y were 92.6% and 92.6% for NOLUS(+), and 97.7% and 93.8% for NOLUS(−) (HR, 3.01; 95%CI: 1.48-6.09, p = 0.001). NOLUS(−) patients showed statistically better PFS with first-line therapy than with second-line therapy. However, NOLUS(+) patients showed no prognostic difference between the first and second therapeutic lines, suggesting CDK4/6i inefficacy. (Conclusion) CDK4/6i efficacy and prognosis were significantly different between NOLUS(+) and NOLUS(−) resistance and help select a better therapeutic approach to overcome resistance.

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Constitutively active HER2 signaling, e蒙古ucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) modulation of tumor microenvironment and breast cancer response to neoadjuvant therapy.

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Background - Clinical use of anti-HER2 agents has demonstrated the importance of engaging HER2-specific immune responses for anti-tumor efficacy. Co-existence of full-length HER2 with its altered isoforms increases the heterogeneity of HER2-positive breast cancer. Yet, the molecular underpinnings involved in the interplay between constitutively active HER2-signaling and microenvironment and their clinical value are largely unexplored. Material and methods - Transgenic mouse models expressing either HER2 or its variant HER2 Δ16 in the mammary epithelium in a doxycycline inducible fashion were generated to evaluate the role each variant contributes to mammary tumorigenesis. HER2Δ16 determinants were sought in human primary tumor using gene expression profile (Clariom S, ThermoFisher) of baseline biopsies of HER2-positive breast cancer patients treated with lapatinib, trastuzumab or their combination plus chemotherapy in the NeoALTTO study. Univariate and multivariable logistic and Cox regression models were used to assess the associations with pathological complete response (pCR) and event free survival (EFS), respectively. We used Kruskal-Wallis test to evaluate the associations between continuous and categorical variables and Spearman’s correlation coefficient (r) for continuous variables. Results - In our model, HER2Δ16 driven tumors exhibit an immune cold phenotype, and express elevated levels of ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1). ENPP1 was shown to negatively regulate the stimulator of interferon genes activation and inflammatory cytokine expression. We further validated the correlation between ENPP1 and cytokine expression in several human datasets. A total of 180 NeoALTTO patients, including 51 (28%) with pCR and 53 (29%) EFS events, were analyzed. A positive correlation was observed between gene expression of ENPP1 and HER2 (r= 0.26, 95%CI 0.12;0.39) and HER2Δ16 metagene (r= 0.33, 95%CI 0.19;0.45). ENPP1 was higher in estrogen receptor (ER)-positive compared with ER-negative tumors (p= 0.03). ENPP1 was directly related with M2 macrophage abundance in ER-positive (r=0.31, 95%CI 0.11;0.49), and inversely related with CD8 (r=-0.32, 95%CI -0.49;-0.12) and CD4 T (r=-
0.34, 95%CI 0.51;-0.14) in ER-negative tumors. No significant correlation was found for any of the 5 immune-related metagene tested (hemopoietic cell kinase, lymphocyte-specific kinase, Interferon, MHCII, and STAT1). ENPP1 had no predictive value overall as well as within treatment arm. Although the interaction between ENPP1 and ER status was not significant at a alpha level of 0.05 (p-
with pCR in ER-positive (odds ratio [OR] = 2.6, 95%CI 1.05;6.34) but not in ER-negative tumors (OR= 1.09, 95%CI 0.69;1.73). Notably, a similar result was retained by implementing a multivariate model including ENPP1 with clinical variables, immune cell populations and the first order interaction term between ENPP1 and ER status. For EFS, ENPP1 had no significant prognostic value overall (Hazard ratio [HR] 0.85, 95%CI 0.64;1.14), neither according to ER-status, HR 0.70 (95%CI 0.45;1.08) in ER-positive and 0.98 (95%CI 0.65;1.46) in ER-negative cases. Conclusion - ENPP1 is a functional regulator of immune cold microenvironment in breast cancer models with constitutively active HER2 signaling. Primary tumors featuring ENPP1 expression are likely to exhibit an immune profile characterized by a depletion of T cells and an enrichment of M2 macrophages in ER-negative and -positive, respectively, and respond differently to treatments according to ER status. These findings support ENPP1 as an exploitable predictive biomarker and a new target for targeted therapeutic strategies in HER2-positive breast cancer.

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Cell-free DNA detection of GATA3 mutations in metastatic hormone receptor positive breast cancer: a retrospective, observational multi-institutional analysis

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Background GATA3 mutations (GATA3mut) have been reported in 10-20% of hormone receptor positive (HR+) breast cancers. It has been shown that targeting GATA3mut HR+ breast cancer with MDM2 inhibitors invokes synthetic lethality. MDM2 is an E3 ubiquitin ligase that targets p53 for degradation, and research suggests that restoring p53 by blocking MDM2 may be effective in treating GATA3mut HR+ breast cancer. One potential mechanism of this efficacy has been shown to be through the PI3K-AKT pathway. We thus sought to characterize the GATA3mut landscape in a multi-institutional cell-free DNA (cfDNA) analysis and to determine the association between GATA3mut and TP53 mutations, as well as alterations in the PI3K-AKT pathway and the impact of GATA3 on survival. Methods We analyzed cfDNA data collected at the Massachusetts General Hospital and at Washington University in St Louis via Guardant360, a next generation sequencing assay that analyzed up to 74 genes during the study period. The association of GATA3mut and co-mutations as well as number of prior therapies was estimated using Pearson’s chi-squared test for categorical variables, two-sample Wilcoxon rank-sum test for continues variables, and multivariable logistic regression. The impact of GATA3mut and GATA3 wildtype (WT) on progression-free survival (PFS) and overall survival (OS) was analyzed using multivariable Cox regression analysis, adjusting for age, number of prior therapies, visceral metastases, and de novo metastases. Results Out of 647 patients with HR+ MBC, 10% (n = 68) had non-synonymous GATA3 mutations. Among these 68 GATA3mut patients, 37% (n = 25) were mutations in exon 5, all but two of which were in the second zinc finger, and 62% (n = 42) were frameshift mutations, 20% (n = 14) were indels, and 18% (n = 12) were point mutations. Median mutant allele fraction (MAF) of GATAmut was 0.95% (range 0.03 – 30.5%). There was no statistically significant association of GATA3mut with the number of prior therapies, PR status, or the presence of ESR1, TP53, or PI3K-AKT pathway mutations. In the GATA3mut population, TP53 co-mutations (n = 21) were found with a median MAF of 0.6%. PI3K-AKT pathway alterations occurred in 47% (n=32) of GATA3mut patients (PIK3CA n = 27; AKT n = 2; PTEN n = 3). In the combined cohort, there was no significant difference in PFS or OS after adjusting for visceral metastases, de novo disease, number of prior therapies, and age. In a cohort of 80 patients that received endocrine monotherapy (GATA3 WT n = 74, GATA3mut n = 6), GATA3mut were associated with borderline worse PFS (HR 2.6; p = 0.061) and worse OS (HR 4.5; p = 0.009). There was no statistically significant difference in PFS or OS in a subgroup that received chemotherapy. Conclusions GATA3 mutations can be identified via cfDNA in patients with HR+ MBC. Co-mutations in TP53 occurred at overall low MAF. Further research is needed to characterize the functional impact of these low level TP53 co-mutations and develop therapeutic strategies to target GATA3 mutant MBC.

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Biomarker associated with response to CDK4/6 inhibitors in metastatic hormone receptor positive breast cancer

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Background: In spite of widespread use and known mechanism of action, predictive biomarkers for the use of CDK4/6 inhibitors in conjunction with endocrine therapy have yet to emerge. Here a cohort of patients treated with standard-of-care combination regimens was utilized to explore features of disease and determinants of progression-free survival (PFS). Patients and Methods: In this cohort of 235 patients, >90% of patients were treated with Palbociclib in combination with either an aromatase inhibitor (AI) or fulvestrant (FUL). The PFS mirrored that observed in randomized clinical trials. A total of 151 patient tumor tissues were used for targeted gene expression analyses with the HTG-Oncology Biomarker Panel. The association of disease state and gene expression analyses were interrogated for disease evolution and association with PFS. Results: HER2 immunohistochemistry (HER20, Her21+, Her22+) was not associated with PFS in full cohort, or AI and FUL subgroup analyses. The lack of progesterone receptor (PR+, PR-), was associated with shorter PFS in the full patient cohort (p=0.012) and selectively in patients treated with AI (p=0.005), but not FUL. Gene expression-based subtyping indicated that the majority of patients, as expected, had luminal breast cancer; however, the predominant subtypes changed with treatment and disease evolution. Primary tissue from tumor resection was dominated by luminal A subtype, which diminished in the context of metastatic disease, and was rare in post-progression specimens. The luminal B, HER2, and basal subtypes exhibited shorter PFS in CDK4/6 inhibitor combinations (AI, p=0.01; FUL, p=0.03). Existing clinically developed breast cancer signatures (e.g. breast cancer index) had variable associations with PFS; however, high expression of gene signatures associated with cell cycle were broadly associated with short PFS. Concordantly, utilizing unbiased analyses, gene expression programs linked to cell cycle were associated with short PFS, while interferon response processes were associated with longer PFS. Algorithms that incorporated standard pathological and clinical variables with the gene expression data were developed that exhibited potent predictive power. Conclusions: Tumor evolution occurs on treatment with CDK4/6 inhibitors; however, analyses of pretreatment biopsies can inform the duration of PFS. These data support discrete biological processes associated with sensitivity/resistance. Predictive algorithms could be developed to inform features of treatment decision which will require prospective validation which is ongoing.

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Agnieszka Witkiewicz, n/a: No financial relationships to disclose
Quantitative analysis of fiber-level collagen features in H&E whole-slide images predicts neoadjuvant therapy response in patients with HER2+ breast cancer

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Background: Neoadjuvant treatment (NAT) combining chemotherapy and HER2-targeted agents is frequently administered to HER2-positive (HER2+) breast cancer (BC) patients, with some experiencing a pathological complete response (pCR) and others having residual disease measured by the residual cancer burden (RCB) score. Here, we use a physics-guided machine learning (ML)-based approach to extract fiber-level collagen features from hematoxylin and eosin (H&E)-stained whole slide images (WSIs) and identify collagen-related associations with treatment response in HER2+ patients receiving NAT.

Methods: Clinical data and specimens from stage II-III HER2+ BC patients enrolled on the De-escalation to Adjuvant Antibodies Post-pCR to Neoadjuvant THP (DAPHNe; NCT03716180) clinical trial and treated with neoadjuvant paclitaxel/trastuzumab/pertuzumab were analyzed. An ML-based model trained to identify regions of BC tissue as invasive carcinoma, ductal carcinoma in situ (DCIS), diffuse inflammatory infiltrate, stroma, necrosis, or normal tissue was deployed on WSIs of H&E-stained diagnostic core needle biopsies (N=89) to generate tissue overlays. Additional tissue areas were computed from the tissue model predictions using heatmap transformation, including tumor nests (continuous regions predicted as invasive nests), and bulk tumor borders (st nests). A separate ML-based model trained to identify fiber-level collagen features in WSIs of H&E-stained specimens was also deployed to generate collagen overlays. A fiber feature extraction pipeline was utilized to characterize properties of all identified collagen fibers in the WSI (on the order of hundreds of thousands per slide), including length, width, tortuosity, and angle. These fiber features were then assessed based on their position within the tumor (e.g. relative to the tumor nest border). Combinatorial features (e.g. angle of fibers with respect to tumor boundary) were then explored univariately for associations (N=609) with treatment response. Patients with pCR (RCB=0; N=53) were considered responders, while all other cases
(RCBI-III; N=36) were designated non-responders. Due to the small size of the cohort analyzed here, raw p-values are reported.

Results: Using estrogen receptor status as a clinical covariate, a logistic regression-based univariate analysis of 609 collagen-associated features revealed six features to strongly associate with pCR (p< 0.05, AUC≥0.75; Table 1). Notable feature themes were identified: 1) fiber tortuosity in tumor nest borders and tumor borders, 2) angle of fibers in tumor border with respect to tumor boundary, and 3) distribution patterns of fiber width in tumor nest borders. The presence of fibers perpendicular to tumor boundary tangents was negatively associated with pCR, as was higher fiber tortuosity and thickness in tumor nest borders.

Conclusions: Improved prediction of response to NAT in patients with BC is needed to determine appropriate treatment strategies for each patient. Here, using ML-based models to identify tissue features and collagen fibers, we identify collagen-associated features, measured directly from WSIs of H&E-stained diagnostic BC biopsies, that negatively correlate with pCR. Additional development of this strategy, including the addition of cell identification models and known clinical information, is underway to further refine this novel predictive model.

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<th>AUC</th>
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<td>0.78</td>
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In-silico approaches that detect immune contexture to trastuzumab response in neo-adjuvant studies

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Introduction: Computational approaches have aided in estimating cellular composition of the tumour microenvironment. The evaluation of immune composition in tumours before treatment may predict pathologic complete response (pCR). The aim of the study was to perform a meta-analysis of HER2-positive breast cancer subjects who received neoadjuvant trastuzumab to detect associations between immune cells measured by CIBERSORT and ESTIMATE and pCR. Methods: PubMed was used to identify transcriptomic data of HER2-positive breast cancer patients who received neoadjuvant trastuzumab. Baseline data from eight neoadjuvant studies (N=338) was downloaded from GEO. Data from each study was background corrected and quantile normalised using 'limma' or 'oligo' packages in R. Immune profiles per sample was generated using computational softwares CIBERSORT and ESTIMATE, and were then linked to pCR status. Correlations between immune contexture and pCR for each study were interpreted using statistical testing. Meta-analysis by a logistic regression model was conducted on studies which passed assumptions to identify CIBERSORT immune subsets robust to pCR. Results: CIBERSORT results showed that three studies had reduced T follicular helper cells (Tfh) (Brodsky p=0.38, CHER-LOB p=0.17, TransNOAH p=0.25) and two studies had reduced plasma cells (CHER-LOB p=0.15, Brodsky p=0.38) in the pCR group, but was not significant after multiple correction. ESTIMATE analysis showed that data from two studies had elevated immune infiltration in pCR (Brodsky p=0.19, CHER-LOB p=0.10) but was not significant. A meta-analysis of pooled data from four studies (TRIO-US B07, 03-311, TransNOAH, CHER-LOB) showed that low Tfh (p=0.053, OR=0.04, CI [0.0012-0.99]) and high memory B-cells (p=0.008, OR=2126.9, CI [8.12-7.65x10+5]) prior to trastuzumab treatment may be associated with a better chance of achieving pCR. Conclusion: Results from our meta-analysis proposed that memory B- and T follicular helper subsets may predict a role in achieving pCR. Incorporating studies with larger sample cohorts such as the CALGB-40601 (N=265) study can achieve statistical power of this analysis.

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Dalal AlSultan, BSc, MSc: No financial relationships to disclose
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Immune cell profile of tumors from patients with metastatic (met) HER2+ breast cancer (BC) with < 30 months overall survival (OS).

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Background: The “Thousand Patient HER-2 database” project at Saint Vincent’s University Hospital (SVUH) Dublin has been used to identify HER2+ BC patients with durable complete response (never relapsed) to trastuzumab-based therapy. ~10% of met HER2+ BC patients achieve a durable complete response to trastuzumab, meaning the majority of patients progress on treatment. Higher stromal tumour immune infiltrate has been associated with longer OS in met HER2+ BC. There is limited tumor immune profile and PD-1 expression data available for patients with met HER2+ BC with short OS. Using the SVUH database, we have identified a preliminary cohort of 21 met HER2+ BC patients that received trastuzumab and had an OS < 30 months. This study examines the levels of pan T cell marker CD3, cytotoxic T cell marker CD8, Natural Killer (NK) cell marker CD56 and immune checkpoint PD-1 by immunohistochemistry (IHC) in this preliminary cohort. Methods: Formalin-fixed, paraffin-embedded (FFPE) biopsy specimens (n=21 primary, n=7 matched metastatic biopsies) and associated clinico-pathological data were curated. Tumor biopsies were processed for IHC staining of CD8 (Agilent IR62361-2), CD3 (Agilent IR50361-2), CD56 (Agilent IR62861-2) and PD-1 (Roche 07099029001). PD-1 staining was available for 20/21 samples. Staining was performed using the DAKO Link 48 Autostainer as per the manufacturer’s instructions using positive (tonsil tissue) and negative controls (isotype controls). Slides were processed using the Aperio AT2 Digital Slide Scanner (Leica Biosystems), reviewed using Aperio ImageScope 12.4 annotated to outline tumor areas and an algorithm was trained to identify cells and classify them as either tumor or stromal. Data was expressed as number of positively stained cells/mm2 breast tumor or stromal tissue. Survival studies utilized the Kaplan Meier method. The paired Student’s T test was utilized for primary vs metastatic site comparisons. Results: Designating samples with > 1 stained cell/mm2 breast tumor as positive (pos) and zero stained cells as negative (neg), 19/21 (90.5%) primary samples were pos for CD3, 15/21 (71.4%) for CD56, 14/21 (66.6%) for CD8, and 10/20 (50%) for PD-1. Within the stromal compartment, 20/21 (95.2%) primary samples were pos for CD8, 18/21 (85.7%) for CD56, 16/21 (76.2%) for CD3 and 8/20 (40%) for PD-1. PD-1 expression in the primary tumor (median OS PD-1pos 7.85 mo vs PD-1neg 5.39 mo, hazard ratio (HR) 0.642 (95% CI 0.256-1.613), p=0.346) or the stroma (median OS PD-1pos 8.84 mo vs PD-1neg 5.39 mo, HR 0.495 (95% CI 0.197-1.244), p=0.135) was not significantly associated with OS. When comparing matched primary and metastatic samples (n=7), increased stromal levels of CD3 (4/7), CD8 (4/7), CD56 (5/7) and PD-1 (4/7) were observed. Increased levels of CD3 and CD8 were observed for 2/7 samples, and increased levels of CD56 and PD-1 for 4/7 samples. With the exception of tumor CD8 levels which decreased, mean values for tumor and stromal CD3, CD56, PD-1 and stromal CD8 levels were higher in metastatic sites but all differences were not found to be significant (p>0.05). Conclusions: Our results suggest that met HER2+ BC patients with < 30 months OS have significant T cell and NK cell presence in the tumor and stromal compartments in both primary and metastatic sites. Further expansion of this limited dataset is planned to gain greater insight in to the immune cell profiles and PD-1 status of met HER2+ BC patients with short OS.

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Prognostic relevance of PD-L1 expression on circulating tumor cells in metastatic breast cancer patients treated with anti-PD-1 immunotherapy

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Rationale: Breast cancer has become the leading cause of cancer mortality in women. Although immune checkpoint inhibitors targeting programmed death-1 (PD-1) are promising, it remains unclear whether PD-L1 expression on circulating tumor cells (CTCs) has predictive and prognostic values in predict and stratify metastatic breast cancer (MBC) patients who can benefit from anti-PD-1 immunotherapy. Methods: Twenty six MBC patients that received anti-PD-1 immunotherapy were enrolled in this study. The peptide-based Pep@MNPs method was used to isolate and enumerate CTCs from 2.0 ml of peripheral venous blood. The expression of PD-L1 on CTCs was evaluated by an established immunoscoring system categorizing into four classes (negative, low, medium, and high). Results: Our data showed that 92.3% (24/26) of patients had CTCs, 83.3% (20/26) of patients had PD-L1-positive CTCs, and 65.4% (17/26) of patients had PD-L1-high CTCs. We revealed that the clinical benefit rate (CBR) of patients with a cut-off value of ≥ 35% PD-L1-high CTCs (66.6%) was higher than the others (29.4%). We indicated that PD-L1 expression on CTCs from MBC patients treated with anti-PD-1 monotherapy was dynamic. We demonstrated that MBC patients with a cut-off value of < 35% PD-L1-high CTCs had longer PFS (P< 0.05) and OS (P< 0.01) compared with patients with a cut-off value of < 35% PD-L1-high CTCs. Conclusion: Our findings suggested that PD-L1 expression on CTCs could predict the therapeutic response and clinical outcomes, providing a valuable predictive and prognostic biomarker for patients treated with anti-PD-1 immunotherapy.

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Yanlian Yang, n/a: No financial relationships to disclose
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TRK inhibitor in a patient with metastatic triple negative breast cancer and NTRK fusions identified via cell-free DNA analysis.

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Introduction: Tissue-agnostic indications for targeted therapies are expanding options for patients with advanced solid tumors. The FDA approvals of the PD-1 inhibitor pembrolizumab and the TRK inhibitors larotrectinib and entrectinib provide rationale for next generation sequencing (NGS) in effectively all advanced solid tumor patients, as findings may indicate targeted therapy even in disease that may seem otherwise refractory. Here, we present the case of a post-menopausal woman with metastatic triple negative breast cancer (TNBC) who had disease progression on multiple lines of therapy prior to the identification of two actionable NTRK mutations, identified via cell-free DNA (cfDNA) and tissue-based NGS. She was subsequently started on the TRK inhibitor larotrectinib and had a marked clinical response.

Case Presentation: A 64-year-old woman presented with metastatic TNBC five years after being treated for a localized breast cancer. The cancer rapidly progressed through 4 lines of therapy in the metastatic setting, including immunotherapy [atezolizumab/nab-paclitaxel (progression after 5 months)], antibody-drug conjugate-based therapy [sacituzumab govitecan (progression after 2 months)], and chemotherapy [gemcitabine/carboplatin (progression after 3 months), eribulin (progression after 2 months)]. Her CA 15-3 had also been consistently increasing to a peak of 206 IU/mL. Germline genetic testing was negative. Ultimately, NGS evaluation of cfDNA via an 83-gene assay (Guardant Health, Inc.) identified two NTRK3 fusions: an ETV6-NTRK3 fusion [mutant allele fraction (MAF) = 10.9%] associated with the rare secretory breast carcinoma, and CRTC3-NTRK3 (MAF = 3.2%), a fusion partner previously undescribed in breast cancer. Liver biopsy was sent for whole exome sequencing and RNA-seq analysis (BostonGene, Inc), which provided orthogonal confirmation of both the ETV6-NTRK3 and CRTC3-NTRK3 fusions. Review of the tumor pathology showed invasive ductal carcinoma with secretory features; this pathology and the ETV6-NTRK3 fusion were consistent with a diagnosis of secretory breast carcinoma. She was started on the TRK inhibitor larotrectinib, and she had a significant clinical and radiographic response after only two months of therapy.

Recheck of her CA 15-3 showed a decrease to 48 IU/mL, the lowest level in our records. Repeat cfDNA testing showed a decrease of the ETV6-NTRK3 fusion to MAF 0.40% and the CRTC3-NTRK3 fusion to MAF 0.07%. The patient took larotrectinib for 7 months with good disease control. Unfortunately, unrelated to her therapy, she had experienced multiple fractures secondary to her existing osseous metastases, and these led to significant morbidity. She and her family elected to transition to comfort measures, after which she passed away. Discussion: In the presented case, the identification of NTRK fusions by plasma-based genotyping resulted in matched selection of genotype-directed therapy, and this otherwise refractory TNBC exhibited marked response to targeted therapy. While TNBC had historically been considered a subtype of breast cancer without targetable options, the expanding roles of NGS testing and targeted therapies are changing the paradigm. The actionability of rare genomic events such as NTRK fusions makes identifying them critical for individual patients, particularly in heterogeneous diseases such as TNBC. Tissue-agnostic targeted therapies now give reason for NGS testing in most solid tumors, as reflected in updated consensus guidelines. This case demonstrates the significant potential benefits of NGS testing in advanced and refractory cancers.

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Identification of mechanisms of acquired resistance to ribociclib plus endocrine therapy using baseline and end-of-treatment circulating tumor DNA samples in the MONALEESA-2, -3, and -7 trials

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Background: Genetic alterations that contribute to resistance to therapy may be acquired during previous pooled analysis of circulating tumor DNA (ctDNA) in MONALEESA (ML)-2, -3, and -7 identified potential predictive biomarkers for response and resistance to ribociclib (RIB) at baseline (BL). Here, we describe an analysis of paired BL and end of treatment (EOT) samples from ML-2, -3, and -7 to identify acquired mechanisms that may impact resistance to RIB + endocrine therapy (ET) vs placebo (PBO) + ET. Methods: ML-2 (NCT01958021), ML-3 (NCT02422615), and ML-7 (NCT02278120) evaluated efficacy and safety of RIB + ET vs PBO + ET in pre- and postmenopausal patients -line (1L) and second-line (2L) settings. Plasma samples were collected at cycle 1 day 1 (C1D1; prior to first therapy exposure) and at EOT (± 28 days of recorded progression). ctDNA was sequenced using a targeted next-generation regardless of their frequency at BL, were included. Tumor mutational burden (TMB) was assessed by tx arm; a TMB cutoff of 10 mutations/MB was used to categorize pts as TMB high vs low. To assess differences in the presence of alterations, a McNemar test was performed on paired samples and adjusted (adj) for multiple testing using the false discovery rate (FDR). A Bayesian mixed effects model was used to account for ctDNA fraction and trial and to test for tx-specific resistance by including a tx × visit interaction term. Results: A total of 905 paired samples from ML-2, -3, and -7 were included in this analysis, 441 and 464 samples from pts treated with RIB + ET and PBO + ET, respectively. Overall, 17 genes had an alteration frequency of >5% at EOT. The ctDNA fraction was higher at EOT vs C1D1 in both the RIB (P=.037) and PBO (P=.033) arms. The frequency of alterations in RB1 (10.4% vs 2.0%), ATM (11.3% vs 8.4%), FAT1 (4.8% vs 3.0%), and FAT3 (5.0% vs 2.5%) was higher at EOT vs C1D1 in the RIB arm (FDR-adj P<.10). Alterations in ESR1 were also higher at EOT vs C1D1 in both the RIB (26.3% vs 9.1%) and PBO arms (28.9% vs 5.4%) (FDR-adj P<.0001). Conversely, alterations in GATA3 were higher at EOT in the PBO arm (FDR-adj P=.11). These results were consistent after adjusting for ctDNA fraction. The most common ESR1 mutations were D538G, nd L536H/P/R. Tx × visit interaction effects were observed for RB1 in the RIB arm and GATA3 in the PBO arm, suggesting tx-specific resistance. A tx × visit interaction for ESR1 was also observed, suggesting a larger relative increase in ESR1 mutations with PBO vs RIB. The percentage of pts with high TMB (>10) at EOT increased from 1.1% to 5.7% in the RIB arm and from 1.7% to 3% in the PBO arm. After accounting for ctDNA
fraction and trial, a larger numerical increase in TMB was observed for RIB (odds ratio [OR], 9.0; 95% CI, 2.9-32.7) vs PBO (OR, 2.1; 95% CI, 0.7-6.5); however, the model did not support a differential tx effect. Conclusions: This comprehensive analysis of pooled samples from ML-2, -3, and -7 identified acquired gene alterations in pts with H2L RIB + ET or PBO + ET. The frequency of several genes known to contribute to resistance (ESR1, RB1, ATM, FAT1, and FAT3) was higher at EOT vs C1D1 in pts treated with RIB + ET, while ESR1 and GATA3 alterations were higher at EOT vs C1D1 in pts treated with PBO + ET.

CDK4/6 inhibitor and ET is the largest to date and could be used to validate and confirm acquired resistance mechanisms with low alteration frequency.

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WITHDRAWN
SPEN is a biomarker for CDK4/6 inhibitor resistance in patients with metastatic hormone receptor positive (HR+)/HER2- breast cancer

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Background: Despite significant improvements in the treatment of breast cancer (BC), metastatic disease remains the principal cause of BC-related death. Through analysis of rapid autopsy collected biospecimens, we have previously identified Split Ends (SPEN) alterations in patients with metastatic HR+/HER2- BC (Savas et al. 2016). The role of SPEN in BC is poorly defined. Here we aimed to further explore the function of this gene in metastatic HR+/HER2-metastatic BC (mBC). Methods: We explored the clinical and genomic characteristics of SPEN altered mBC in human sequencing datasets. We created a model of SPEN loss using a gene knockdown (KD) via siRNA in MCF7 cells. Flow cytometry and western blot analysis was utilized to investigate the molecular impact of SPEN loss. The KD and non-targeting control cells were then subjected to a high throughput kinase inhibitor screen (n=480 compounds) to identify sensitive and resistant therapeutics. Finally, we used an in-house metastatic HR+/HER2- BC patient cohort treated with CDK (cyclin-dependent kinase) 4/6 inhibitors to validate SPEN loss as a marker of resistance. Results: Using a cohort of 7519 BC samples, SPEN alterations (mutation and copy number deletions) were found to be significantly enriched in HR+ mBC vs primary HR+ disease (29% vs 7%, respectively p< 0.0001). SPEN altered compared with SPEN wild type (WT) HR+ mBCs were significantly associated with higher tumor mutational burden (median 4.6 vs 1.7, p < 0.0001), more large-scale transitions (median 20 vs 14, p= 0.006), increased fraction of genome altered (52% vs 35%, p< 0.0001), and enrichment of APOBEC-induced mutations (65% vs 42%, p=0.004) respectively. Taken together, these results suggest greater genomic instability in patients with tumors with SPEN loss compared with WT. This hypothesis was further supported when SPEN KD cells showed staining (p=0.03) compared with control cells. In a kinase inhibitor compound screen, SPEN KD cells displayed significant resistance to the CDK4/6 inhibitor palbociclib (p< 0.0001) compared with WT cells. We validated this finding in vitro by demonstrating SPEN KD cell resistance to other CDK4/6 inhibitors ribociclib and abemaciclib (p= 0.02 and 0.0004 respectively). In our in-house cohort of 56 patients with HR+ mBC treated with CDK4/6 inhibitors, we found that the HR+ mBC patients with a SPEN alteration have significantly decreased overall survival (OS) compared with WT patients, (median OS 34 months vs not reached, respectively; HR 3.18, 95%CI 0.94-10.73, p=0.049). Conclusion: These results provide the first clinical evidence that SPEN alterations are enriched in HR+ mBC. Additionally, SPEN may be a biomarker for CDK4/6 inhibitor resistance in this subtype. These results warrant further analysis into the role of SPEN in BC and its relevance in clinical management. Reference: Savas P, Teo ZL, Lefevre C, et al. The subclonal architecture of metastatic breast cancer: Results from a prospective community-based rapid autopsy program "cascade". PLoS medicine 2016;13:e1002204.

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Prognostic and predictive role of RBsig and CCNE1/RB1 gene-expression signatures in patients with advanced breast cancer treated with palbociclib in combination with endocrine therapy in the PALOMA-2 and 3 trials

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Background: We have previously identified two potentially predictive signatures of palbociclib resistance: the RBsig, composed of E2F1/E2F2 dependent genes, which is correlated with genetic loss of RB1, and the ratio between the gene expression levels of CCNE1 to RB1 (CCNE1/RB1). Both signatures have been previously tested in vitro and in neoadjuvant studies with palbociclib. The present analysis aims to explore the prognostic and predictive role of RBsig and CCNE1/RB1 in the pivotal phase III randomized trials PALOMA-2 and PALOMA-3.

Materials and methods: Gene expression data from the PALOMA-2 and PALOMA-3 datasets were generated using the HTG EdgeSeq Oncology BM Panel, as previously described. Of the 87 genes composing RBsig, 46 were available within the EdgeSeq dataset and were used for the analyses; CCNE1 and RB1 were both available. RBsig was calculated as the mean of the Z-score scaled gene expression (log) of the 46 genes; CCNE1/RB1 was computed as the log ratio between the mRNA expression of CCNE1 and RB1. High and low values of RBsig and CCNE1/RB1 were defined based on the third quartile (Q3) as cutoff or as continuous variables. The prognostic/predictive effect of the signatures in terms of PFS was tested using Cox proportional hazard models and the Wald test.

Results: The 46-genes RBsig versus the original signature showed excellent correlation in the METABRIC dataset (R=0.99), confirming its reliability as a surrogate of the original RBsig using EdgeSeq data. In both PALOMA-2 and PALOMA-3, RBsig high was significantly associated with a worse outcome compared to RBsig low in the palbociclib arm but not in the control arm [PALOMA-2: HR 1.4 (95% CI 1.0, 2.0) p=0.029 for palbociclib arm; HR 1.1 (95% CI 0.7, 1.6) p=0.71 for control arm. PALOMA-3: HR 1.7 (95% CI 1.1, 2.6) p=0.01 for palbociclib arm; HR 1.2 (95% CI 0.7, 1.9) p= 0.49 for control arm]. However, in both studies RBsig was not predictive of palbociclib resistance both when considered as a continuous variable and when dichotomized at Q3. Similarly to RBsig, in PALOMA-3 patients with CCNE1/RB1 high tumors treated in the palbociclib arm showed a significantly worse outcome compared to those with CCNE1/RB1 low but this effect was not observed in those treated in the control arm [HR 1.6 (95% CI 1.1- 2.5) p= 0.03 for palbociclib arm; HR 1.2 (95% CI 0.7, 1.9) p=0.5 for control arm]. In addition, CCNE1/RB1 as a continuous variable was predictive of palbociclib benefit in PALOMA-3 (interaction p= 0.047). These effects were not observed in PALOMA-2. Conclusions: RBsig is a prognostic biomarker in patients treated with palbociclib, suggesting it may help in patients’ risk stratification. CCNE1/RB1 is predictive of palbociclib benefit in PALOMA-3, but not in PALOMA-2 probably due to the different patient populations and characteristics. Further studies of these biomarkers in patients treated with CDK4/6 inhibitors in the metastatic as well in the adjuvant setting are warranted.

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HER2 status and response to neoadjuvant anti-HER2 treatment among patients with breast cancer and Li-Fraumeni syndrome

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Background: Breast cancer (BC) is the most common tumor in women with Li-Fraumeni syndrome (LFS), with a cumulative incidence of 85% by the age of 60 years. However, LFS-related BC characteristics are still underexplored since most data derive from small
retrospective cohorts. A variable enrichment in HER2-positivity (ranging from 34 to 80%) has been reported, but information regarding the response to anti-HER2 treatments are currently lacking. Moreover, data regarding the new emerging category of HER2-low are missing.

Methods: Invasive BCs diagnosed in patients (pts) with TP53 germline pathogenic/likely pathogenic variant between 2002-2022 at Institut Gustave Roussy (France), Dana-Farber Cancer Institute (USA) and Hospital Sírio-Libanês (Brazil) were included. HER2 and hormone receptor (HR) expression were retrospectively retrieved from pathology records and evaluated according to ASCO/CAP recommendations in place at the time of diagnosis. HER2-positive cases were defined by an immunohistochemistry (IHC) score of 3+ and/or HER2 gene amplification by ISH; HER2-negative cases were classified as HER2-low (IHC 1+ or 2+ with negative ISH assay) or HER2-zero (IHC score 0). Pathologic complete response (pCR) was defined as ypT0/is and ypN0. Results: Among 197 invasive BCs identified in a total of 176 pts, 50.3% (n=99) were HER-positive. Among those, median age at BC diagnosis was 33 years (range 21-61) and the most frequent TP53 variants were missense mutations (n=68), affecting the DNA-binding domain in 70.6% of cases and the tetramerization domain in 29.4% of cases. Most BCs were invasive ductal carcinoma (n=90), with histologic grade 3 in 56.6% of cases. At diagnosis, most pts had early stage disease (34.3% stage I; 32.3% stage II; 21.2% stage III), while 6 pts presented de novo stage IV disease. Most tumors were HR-positive (76.8%, n=76), while 23.2% were HR-negative. 38 patients with HER2-positive BCs were treated with neoadjuvant therapy, 32 cases had post-neoadjuvant pathology reports available for pathological response classification. Among those, 26 (81.2%) were HR-positive and 6 (18.8%) HR-negative. Among pts with neoadjuvant treatment data, 87.1% received trastuzumab, which was combined with pertuzumab in 43.3% of cases; chemotherapy regimens included taxanes in all pts, anthracycline in 43.3% and platinum in 16.7%. 71.9% (n=23) of pts reached a pCR (69.2% among HR-positive and 83.3% among HR-negative), while 9 (28.1%) had residual disease; pCR rate was 82.4% among pts treated with an anthracycline-free regimen. At a median follow-up of 36 months, only one patient relapsed. Among HER2-negative BCs with available IHC score and ISH for HER2-low classification (n=85), 28 (32.9%) were HER2-zero. Conclusions: In this first report of treatment results in BC pts with LFS, enrichment of HER2-positive BCs was confirmed and a remarkable pCR rate was observed with neoadjuvant treatment. Our findings require validation in a larger cohort, which is in progress. Collaborative efforts are essential for high quality data about BC treatment in this subgroup of pts.

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ctDNA as dynamic marker of response to fulvestrant and everolimus in CDK4/6 inhibitor-pretreated ER+ HER2- metastatic breast cancer patients: a prospective study.

Background
The combination of fulvestrant with everolimus is recognized by NCCN and ESMO guidelines as a valid second line treatment option for ER+ HER2- metastatic breast cancer (mBC), upon
progression on CDK4/6 inhibitor. The underlying evidence consists in a single randomized phase 2 trial (PrE0102, JCO 2018), in which N=66 patients allocated to fulvestrant and everolimus achieved a median PFS of 10.3 months (95%CI [7.6-13.8]). However, none of PrE0102 patients were pre-treated with CDK4/6 inhibitors. We set up a prospective study to document the PFS achieved by fulvestrant and everolimus in the pre-treated patients and investigated the clinical validity of ctDNA early changes as pharmacodynamic marker. Methods Eligible patients had ER+ HER2- mBC and had to be pre-treated by CDK4/6 inhibitor. Upon the signature of informed consent, patients were enrolled in the prospective observational ALCINA study (NCT02866149) and had their blood drawn at baseline (prior to treatment start), after 1 month on treatment, at first radiological assessment (3-4 months) and at disease progression. DNA from archived tumor tissue sample (or, when missing, from plasma obtained at baseline) was subjected to a large panel next generation sequencing. ctDNA levels were then assessed on the matched serial plasma samples by targeting the identified somatic mutation(s) with droplet digital PCR (ddPCR). Associations between clinico-pathological characteristics, ctDNA levels and prospectively registered patient outcomes (PFS and OS) were then analyzed.

Results Fifty-seven patients have been included, with a median age of 56.8 years. N=30 patients had visceral metastases. Most patients (N=48, 84.2%) had only one prior line of treatment in the metastatic setting. After a median follow-up of 17.7 months, the median PFS was 6.9 months (95%CI[5.3-10.7]) and the median OS was 38.3 months (95%CI[26.9-NA]). The ORR was 33.3% (N=19 PR, no CR) whereas N=22 (38.6%) patients had a stable disease at best response. In the subgroup of N=22 (38.6%) patients with somatic PIK3CA mutations, median PFS was 3.1 months (95%CI[2.87-10.9]), while median OS was not reached. In multivariate analysis, somatic PIK3CA mutation was associated with a trend toward a shorter PFS (HR=1.84, 95%CI[0.97-3.99], p=0.06) and OS (HR=2.23, 95%CI[0.88-5.69], p=0.09). Duration of CDK4/6 inhibitor treatment had no overt impact on PFS (HR=0.68, 95%CI[0.38-1.22], p=0.2). Ten (19.6%) patients discontinued everolimus due to toxicity and 17 (29.9%) had at least one dose reduction due to an adverse event. The most grade 3 adverse event were mucositis (10.5%) and hypertriglyceridemia (3.5%), only 1 patient had a grade 3 pneumopathy. At least one mutation trackable by ddPCR was found in N=48 patients. As of July 2022, ctDNA levels have been analyzed in 34 patients (PIK3CAmut: N=19; ESR1mut: N=6; TP53mut: N=4; AKTmut: N=2; CUX1mut: N=1; GATA3mut: N=1; PTENmut: N=1). At baseline, N=26/34 patients (76.5%) of patients had detectable ctDNA levels. Baseline ctDNA positivity had no prognostic impact on PFS (HR=0.93, 95%CI[0.4-2.13], p=0.86). ctDNA monitoring in the whole cohort will be available for the congress. Conclusion To our knowledge, this is the first prospective study to evaluate the efficacy of fulvestrant-everolimus after progression on CDK4/6 inhibitor. Efficacy data on 57 patients shows that fulvestrant-everolimus is an active regimen in this population. The PFS observed under fulvestrant-everolimus in patients with PIK3CA-mutant mBC appears shorter than previously reported with alpelisib in the BYLIEVE study. Results of ctDNA to monitor the individual response to therapy will be presented at the congress.

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Correlative and longitudinal transcriptomic profiling predicts patient outcomes and the efficacy of neoadjuvant HER2-targeted treatments in the randomized PREDIX HER2 trial

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Background: The PREDIX HER2 trial compared standard neoadjuvant therapy with 6 cycles of docetaxel, trastuzumab, and pertuzumab (DTP), versus 6 cycles of trastuzumab emtansine (T-DM1) in 197 patients with HER2-positive breast cancer. There was no difference in pathologic...
complete response (pCR) rate and event-free survival (EFS) between the two treatments (Hatschek, JAMA Oncology 2021). Here we systematically evaluate the prognostic and predictive molecular biomarkers during neoadjuvant HER2-targeting therapy. Methods: Longitudinal fresh-frozen tissue biopsies (pretreatment (n=194) and after 2 cycles (n=167)) and surgical specimens (n=126) were collected and sequenced by RNA-sequencing (RNA-seq). Differential gene expression (DGE) analyses were conducted using zero-inflated negative binomial mixed model, and P-values were adjusted by the Benjamini-Hochberg method. Potential prognostic and predictive markers including PAM50 intrinsic subtype, cancer hallmark signature (n=50) score, tumor infiltrating lymphocyte fraction (n=9), and immune/stromal score were calculated based on normalized count data. The correlations between above biomarkers and pCR and EFS were analyzed using multivariate logistic and Cox regressions, respectively. We integrated the least absolute shrinkage and selection operator (LASSO) regression and bootstrapping algorithm (iteration=10,000, nfold=5) to choose best predictive features. Results: Downregulation of proliferation-related and extracellular matrix pathways (DGEs with false discovery rate (FDR) < 0.05, |log fold change|>1) was observed throughout treatment in both arms. DTP resulted in early (on-treatment vs baseline) inflammatory (IL-17, TGF-signaling pathways) and immune (B cell, NK cell and cytokine signaling) responses, whereas late responses occurred in the T-DM1 arm (post-treatment vs on-treatment). Interestingly, a rebound of HER2 and PI3K-AKT signaling was observed within residual disease after T-DM1. Immune and stromal scores showed similar kinetics between the two treatment arms, with increase after first two cycles and later decrease to baseline levels. PAM50 intrinsic subtype at baseline was independently associated with pCR and EFS after adjusting for treatment arm, tumor size, lymph node status, hormone receptor status, and Ki-67. Luminal A (pCR rate, 11.1%, odds ratio (OR), 0.64, 95% confidence interval (CI): 0.49 to 0.84, P=0.001), Luminal B (pCR rate, 20.0%, OR, 0.63, 95% CI: 0.53 to 0.76, P<0.001) and basal-like (pCR rate, 33.3%, OR, 0.70, 95% CI: 0.53 to 0.93, P=0.02) subtypes had lower pCR rates compared to HER2-enriched subtype (68.9%). Patients with basal-like tumors at baseline had worse EFS than those with HER2-enriched tumors (hazard ratio (HR), 4.66, 95% CI, 1.28 to 16.90, P=0.02). Moreover, pair-wise analyses revealed that patients with HER2-enriched tumors at baseline switching to other PAM50 subtypes after two cycles, had improved pCR (OR, 1.54, 95% CI: 1.31 to 1.80, P<0.001) and EFS (HR, 0.26, 95% CI, 0.08 to 0.83, P=0.02) than the remaining patients. Machine learning based analyses identified best biomarkers for pCR (hallmark estrogen response early, hallmark androgen response, hallmark PI3K AKT mTOR signaling) and EFS (NK and Treg cells fraction, hallmark apical surface). Patients with higher hallmark apical surface score could benefit from T-DM1 (HRT-DM1 vs. DTP = 0.13, 95% CI, 0.02 to 0.79, P=0.03) and vice versa (HRT-DM1 vs. DTP = 5.02, 95% CI, 1.06 to 23.76, P=0.04). Conclusion: This study sheds light on how the tumor transcriptome evolves under anti-HER2 therapy and potentially provides prognostic and predictive biomarkers for standard chemotherapy with dual HER2 blockade versus monotherapy with an antibody-drug conjugate. Further investigations evaluating the spatial and single-cell heterogeneity of HER2-positive BC are ongoing.

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Antibody-drug conjugates (ADCs) have demonstrated impressive activity in recent clinical trials in breast cancer. Such targeted therapeutics strongly depend on the presence of target molecules on the tumor cells, and the presence of such target molecules may determine the response of ADCs. However, ADCs are also dependent on cellular uptake, and factors regulating endocytosis as well as intracellular trafficking may strongly influence ADC activity. We have recently demonstrated that the activity of the HER2 targeted ADC trastuzumab emtansine (T-DM1) is dependent on the expression of RAB5A, a protein regulating endocytosis (1). A significant correlation between Rab5A expression and T-DM1 efficacy was found in a panel of HER2 expressing breast- and ovarian cancer cell lines. This result was verified in the I-SPY2 clinical trial where patients with high RAB5A expression were more likely to achieve a pathological complete response following T-DM1 as a neoadjuvant. The result was further validated in patients treated with T-DM1 in the Kamilla study where patients with a high RAB5A had a longer progression free survival. All ADCs should in principle be dependent on endocytosis to exert their activity. This triggered the investigation of proteins regulating endocytosis as predictive biomarkers for ADCs in general. METHODS: HER2-positive breast and ovarian cancer cell lines were evaluated with respect to the sensitivity and efficacy of treatment with T-DM1, trastuzumab deruxtecan, sacituzumab govitecan and the targeted toxin MH3B1/rGel. The expression levels of proteins involved in endocytosis and endocytic trafficking including RAB4A, RAB5A and RAB11A were investigated in addition to the molecular drug targets (HER2 and TROP2). Cellular drug sensitivity was correlated to the expression levels of the investigated proteins using both RNA and protein as readout. RESULTS: The early endosome marker RAB5A, was found to correlate positively to the activity of trastuzumab
deruxtecan, sacituzumab govitecan and MH3B1/rGel in the HER2 positive cell line panel, confirming the importance of RAB5A expression for the activity of these drugs. A significant correlation was found between RAB5A and drug efficacy using both protein and RNA as a readout. CONCLUSION: The present results indicate RAB5A as a generic predictive biomarker for both ADCs and targeted toxins which both depend on cellular uptake for cytotoxic efficacy. The results supports using both protein and RNA as a readout for RAB5A expression and point towards the development of a RAB5A stratification procedure for ADC and targeted toxin treatment.


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Circulating Tumor DNA Genotyping of Intrinsic and Acquired Gene Alterations in Patients With Advanced Breast Cancer Receiving the Cyclin-Dependent Kinase 4/6 Inhibitor Palbociclib: Biomarker Results from POLARIS

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Background: POLARIS is a prospective, real-world study of palbociclib in patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) in the United States and Canada. We present results from analyses of serial circulating tumor gene alteration profiles from patients treated with palbociclib in the first and second or later lines of ABC treatment to illustrate the potential mutagenic drivers of resistance (intrinsic/acquired) and carrier-mutations (intrinsic/maintained). Methods: The clinical database cutoff date was March 30, 2022. Patients in the biomarker analysis group combination treatment The Guardant360 platform with somatic single-nucleotide variants in complete or critical exons of 73 genes was used. Tumor gene alteration profiles (at baseline, on-treatment at Cycle 2 Day 1 [C2D1], and at end of treatment [EOT]) were evaluated. Cox proportional hazard models were used to estimate hazard ratios and 95% CIs. Results: Patient samples (n=345) were analyzed and gene alterations were detected in 85% of baseline samples (n=337), 72% of on-treatment samples (n=280), and 85% of EOT samples (n=104). Most frequently altered genes were PIK3CA (38%), TP53 (28%), and ESR1 (15%) at baseline; TP53 (28%), PIK3CA (24%), and NF1 (10%) at C2D1; and TP53 (40%), PIK3CA (40%), and ESR1 (33%) at EOT. Most frequent gene amplifications (amp) were detected in CCND1 (8.3%), FGFR1 (7.7%), and EGFR (5.9%) at baseline; FGFR1 (5.0%), CCND1 (4.3%), and EGFR (3.2%) at C2D1; and CCND1 (13.5%),
FGFR1 (9.6%), and EGFR (9.6%) at EOT. Baseline mutations of ESR1 and PIK3CA led to shorter real-world progression-free survival (rwPFS) than wild-type (hazard ratio [95% CI], 1.99 [1.38, 2.86] and 1.67 [1.24, 2.25], respectively). Baseline amp of CCND1 and FGFR1 also led to shorter rwPFS than wild-type (2.13 [1.36, 3.34] and 1.93 [1.20, 3.10]). Acquired mutations in ESR1, ATM, and RB1 were observed at EOT. Most frequently acquired ESR1 mutations at EOT were D538G, Y537N, and Y537S. Patients with all mutations cleared at C2D1, had longer rwPFS than those without (hazard ratio [95% CI], 0.58 [0.41, 0.83]). Conclusion: Patients with mutated ESR1 and PIK3CA or CCND1 and FGFR1 amp at baseline had shorter rwPFS than patients with wild-type genes. Genotyping analysis of progression ctDNA highlights the emergence of mutations in estrogen receptor and cell cycle pathways under selective therapeutic pressure and could guide monitoring and therapeutic sequencing for patients with HR+/HER2– MBC. ClinicalTrials.gov: NCT03280303

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Association of Neutrophil-to-Lymphocyte Ratio and Absolute Lymphocyte Count with Clinical Outcomes for Patients with Advanced Breast Cancer in the MONARCH 2 Trial

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Background: Pretreatment neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC) are putative prognostic factors in patients with advanced breast cancer (ABC). Little information is available on the prognostic value of these immune status markers in patients treated with abemaciclib (ABE). In this study, we investigated the relationship between baseline NLR and ALC and clinical outcomes using data from the phase 3 MONARCH 2 (M2) trial.

Methods: The M2 study compared ABE/fulvestrant to placebo (PBO)/fulvestrant in patients with estrogen-receptor positive, human epidermal growth factor receptor 2-negative ABC that had progressed on prior endocrine therapy. The current post hoc analyses used baseline laboratory data and outcome data from the June 20, 2019, cutoff date (median follow-up: 47.7 months). For both baseline NLR and baseline ALC, patients were divided into high and low categories, defined by a cutoff of 2.5 for NLR and 1.5×10⁹/L for ALC. The association of baseline NLR and ALC with investigator-assessed progression-free survival (PFS) and overall survival (OS) was explored using Cox models stratified by treatment and described using Kaplan-Meier estimates. After assessing the prognostic value of baseline NLR and ALC for PFS and OS using a univariate analysis, a multivariate model was used to determine whether baseline NLR and
Results: Data were available for 426 and 219 patients in the ABE and PBO arms, respectively. Median baseline NLR was 2.5 and 2.4 in the ABE and PBO arms, respectively. Median baseline ALC was 1.4×10^9/L in both arms. The numbers of patients categorized into the high and low categories were well balanced for analysis of both NLR and ALC.

and OS (2-sided p< 0.0001). Patients with low baseline NLR consistently had better PFS and OS than those with high baseline NLR, and the treatment effect of ABE against PBO was consistently observed regardless of NLR category (Table 1). Univariate analyses showed that baseline ALC (< 1.5×10^9/L, ≥1.5×10^9/L) was also a prognostic factor for PFS and OS (2-sided p=0.0116 and 0.0032, respectively). PFS and OS were better for patients with high baseline ALC than for those with low baseline ALC, and the treatment effect of ABE against PBO was observed regardless of ALC category (Table 1).

For PFS, the multivariate model was adjusted for Eastern Cooperative Oncology Group performance status (ECOG PS), tumor grade, presence of liver metastasis, and bone-only disease. For OS, the multivariate model was adjusted for sensitivity to endocrine therapy, ECOG PS, presence of liver metastasis, and bone-only disease. When adjusting for these additional prognostic factors, baseline NLR, but not baseline ALC, remained statistically significant in the multivariate model (2-sided p< 0.0001).

Conclusions: These exploratory analyses suggest that while both baseline NLR and ALC are prognostic of clinical outcomes, only baseline NLR is independently prognostic of PFS and OS. Low baseline NLR was associated with better PFS and OS outcomes, but the benefit of adding ABE to fulvestrant was similar regardless of baseline NLR status.

Table 1. Summary of outcomes by treatment arm for NLR and ALC categories

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Factor</th>
<th>Abemaciclib + Fulvestrant</th>
<th>Placebo + Fulvestrant</th>
<th>Hazard Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median (95%CI) Months</td>
<td>Median (95%CI) Months</td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>Low NLR (&lt;2.5)</td>
<td>21.5 (16.5, 29.0)</td>
<td>11.2 (7.9, 15.0)</td>
<td>0.486 (0.373, 0.633)</td>
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<td>High NLR (≥2.5)</td>
<td>14.6 (12.0, 17.4)</td>
<td>7.1 (5.0, 10.2)</td>
<td>0.540 (0.415, 0.703)</td>
</tr>
<tr>
<td></td>
<td>Low ALC (&lt;1.5×10^9/L)</td>
<td>16.4 (14.1, 18.5)</td>
<td>7.4 (5.0, 10.2)</td>
<td>0.458 (0.357, 0.588)</td>
</tr>
<tr>
<td></td>
<td>High ALC (≥1.5×10^9/L)</td>
<td>17.6 (14.1, 24.2)</td>
<td>11.6 (7.9, 15.7)</td>
<td>0.600 (0.453, 0.794)</td>
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<tr>
<td>OS</td>
<td>Low NLR (&lt;2.5)</td>
<td>55.5 (45.5, NR)</td>
<td>43.6 (35.6, NR)</td>
<td>0.704 (0.505, 0.982)</td>
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<tr>
<td></td>
<td>High NLR (≥2.5)</td>
<td>36.5 (30.9, 43.6)</td>
<td>33.8 (25.8, 39.8)</td>
<td>0.774 (0.571, 1.050)</td>
</tr>
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<td></td>
<td>Low ALC (&lt;1.5×10^9/L)</td>
<td>39.0 (34.8, 52.2)</td>
<td>34.4 (26.9, 40.0)</td>
<td>0.750 (0.558, 1.007)</td>
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<tr>
<td></td>
<td>High ALC (≥1.5×10^9/L)</td>
<td>51.3 (44.4, NR)</td>
<td>41.7 (35.5, 47.8)</td>
<td>0.735 (0.520, 1.038)</td>
</tr>
</tbody>
</table>

ALC, absolute lymphocyte count; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

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Whole genome sequencing of long-term, never relapse exceptional responders HER2+ advanced metastatic breast cancer

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Background: Anti-HER2 therapies such as trastuzumab used for the treatment of patients with HER2+ metastatic breast cancer (MBC) have led to significant improvements to disease progression. We previously identified cases from the “Thousand Patient HER2 database” project at Saint Vincent's University Hospital (SVUH) Dublin, of HER2+ MBC long-term durable complete responders to trastuzumab, and reported that Copy Number Aberration (CNA) burden may represent a novel prognostic predictor to trastuzumab response from the exome analysis of in HER2+ MBC “exceptional responders” (ExRs). However, whole-genome sequencing (WGS) allows a better understanding of how CNA affects the MBC genome and to-date, the
complete genome of this “exceptional” cohort has never been described. Methods: We performed WGS analysis to characterise the CNA profiles of 9 ExRs from our HER2+ MBC cohort treated with trastuzumab. Samples were obtained from patients who never progressed/relapsed for more than 5 years (OS > 60 months). DNA was sequenced from tumours (primary or metastases) and matching control (blood or normal tissue) at a mean depth of 60X and 30X, respectively (18 samples). Somatic single nucleotide variants (SNV) were detected using GATK4 Mutect2 and CNA were identified using Control-FREEC. Results: Eighty-five HER2+ MBC were identified with OS > 60 months, of which 28 were ExRs with bone, lung, liver and lymph metastasis who responded exceptionally to trastuzumab, with a mean OS of 108 months (range 61-236 months). This cohort includes patients who were diagnosed between 31 and 80 years old (median=51). WGS analysis revealed CNA in chr6p21 with amplification of CCND3 and in chr17q12 with amplification of RAD51D. SNV were identified in genes involved in the DNA damage repair (DDR) pathway such as ATM, BRCA2, RAD50 and FANCA. On-going analysis will allow the CNA profiles of all ExRs to be presented and their CNA burden calculated in order to investigate the relationship between whole genome CNA burden and HER2+ MBC patient survival. Conclusion: To our knowledge, this is the first study to sequence the whole genome of HER2+ MBC, never relapse exceptional responders. The identification of the genomic aberrations of these metastatic patients increases our understanding of the mechanisms involved in MBC progression. CNA burden may represent a novel prognostic predictor to trastuzumab response and new outcomes for patients, particularly as MBC is generally termed incurable.

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Transcriptional profiling of CTCs in metastatic breast cancer patients in the course of CDK4/6 inhibition

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Background: De novo resistance defined as progression within six months and acquired resistance are one of the major problems in the subset of metastatic (M), hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer (BC) patients without visceral crisis receiving CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (TX). Here, we aim to identify predictive and monitoring markers of CDK4/6i resistance by conducting transcriptional profiling of circulating tumor cells (CTCs) that represent a real-time snapshot of the heterogeneity.

Methods: Blood of (A) 60 HR+/HER2- MBC patients drawn at baseline of Palbociclib plus endocrine TX (TX as first line n=31, second or more lines n=29), (B) 19 HR+/HER2- MBC patients drawn before the initiation of endocrine monoTX (control) and matched blood samples of these patients after six months under TX (n=72) and at the time of progression (n=42) were analyzed. To enlarge the global CDK4/6i cohort at baseline, blood of (C) 32 patients before the initiation of Ribociclib plus endocrine TX was also drawn. Patients with progression within six months were defined as non-responders. Isolation of CTCs was conducted using positive immunomagnetic selection (AdnaTest EMT2/StemCell Select) and preamplified cDNA was analyzed by a multimarker qPCR panel utilizing QuantiNova LNA Probe assays targeting 25 genes involved in the DNA damage -, MAPK -, STAT -, Hippo – pathway or cell cycle, chemokine sensing, multidrug resistance and cell adhesion. qPCR data was normalized to CD45 and data of 20 healthy female donor controls to identify BC CTC specific overexpression signals with a specificity of >90% for all targets. Statistical analysis included log-rank testing and univariate Cox regression. Results: For first line CDK4/6i...
treated patients at baseline, CETN2 and E2F1 signals correlated significantly with worse progression-free survival (PFS) while CETN2 signals also related significantly to non-response. Furthermore, CETN2 and PCNA signals were significantly associated with worse overall survival (OS). Analyzing the Palbociclib cohort after six months of TX, PCNA signals correlated significantly with a decreased PFS while EpCAM signals showed a significant association with OS. In addition, CETN2, CXCR4, EpCAM, MLH3, WWTR1 signals after six months were shown to correlate significantly with a decreased OS and PFS and MAPK1 signals were only found in the non-responders. While non-response was related to appearing (from baseline to six months under TX) ABCC2, JUN and MAPK1 signals, disappearing ABCC2 signals were only found in the responders. Dynamics of ABCC2, CXCR4, EpCAM, JUN, MAPK1, MLH3, STAT1 and WWTR1 signals from baseline to six months under TX correlated significantly with OS and CXCR4 signal dynamics significantly with a worse PFS. At the time of progression, the presence of E2F1, JUN, MAPK1 and STAT1 signals correlated significantly with a decreased OS and in comparison to baseline analysis, the prevalence of ABCC2, EpCAM, E2F1, CETN2 and CXCR4 signals increased. Conclusion: CTC overexpression signals at baseline of targets involved in the cell cycle (CETN2 and E2F1) might be predictive markers for de novo resistance to CDK4/6i as first line TX, while ABCC2 (multidrug resistance), EpCAM (cell adhesion), E2F1, CETN2 and CXCR4 (chemokine sensing) signals could indicate acquired resistance to Palbociclib. In case of disease progression, E2F1, JUN (cell cycle) and targets of the MAPK- and STAT- pathway could be relevant targets for therapeutic strategies beyond Palbociclib TX. Monitoring and prognostic value was shown for single and repeated measurement of signals under TX in genes involved in resistance, cell cycle progression, DNA damage response (MLH3, PCNA), chemokine sensing, cell adhesion and the MAPK-, STAT- and Hippo (WWTR1) pathway.

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The 27-gene IO score is associated with pathologic complete response (pCR) in HR+/HER2- breast cancer patients treated with pembrolizumab in the I-SPY2 Trial.

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Introduction
Immune checkpoint inhibitor (ICI) therapy is efficacious for many tumor types and has been approved in both early-stage and metastatic triple negative breast cancer. However, no such approval exists for hormone receptor positive (HR+) breast cancer (BC) which typically has a lower TMB, lower PD-L1 expression, and lower numbers of tumor infiltrating lymphocytes, leaving an unmet need for a biomarker to determine ICI response. The 27-gene IO score has previously demonstrated association with response to ICI therapy in NSCLC, mUC, and TNBC but has not yet tested a cohort of HR+/HER2- breast cancer.

Methods
To determine the ability of the IO score to identify responders with HR+/HER- BC clinical and expression data from publicly available RNA expression data from the I-SPY2 trial were retrieved from Gene Expression Omnibus (GEO) under accession number GSE194040. Expression data were normalized, combined, batch corrected, and log-transformed by the submitting institution. This left an expression matrix of 19134 genes and 988 samples for analysis as well as corresponding clinical data. Within this sample set, 40 patients were HR+/HER- and received pembrolizumab and cytotoxic chemotherapy while 64 patients comprised the control arm (chemotherapy only).

Results
In the I-SPY2 trial, within the 40 patients who received pembrolizumab, 12 patients achieved pCR (30%) and 19 patients were IO+ (47.5%). Of the 12 pCR patients, 9 were IO+ (75%) and of the 28 RD patients, 18 were IO- (64%), resulting in an odds ratio of 5.4 (95% CI 1.2-24.7, p< 0.03). Considering the 64 HR+/HER- patients in the paclitaxel arm, 10 achieved pCR (15.6%) and 21 were IO+ (32.8%). Of the 10 pCR patients, 5 were IO+ (50%) and of the 54 RD patients, 38 were IO- (70%), resulting in an odds ratio of 2.4 (95% CI 0.6-9.3, p>0.2).

Conclusions
Despite a generally low inflammatory tumor microenvironment characteristic of the HR+ BC phenotype, the IO+ group was 3x more likely to achieve pCR with the addition of pembrolizumab to chemotherapy. These data extend on previous findings in neoadjuvant treatment of TNBC and advanced colon cancer that IO score is associated with response only in the presence of ICI therapy, not in the presence of chemotherapy alone. This is the first study to demonstrate the association of IO score with pathologic complete response to immune therapy in hormone receptor positive BC.

<table>
<thead>
<tr>
<th>Arm</th>
<th>N= (pCR)</th>
<th>IO+ (pCR)</th>
<th>IO- (pCR)</th>
<th>IO score Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (P)</td>
<td>64 (10)</td>
<td>21 (5)</td>
<td>43 (5)</td>
<td>2.4 (0.6-9.3, p&gt;0.2)</td>
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<tr>
<td>P+Pembro</td>
<td>40 (12)</td>
<td>19 (9)</td>
<td>21 (3)</td>
<td>5.4 (1.2-24.7, p&lt;0.03)</td>
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</tbody>
</table>

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Serum thymidine kinase activity as a prognostic marker in women with metastatic breast cancer treated with two different schedules of palbociclib plus second-line endocrine therapy within the CCTG MA38 trial

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Background: Thymidine kinase-1 is a cell proliferation marker downstream of the CDK4/6 pathway, whose activity can be measured in serum to reflect tumor proliferation. The CDK4/6 inhibitor palbociclib (P) is approved for the treatment of patients (pts) with hormone receptor positive metastatic breast cancer (MBC) in first or second line endocrine-based treatment settings. Approximately 10-15% of pts exhibit de novo resistance to P, with circulating levels of thymidine kinase activity (TKa) previously shown as a potential marker of early treatment resistance. Therapeutic strategies to address primary resistance to P are currently lacking. Little is known of the clinical efficacy of alternative dosing schedules of P, and its effect on TKa. Here we report serum TKa measured at different timepoints from samples collected within the MA38 (NCT02630693) study. Methods: MA38 is an open label randomised Phase 2 trial comparing two different schedules of P plus second-line ET in pts with ER-positive, HER2-negative MBC. Pts were assigned to receive physician’s choice ET plus either standard P dosing (125mg daily for 21 days on a 28-day cycle), or 100mg daily continuously. Serum samples were collected at baseline (BL; n=135), at 12 weeks (W12; n=122) and 24 weeks (W24; n=95). TKa was measured with DiviTum®, a refined ELISA-based assay (lower limit of detection [LLOD] = 100 DuA). Kaplan-Meier method estimated BL, W12 and W24 (95% CI) median PFS (mPFS; from randomization until progression by RECIST criteria or death) and overall survival (OS; from randomization until death from any cause) in groups of patients defined by dichotomizing TKa as “high” or “low” at the median. Results: MA38 enrolled 180 pts from December 2015 and February 2017 across Canada. Median follow up was 19 months. Overall, the median age was 60, and 90% of pts were post-menopausal. All pts had estrogen receptor-positive disease, and 64% had visceral metastases. On study, 56% received fulvestrant with P, 34% aromatase inhibitor and 10% tamoxifen. TKa was successfully measured in 100% of samples. Median TKa (mTKa) at BL was 234 DuA (IQR 138.5 - 438). BL TKa was not associated with clinical or pathological characteristics. TKa was prognostic at BL with mPFS of 5.5 months (mo) in pts with high TKa vs 16.3 mo with low TKa (HR=2.43; 95% CI, 1.6-3.7; p< 0.001). Similar results were obtained employing other previously reported cut off values. At multivariate analysis, BL TKa was independent from other prognostic factors including age, ECOG status and presence of visceral metastases (adjusted HR= 2.34; 95%CI 1.5- 3.6; p < 0.001). In terms of OS, BL TKa was an independent prognostic factor (adjusted HR=2.0; 95% CI, 1.1-3.7; p=0.02). At 12 mo, OS rate was 68% in pts with high BL TKa vs 92% in low TKa. Both for PFS and OS, no interaction between BL TKa and study arm was observed. At W12 mTKa was 129.5 DuA (IQR 100 - 219.8) and below LLOD (IQR 100 - 180) at W24. At these timepoints, landmark analyses showed no significant difference in PFS according to TKa. However, at W12 high TKa was significantly associated with worse OS (HR 2.0; 95%CI 1.0-4.0; p=0.03), with a similar trend at W24 (HR 2.5; 95%CI 0.9-6.4; p=0.06). Conclusions: Baseline TKa is a reliable prognostic marker of both PFS and OS in pts treated with P and ET, further substantiating previous data. Monitoring TKa during treatment may provide important clinical information. A significant relationship between TKa and assigned treatment arm was not observed, suggesting TKa is not influenced by P treatment dose or intensity. These data confirm the role of baseline TKa as a new marker for patient stratification, and supports further
investigation for the assessment of the clinical utility of TKα as a monitoring biomarker in the advanced setting.

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p27Kip1 V109G single-nucleotide polymorphism (SNP): pinpointing the hormone-receptor positive breast cancer subpopulation that requires CDK4/6 inhibitors in addition to endocrine therapy.

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Background: CDK4/6 inhibitors benefit a limited percentage of hormone receptor-positive breast cancer (HRPBC) patients in the adjuvant setting: according to the MonarchE study, from all patients treated with the endocrine plus CDK4/6 inhibitor combination, 84% were adequately treated with endocrine therapy alone, ~5% experienced benefit from the combination, and 11% were not rescued from relapse by abemaciclib. Given the side effects and the cost, biomarkers to guide treatment decisions in this setting are appealing. We found that the p27Kip1 V109G SNP was enriched in HRPBC patients experiencing relapse despite endocrine treatment. p27Kip1 binds to cyclins and CDKs, restraining cells from cycling by inhibiting the formation of CDK/cyclin complexes and their kinase activity, resulting in less phosphorylation of Rb. A functionally impaired p27Kip1 could render tumor cells insensitive to endocrine therapy, while being rescued by CDK4/6 inhibitors. Thus, this SNP could narrow down the patient population that requires adjuvant CDK4/6 inhibitors. Methods: Isogenic HRPBC cell lines, wild-type or polymorphic homozygous for the p27Kip1 V109G SNP were generated with CRISPR-Cas9.
Cell cycle and cell viability were assessed with BRDU incorporation and colony assays. Immunoprecipitation coupled with western blot (WB) was used to measure the formation of CDK/Cyclin complexes; Rb phosphorylation was assessed by WB. An in vitro kinase assay was set up to measure the CDK4 activity of p27Kip1/CDK/Cyclin complexes. Patients (n=115) with metastatic, HRPBC receiving endocrine monotherapy or in combination with CDK4/6 inhibitors were genotyped for the p27Kip1 V109G SNP, and PFS by genotype and therapy compared with the Kaplan-Meier method. All statistical tests were two-sided. Results: three isogenic polymorphic clones were generated from the wild-type T47-D hormone-positive cell line. The three clones were resistant to hormonal deprivation compared to wild-type cells. The relative plating efficiency (RPE) in the colony assays of the polymorphic clones exposed to hormonal deprivation compared to that of deprived T47-D cells was 550% (clone C1), 165% (clone E1) and 100% (Clone F5); P< 0.005. The three clones were also resistant to fulvestrant (Fulv) (300%, 170% and 180%, respectively); P< 0.005. Cell cycle (positive BRDU cells) decreased ~3 fold in wild type cells (18% to 6.5%) when exposed to hormonal deprivation or Fulv, but remained unaltered in the polymorphic clones. However, when palbociclib was added to hormonal deprivation or Fulv, the effects in RPE increased and were similar in polymorphic clones and parental cells (>5% RPE compared to vehicle, both in polymorphic and wild-type cells). The p27Kip1 V109G SNP was found in homozygosity in ~15% of metastatic HRPBC patients. When patients received endocrine monotherapy in the first-line setting, polymorphic patients experience rapid failure (N=51) compared to wild-type/heterozygous patients (4.3 vs. 21.1 months; P < 0.0001). However, when patients received hormonal plus CDK4/6 inhibitors, the differences disappeared (18.3 vs. 24.3 months; P=0.85). Mechanistically, we observed that the formation of CDK2/CyclinA, CDK2/CyclinE and CDK4/Cyclin D1 complexes was >200% higher in polymorphic than in wild-type cells (P< 0.05). Regarding CDK4 kinase activity of p27Kip1/CDK/Cyclin complexes, as opposed to wild-type p27Kip1, p27Kip1 V109G was unable to suppress the kinase activity of CDK4 in presence of Fulv or hormonal deprivation. However, palbociclib was able to fully suppress CDK4 kinase activity regardless of the p27Kip1 genotype. Conclusion: Germline p27Kip1 genotyping can constitute a tool for treatment selection: whereas wild-type patients are adequately treated with endocrine monotherapy, polymorphic patients are inherently resistant, but are rescued with CDK4/6 inhibitors. Thus, hormonal+CDK4/6 inhibitor combos could be reserved for the polymorphic patients.

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Background: About 55% of hormone receptor (HR)-positive metastatic breast cancer (mBC) show a low-level expression of human epidermal growth factor receptor 2 (HER2-low). HER2-low is defined as HER2 immunohistochemistry (IHC) expression of 1+ or 2+ with a negative HER2 amplification by in situ hybridization. The efficacy of the antibody-drug conjugate trastuzumab deruxtecan in HER2-low HR+ mBC has been practice changing. However, there are conflicting data on the prognostic value of low HER2-expression in HR+ mBC with some reports showing no impact on prognosis and other showing inferior outcomes in HER2-low patients when treated with cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6is) in combination with endocrine therapy (ET).

Methods: We retrospectively searched for patients treated at MD Anderson Cancer Center with a diagnosis of HR+ treated with ET in combination with a targeted therapy (CDK4/6is, everolimus or alpelisib). Patients were divided into 3 groups: All histologies, ductal histology (IDC) and lobular histology (ILC). We obtained data on demographics, estrogen (ER) and progesterone (PR) receptor status, HER2 expression, menopausal status, treatment duration and survival status. The Kaplan-Meier product-limit method was used to compare progression-free survival (PFS) and overall survival (OS) between the three different groups stratified by HER2 expression (HER2 low versus HER2 0).

Results: We identified 1,649 patients (64% HER2-low, 36% HER2 0) with HR+/HER2- treated with targeted therapy (CDK4/6is, everolimus or alpelisib) in combination with ET. The median age was around 50 years in all groups, 75% were White, 55% premenopausal, 95% ER-
positive and 83% PR-positive. 68% were treated with CDK4/6is (919 patients treated in first line (1L) and 202 treated in second line), 30% everolimus and 2% with alpelisib. In the patients who received first 1L CDK4/6is, 70% received an aromatase inhibitor as their ET backbone and 30% received fulvestrant. All the patients who received 1L fulvestrant recurred while on adjuvant AI. PFS and OS were not statistically different between the HER2-low and HER2 0 groups treated with targeted therapies (TT) plus ET or 1L CDK4/6is plus ET regardless of the histology (Table 1).

Conclusion: In this single institution analysis, HER2-low status did not have a significant impact on prognosis in HR+/HER2- mBC treated with TT plus ET or 1L CDK4/6is plus ET.

Table 1. Progression-free Survival and Overall Survival in HR+/HER2- mBC patients treated with targeted therapies (TT) plus endocrine therapy (ET)

<table>
<thead>
<tr>
<th></th>
<th>(A) TT + ET in all histologies N = 1,649</th>
<th>(D) 1L CDK4/6is + ET in all histologies N = 919</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HER2 0 N = 595 (36%)</td>
<td>HER2 0 N = 340 (36%)</td>
</tr>
<tr>
<td></td>
<td>HER2-low N = 1,054 (64%)</td>
<td>HER2-low N = 579 (64%)</td>
</tr>
<tr>
<td>PFS (mo)</td>
<td>9.1</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>9.1</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>P = 0.434</td>
<td>P = 0.273</td>
</tr>
<tr>
<td>OS (mo)</td>
<td>26.4</td>
<td>31.2</td>
</tr>
<tr>
<td></td>
<td>28.1</td>
<td>32.4</td>
</tr>
<tr>
<td></td>
<td>P = 0.415</td>
<td>P = 0.222</td>
</tr>
</tbody>
</table>

|                | (B) TT + ET in IDC N = 1,327            | (E) 1L CDK4/6is + ET in IDC N = 731           |
|                | HER2 0 N = 466 (35%)                   | HER2 0 N = 261 (36%)                         |
|                | HER2-low N = 861 (65%)                 | HER2-low N = 470 (64%)                       |
| PFS (mo)       | 8.5                                    | 10.1                                          |
|                | 8.5                                    | 12.0                                          |
|                | P = 0.097                              | P = 0.124                                     |
| OS (mo)        | 26.4                                   | 31.1                                          |
|                | 28.8                                   | 34.2                                          |
|                | P = 0.382                              | P = 0.130                                     |

|                | (C) TT + ET in ILC N = 241             | (F) 1L CDK4/6is + ET in ILC N = 152           |
|                | HER2 0 N = 95 (39%)                   | HER2 0 N = 85 (43%)                          |
|                | HER2-low N = 146 (61%)                | HER2-low N = 87 (57%)                        |
| PFS (mo)       | 12.6                                   | 16.6                                          |
|                | 9.5                                    | 12.1                                          |
|                | P = 0.266                              | P = 0.648                                     |
| OS (mo)        | 34.3                                   | 34.7                                          |
|                | 27.9                                   | 28.8                                          |
|                | P = 0.792                              | P = 0.837                                     |

In patients treated with TT + ET in all histologies (A), in IDC (B) and in ILC (C). In patients treated in 1L with CDK4/6is + ET in all histologies (D), in IDC (E) and in ILC (F)

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Genetic determinants of response to patritumab deruxtecan (HER3-DXd) in hormone receptor-positive/HER2-negative (HR+/HER2-) breast cancer: a correlative analysis from SOLTI TOT-HER3 trial

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Background: Baseline HER3 protein or ERBB3 mRNA levels do not seem to predict efficacy from HER3-DXd in early-stage and advanced HR+/HER2- breast cancer (Prat et al. ESMO Breast 2022; Krop et al. ASCO 2022). Here, we evaluated potential baseline pre-treatment genetic determinants of efficacy to HER3-DXd. Methods: SOLTI TOT-HER3 (NCT04610528) is a window of opportunity, multicenter, pre-operative trial which enrolled, in part A, 77 evaluable patients with untreated HR+/HER2- operable (≥1 cm) breast cancer. Patients received a single dose of HER3-DXd (6.4 mg/kg). The primary objective was to evaluate the CelTIL score variation between pre- and post-treatment (day 21) samples. CelTIL combines % of tumor cellularity and % of tumor-infiltrating lymphocytes into a single score. DNA and RNA were purified from pre-treatment baseline FFPE tumor samples. Gene expression was evaluated using a custom 67-gene panel on the nCounter. NGS-based DNA-seq was performed using the VHIO-300 panel, which estimates tumor mutational burden (TMB), identifies copy-number aberrations (CNAs) across the entire genome and calls mutational status of >300 genes. From CNA data, 150 previously defined DNA-based signatures (Xia et al. Nat Comm 2019) trained to capture RNA- and protein-based phenotypes such as the PAM50-related biology were evaluated. Associations of each variable with efficacy (i.e., CelTIL relative changes, and tumor cellularity relative changes) were adjusted for multiple-testing (false discovery rate [FDR] < 5%). The area under the ROC Curve (AUC) was used to estimate the discrimination performance of each variable. Results: RNA and DNA data were obtained from 45 (58%) patients. Baseline characteristics in this subset of patients were generally similar to the original TOT-HER3 population. Among 228 variables (single mutation status, single gene expression, PAM50 signatures, TMB, and DNA CNA-based signatures), 139 (61%) were found significantly associated (FDR< 5%) with CelTIL changes at day 21. Among them, TP53 mutations (n=7) were found associated with higher CelTIL response compared to TP53 wild type (71% [95% CI=-5.4-17.8] vs. 24% [95% CI=15.9-55.4], FDR=2.1%). In addition, RNA-based genes tracking Basal-related biology (e.g., CCNE1, AUC=0.71) or immune expression (e.g., PDCD1, AUC=0.73, or CD68, AUC=0.62), together with RNA/DNA-based signatures tracking proliferation and/or basal-related biology (e.g., retinoblastoma loss-of-heterozygosity [RB-LOH], AUC=0.76), were associated with high CelTIL response. Conversely, RNA/DNA-based signatures tracking endocrine sensitivity/Luminal A-related biology (e.g., Scorr_IE_Correlation, AUC=0.76) were associated with low/lack of CelTIL response. PIK3CA somatic mutations (n=14, 31% of cases), and TMB (range 2.2-12.7) were not found associated with CelTIL
response. Similar overall results were obtained when relative changes in tumor cellularity (instead of CelTIL) was evaluated as the efficacy endpoint. Conclusions: TP53 mutations, immune-related genes, and DNA/RNA-based phenotypic signatures tracking Basal- or Luminal A-related biology such as the DNA-based RB-LOH score or the endocrine sensitivity score (Scorr_IE_Correlation) are associated with CelTIL changes in response to HER3-DXd in HR+/HER2- breast cancer. Further RNA- and DNA-based analyses will be evaluated.

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Differential Gene Mutation Landscape in Patients With PIK3CA-altered and Non-altered Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-negative Advanced Breast Cancer in the SOLAR-1 Clinical Study

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Introduction: The phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) is found mutated (mut) in ~40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC); some of these alterations can lead to PI3K pathway hyperactivation and are associated with endocrine resistance (resist). Alpelisib (ALP), an α-selective PI3K inhibitor and degrader, demonstrated clinical benefit in combination with fulvestrant (FUL) in the SOLAR-1 study in pts with PIK3CA-mut HR+, HER2− ABC. SOLAR-1 (NCT02437318) was a double-blind, placebo (PBO)-controlled, stratified, randomized (per PIK3CA-alt status as determined by QIAGEN PIK3CA RGQ PCR test), Phase III study of ALP in combination with FUL in pts with HR+, HER2− ABC who progressed on/after aromatase inhibitor therapy. Here, we compare the gene alteration landscape in pts with altered (alt) and non-alt PIK3CA and the efficacy of ALP + FUL in pts whose tumors have alterations in both selected genes or cell signaling pathways as well as PIK3CA-alt or non-alt status as determined by next-generation sequencing (NGS).

Methods: In this analysis, retrospective NGS analysis using the FoundationOne CDx 324-gene panel was performed on available FFPE tissue samples. In all, 398 pts were categorized into 2 cohorts based on NGS-tested PIK3CA status. The PIK3CA-alt cohort comprised 237 patients (ALP, n=120; PBO, n=117); the PIK3CA-non-alt cohort 161 patients (ALP, n=81; PBO, n=80). Selected genes altered in >20 SOLAR-1 pts were investigated further. Clinical benefit was assessed by progression-free survival (PFS) based on gene alt status in the PIK3CA-alt and -non-alt cohorts. Hazard ratios (HR) for PFS were estimated using a multivariate Cox PH model by adjusting multiple clinical covariates including age, ECOG performance status, bone lesion, prior CDK4/6 inhibitor treatment, and lung/liver metastasis.

Results: PIK3CA-alt and -non-alt cohorts had differential genomic landscapes; differential PFS benefit was observed among the genes analyzed, including ARID1A, EMSY, FGFR2, MAP3K1, MYC, RAD21, RAD51C, TP53, and a gene set associated with the MAPK pathway. In most pts with analyzed gene alterations, numerically longer PFS was observed with ALP vs PBO in the
PIK3CA-alt cohort than the -non-alt cohort, particularly pts with alterations in ARID1A (median [m] PFS for ALP vs PBO in PIK3CA-alt cohort: 22.11 vs 12.42 mo, HR 0.48; vs mPFS in PIK3CA-non-alt cohort: 6.21 vs 22.31 mo, HR 1.33) and MAP3K1 (PIK3CA-alt cohort: 17.25 vs 7.70 mo, HR 0.50; vs PIK3CA-non-alt cohort: 9.17 vs 5.26 mo, HR 1.32). Full results are found in the Table. Results should be interpreted with caution, as analyses used small sample sizes and were not adjusted for multiple testing.

Conclusions: A differential genomic landscape was observed in PIK3CA-alt and PIK3CA-non-alt populations. Clinical benefit of ALP vs PBO was observed in pts with PIK3CA-alt disease who also had alterations in analyzed genes and/or genes associated with the MAPK pathway. The data from this analysis suggest that, of the genes analyzed, only PIK3CA mutations can predict pt sensitivity to ALP.

Table. PFS in PIK3CA-altered and PIK3CA-non-altered populations by gene alteration

<table>
<thead>
<tr>
<th>Gene</th>
<th>PIK3CA-alt</th>
<th>PIK3CA-non-alt</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP3K1-alt</td>
<td>17.25 (13)</td>
<td>7.70 (13)</td>
</tr>
<tr>
<td>MAP3K1-non-alt</td>
<td>10.31 (10)</td>
<td>5.22 (10)</td>
</tr>
<tr>
<td>ARID1A-alt</td>
<td>22.11 (18)</td>
<td>12.42 (15)</td>
</tr>
<tr>
<td>ARID1A-non-alt</td>
<td>10.91 (16)</td>
<td>5.22 (10)</td>
</tr>
<tr>
<td>PSMD2-alt</td>
<td>9.63 (9)</td>
<td>2.78 (9)</td>
</tr>
<tr>
<td>PSMD2-non-alt</td>
<td>11.01 (11)</td>
<td>5.90 (100)</td>
</tr>
<tr>
<td>TPS5A-alt</td>
<td>8.48 (8)</td>
<td>3.69 (96)</td>
</tr>
<tr>
<td>TPS5A-non-alt</td>
<td>11.90 (98)</td>
<td>7.29 (61)</td>
</tr>
<tr>
<td>RAD51C-alt</td>
<td>12.54 (4)</td>
<td>5.12 (18)</td>
</tr>
<tr>
<td>RAD51C-non-alt</td>
<td>10.97 (16)</td>
<td>5.50 (107)</td>
</tr>
<tr>
<td>ERMT-alt</td>
<td>7.26 (15)</td>
<td>2.49 (15)</td>
</tr>
<tr>
<td>ERMT-non-alt</td>
<td>11.01 (105)</td>
<td>5.62 (102)</td>
</tr>
<tr>
<td>MKP pathway-alt*</td>
<td>10.91 (23)</td>
<td>3.61 (60)</td>
</tr>
<tr>
<td>MKP pathway-non-alt*</td>
<td>11.63 (37)</td>
<td>7.23 (67)</td>
</tr>
<tr>
<td>IFYC-alt</td>
<td>5.8 (13)</td>
<td>6.97 (4)</td>
</tr>
<tr>
<td>IFYC-non-alt</td>
<td>11.63 (107)</td>
<td>5.62 (92)</td>
</tr>
<tr>
<td>PASK-alt</td>
<td>6.11 (9)</td>
<td>7.23 (23)</td>
</tr>
<tr>
<td>PASK-non-alt</td>
<td>11.63 (106)</td>
<td>5.62 (64)</td>
</tr>
</tbody>
</table>

*Includes PIK3CA, ARID1A, PSMD2, TPS5A, ERMT, MKP pathway, and MAP3K1

Results should be interpreted with caution, as sample sizes are small, and results have not been adjusted for multiple testing.

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Deep learning-based assessment of HER2-low expression on breast cancer H&E digital whole slide images

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Background: Antibody drug conjugates (ADCs) against HER2 have shown meaningful clinical activity in HER2 low breast cancers, defined as 1+ or 2+ staining on immunohistochemistry (IHC) without gene amplification by in situ hybridization (ISH) techniques. Given that these methods were originally developed for an accurate detection of HER2 3+, their sensitivity and robustness for the detection of low and ultra-low levels of HER2 are questionable. We have recently described a deep learning algorithm that can detect signatures of HER2 expression based on training utilizing scanned H&E whole slide images (WSI) of breast cancers for which IHC and mRNA expression levels of HER2 were available. Here, we report the application of our algorithm to two independent breast cancer cohorts. Methods: A model was developed based on recognition of invasive breast cancer in whole slide images of H&E staining, and then trained via computational neural network with multiple instance learning for binary classification of cases as HER2 “negative” and HER2 “expressed” (low). For training, true negatives were defined as having HER2 IHC-0 and mRNA level < 7.6. HER2-low cases were defined as IHC-1+/2+ and mRNA >9. IHC-0 cases with mRNA >7.6 were excluded from the training cohorts. The resulting model (HER2Complete) was able to distinguish HER2-negatives from HER2-low cases with an AUC of 0.91 (+/- 0.08). Here we use Her2Complete to assess HER2 in two additional cohorts that include 901 ER+/HER2 IHC-0 and 52 HER2 IHC 0+ breast cancers from MSK and TCGA cohorts, respectively. For the TCGA cohort, concomitant transcriptomics data (RNASeq) as a reference for HER2 mRNA expression were retrieved and “HER2 expressed” defined as RNASeq expression of HER2 greater than the 90th percentile of the geometric mean of expression of three reference genes not expressed in breast tissues (TTN, MUC13, OR10A6). Values less than this reference cut-off in the TCGA cohort were considered “HER2 not expressed.” Results: Among the 901 IHC-0 test cases from the MSK cohort, the model
identified 82 as ‘negative’, whereas 819 were found to have features of HER2 expression (HER2-Low). Of the 82 negative cases in the MSK cohort, all except 13 cases expressed mRNA levels < 9, and 786/819 of the HER2-low cases expressed mRNA levels >8. Of the 52 IHC 0+ cases in the TCGA cohort, 33 also had "HER2 not expressed" by our reference based RNASEq expression cut-off. Our model identified 15 of these 33 as ‘negative’, while 15 of the 19 TCGA cases with IHC 0+ and HER2 ‘expressed’ by our cut-off were identified as ‘HER2-Low’ by our model. Conclusions: AI tools based on the analysis of WSIs of routinely prepared H&E sections may predict HER2 status in breast cancer. This work requires further investigation using treatment response data to demonstrate that cases with morphologic features of low level HER2 expression will respond to ADCs.

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Background: KN026 is a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes (two different HER2 epitopes shared by trastuzumab and pertuzumab). KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1/CD80 and CTLA-4 interaction with CD80/CD86. Our on-going multi-centered phase II trial (NCT04521179) demonstrated that in advanced HER2-positive breast cancer (HER2+ BC) patients, who have progressed after prior anti-HER2 combinational therapies, the objective response rate (ORR) of this chemo-free therapy of KN026 in combination of KN046 was about 50.0% (SABCS 2021 poster P5-16-04). To explore the underlying mechanism of this regimen, we collected tumor specimens from patients before and after receiving this combinational treatment for single-cell analysis to provide an in-depth description of the tumor immune microenvironment and its correlation with treatment response. Methods: Paired tumor specimens before and after treatment of patients enrolled in the trial were collected for single-cell transcriptome and TCR sequencing. In addition, to reveal the immune cell characteristics of anti-HER2 resistant patients, we compared our data with previously reported single-cell analysis of treatment-naïve HER2+ BC. Results: We obtained 30 specimens from 17 patients, including 17 of pre-treatment and 13 of post-treatment. TCR expansion did not correlate with clinical efficacy. In-depth analysis of subpopulations revealed that compared to treatment-naïve HER2+ BC, these enrolled prior anti-HER2-resistant patients had an additional population of T cells subpopulation characterized by CD4-low and CD8-low in their baseline tumor tissues, and the proportion of this subpopulation was significantly decreased after KN046 plus KN026 treatment in
responding patients. Moreover, we found that patients with baseline CD8+ T/naïve T >1 tended to benefit more from this regimen. Conclusion: We identified a subpopulation of CD4-low and CD8-low T cells that may be associated with anti-HER2 resistance. And decreased of this subpopulation of T cells was associated with better ORR of KN046 in combination with KN026 treatment in heavily pretreated advanced HER2+ BC. Baseline CD8+ T/naïve T ratio in tumor is expected to be a predictor of ORR as well.

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Radiomic biomarkers to predict the efficacy of anti-PD-1 immunotherapy-based combinational treatment in advanced breast cancer: a multi-center study

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Introduction: Immunotherapy, especially immune checkpoint inhibitors, is regarded as one of the major breakthroughs in breast cancer treatment. However, it is an important challenge to accurately locate the patients who benefit from immunotherapy, because there is still a lack of universal and robust predictors of the efficacy of immunotherapy. Radiomics can extract quantitative imaging features in a high-throughput manner and assess tumor microenvironment and heterogeneity. This study investigated the correlation between deep learning radiomic
biomarkers, including its predictive value for immunotherapy response in advanced breast cancer (ABC) patients. Methods: 240 patients with metastatic breast cancer treated with anti-PD-1 immunotherapy in three institutions from February 2018 to January 2022 were studied retrospectively, among which, the data of 61 patients were collected through prospective clinical trials. For these data, 189 ABC patients from prospective clinical trials and Sun Yat-sen University Cancer Center were evaluated as a training set to establish a radiomic model to predict value of immunotherapy, then this model was independently validated with 51 ABC patients from Sun Yat-sen Memorial Hospital. The CE-CT (contrast enhanced computed tomography) images of patients within one month before immunotherapy were were delineated with regions of interest (ROI) and radiomics features extraction. Data dimension reduction, feature selection and radiomic model construction were carried out with multilayer perceptron (MLP) deep learning. Combined with the radiomics signatures, independent clinical characteristics and pathological risk factors, the predictive model was established by multivariable logistic regression analysis. ROC curve (receiver operator area under receiver operator area, AUC) and Delong test were used to evaluate and compare the prediction performance of the model. Finally, decision curve analysis (DCA) is used to determine the net benefits predicted by the model. Results: The radiomic biomarker performed well in predicting response to immunotherapy, reflfected by the AUCs in the training set(AUC=0.885, 95% CI: 0.829-0.941) and validation set (AUC=0.871, 95% CI: 0.752-0.991), respectively. The accuracy of this radiomics model was better than those of clinical indicators, including PD-L1 expression. Conclusions: By combining deep learning technology and CT images and PD-L1 expression, we developed an independent predictive model that could identify MBC patients most likely to benefit from immunotherapy, and may effectively improve more precise and individualized decision support.

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Proteogenomic profiling of fresh frozen core biopsies from CALGB 40601

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Background: Targeted therapy for HER2+ breast cancer has significantly improved outcomes for this aggressive subtype. However, a subset of patients do not achieve pathological complete response (pCR). In CALGB 40601, a randomized Phase III Trial for neoadjuvant treatment of HER2+ primary breast cancer with Paclitaxel (T: taxane) combined with HER2 antibody therapy (H: Herceptin/Trastuzumab), the small molecule inhibitor Lapatinib (L), or the antibody-inhibitor combination, pCR frequency was 56% for the combination (THL arm), 46% for Trastuzumab (TH arm), and 32% for Lapatinib (TL arm, closed early because of lower efficacy) (PMID: 26527775). While a recent publication reports relapse-free survival (RFS), overall survival (OS), and RNA-based gene expression signatures that can predict pCR (PMID: 33095682), understanding the proteogenomic landscape of treatment response should facilitate identification of alternative and therapeutically tractable protein targets for treatment-resistant tumors. Methods: Microscaled proteogenomic profiling (PMID: 31988290) was performed on treatment-naïve, flash-frozen core needle biopsies from the CALGB 40601 trial obtained from the Alliance for Clinical Trials in Oncology tissue bank. Multi-omics profiling included whole-exome sequencing (WES), RNA-sequencing, and mass spectroscopy-based proteomics and phosphoproteomics from one or two cores from each patient. Results: Eighty baseline core biopsies from 54 patients, including 22 patients from the THL arm, 24 from the TH arm, and 8 from the TL arm, from the CALGB 40601 tissue archive were of sufficient quality to yield genomics, transcriptomics, and/or proteomics profiling data. The frequency of pCR for profiled samples was representative of the overall trial cohort. Linear models were employed to identify baseline determinants of pCR for each arm and to assess differences in genes associated with response between the TH and THL arms. Pathways associated with RNA processing, translation, and the proteasome were elevated in pCR tumors in TH and THL arms, while cell cycle, DNA replication and repair pathways were higher in pCR only in the THL arm. While
enrichment of similar pathways was observed in pCR in the transcriptome, the proteome specifically showed enrichment of pathways associated with extracellular matrix and EMT in non-pCR in the THL but not the TH arm. In particular, “EMT”, “ECM-receptor interaction”, and “extracellular structure organization” constituted the most enriched pathways and GO terms that were higher in non-pCR than in pCR tumors from the combination arm (THL) in the proteomics data despite showing no enrichment in the transcriptomics data. Driving this pathway enrichment were several collagens and matrix metalloproteinases that were significantly elevated in non-pCR tumors at the protein but not the RNA level. Finally, kinase target enrichment of differential phosphorylation sites suggested that the activity of PAK1, a regulator of cytoskeletal remodeling, is elevated in non-pCR tumors from the THL arm (p=0.006), but not the TH arm (p=0.69). Conclusion: Proteogenomic analysis of archival HER2+ breast cancer core biopsies provides opportunities for identifying proteins and phosphorylation sites in treatment-naive tumors that are associated with pCR to neoadjuvant Paclitaxel/anti-HER2 therapy. Notably, proteomic but not transcriptomic data showed that ECM and EMT pathways were elevated in non-pCR tumors; thus, signatures encompassing these pathways may serve as biomarkers for aggressive HER2+ breast cancer that is more likely to evade treatment. Non-pCR tumors in the THL arm were also marked by elevated levels of PAK1 target phosphorylation sites, suggesting that this kinase may be a potential therapeutic target in HER2+ breast cancer that is refractory to combination anti-HER2 therapy.

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Multi-omics approach to identify markers of resistance to endocrine therapy + CDK4/6 inhibitors in first line HR+/HER2- metastatic breast cancer (MBC) patients.

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CONTEXT: Endocrine therapy combined with CDK4/6 inhibitor is the standard frontline treatment for the vast majority of HR+/HER2- MBC patients. Despite an overall survival benefit, patients eventually progress and mechanisms of resistance to this combination are not well identified. METHODS: EPICURE is an ongoing pilot prospective cohort study of heterogeneous and massive data integration, ie. multi-omics approach in MBC patients. The present study aims at identifying progression markers in patients with HR+/HER2- MBC receiving frontline endocrine therapy+iCDK4/6 by means of transcriptomics, genomics and proteomics data. All patients had a tumor biopsy at the entry in the study (B1) and a biopsy was repeated at progression if feasible (B2). Transcriptomic (RNAseq: NextSeq550, Illumina), genomic (whole exome sequencing: NextSeq550, Illumina) and proteomic (DIA mass spectrometry: TimsTOFPro2, Bruker) were performed on B1 and B2 according to available tumor tissue. RESULTS: Fifty-one patients matching inclusion criteria were included. B1 was done at inclusion for all patients (B1) (n = 51) and B2 was performed in 8 patients. (B2) (n = 8). Eight metastatic sites were biopsied: node (n = 17); liver (n = 16); bone (n = 8); breast local recurrence (n = 5); chest wall (n = 5); skin (n = 4); pleural (n = 3); ovary (n = 1). Transcriptomic, genomic and proteomic analysis of paired biopsies (B1 and B2) was performed in parallel and separately for 8, 7 and 2 patients, respectively. Exploratory data analysis of transcriptomic and proteomic data showed that liver biopsies clustered together. In order to eliminate this anatomic bias, specific genes and proteins of liver metastases were identified by means of DESeq2 analysis (12 liver vs 39 other sites) for transcriptomic data (n = 2654) and LIMMA (4 liver vs 14 other sites) for proteomic data (n = 227), and excluded for the rest of the analysis. Differential analyses (ie. gene expression, non-synonymous mutations and protein expression) between B1 and B2 were performed for each patient. These three kind of lists were finally submitted to ToppGene, DAVID and GOrilla for Gene Ontology terms enrichment analyses. Transcriptomic analyses of the 8 paired biopsies highlighted immune response (IR) in seven B1, IR in four B2 and neurogenesis in three B2. Genomics data evaluation between B1 and B2 pointed out “transposon integration” as an important pathway. Proteomic data of the 2 paired biopsies analysed underlined high immune response in B1, and muscle development/contraction and response to tumor necrosis factor in B2 for one patient. For the second one, liver metabolism in B1 and extracellular matrix and p38 MAPK cascade were emphasised. CONCLUSION: This preliminary study based on transcriptomic, genomic and proteomic data represents an encouraging first step of the EPICURE project. In a near future, additional paired biopsies and other kinds of omics data (epigenetics, radiomics, microbiomics, exposomics) will be available. Furthermore, omics data will be analysed in an integrated manner (ie. artificial intelligence), which will make it possible to detect synergies across the different omics data.

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Leptin receptor (Ob-R)/leptin axis significantly modulates tumour-infiltrating lymphocytes (TILs) and PD-1 expression in early HER2+ breast cancer (BC) emerging as a new surrogate marker for immunotherapy.

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Leptin receptor (Ob-R)/leptin axis significantly modulates tumour-infiltrating lymphocytes (TILs) and PD-1 expression in early HER2+ breast cancer (BC) emerging as a new surrogate marker for immunotherapy. Background: There is strong pre-clinical evidence that obesity produces T-cell dysfunction and high PD-1 expression resulting in a paradoxical benefit from immunotherapy. This effect is driven, at least in part, by leptin that exerts its action through binding Ob-R, which is known to be highly expressed in HER2+ BC. TILs correlate with pathological response and long-term outcomes in BC; however the precise mechanism by which these T-cells are activated in and around tumour remains partially unknown. The primary aim of this study was to investigate the role of Ob-R/leptin axis in modulating TILs and PD-1 expression and its effect in pathological response in early HER2+ BC patients who have received neoadjuvant systemic treatment (NST). Methods: Women with HER2+ BC receiving anti-HER2-based NST followed by surgical resection were evaluated. Patient’s height and weight were measured before NST to calculate the body mass index (BMI). Based on the IHC results in diagnostic biopsy, tumors were categorized as HER2+/HR+ and HER2+/HR-. Ob-R expression was routinely measured in the diagnostic biopsy using the BOND RX Research Platform (Leica Biosystems). The Ob-R was classified as over-expressed if there were more than 50% positive cells with weak or strong staining. TILs and PD-1 expression were scored centrally in pre-treatment biopsy. TILs were considered as binary, < 30.0% versus ≥30.0% and PD-1 positive (>1%). Associations with pathological complete response (pCR; ypT0/isN0) were assessed using chi-squared or Wilcoxon test. Results: Of the 74 HER2+ BC patients included in the study, 47 (63.5%) had over-expression of Ob-R, 26 (35.1%) were overweight/obese (BMI ≥25kg/m2), and 42 (56.8%) had pCR status. Ob-R expression was similar regardless of menopausal status, age or HR expression. Patients with Ob-R overexpressed were 21 (80.8%) of 26 with BMI ≥25kg/m2 versus 26 (54.2%) of 48 with BMI < 25Kg/m2 (p=0.023). Tumors with Ob-R overexpressed had significantly higher mean levels of TILs than those with non-overexpressed Ob-R (21.4% [IQR, 7.5-30] vs 12.4% [IQR, 5-10]; p=0.009). Despite higher rates of TILs, the rate of pCR in Ob-R overexpressed tumours (57.4% [27 of 47 patients]) was not higher than in non-overexpressed tumours (55.6% [15 of 27 patients]; p=0.874). This could be due to the fact that Ob-R-overexpressed tumours had a significant higher median PD-1 expression than Ob-R-negative tumours (2% [IQR, 0.5-7.5] vs 0% [IQR, 0-1]; p< 0.001). Finally, no differences were found in terms of Ob-R expression and pathological response by hormone receptor expression. Conclusions: This multidisciplinary clinical study decodes for the first time how obesity, through the OB-R/leptin axis, might activate TILs but apparently dysfunctional as it is not translated into higher pCR; probably due to the presence of exhausted features such as high PD-1 expression. The role of Ob-R together with PD-1 as a potential biomarker for immunotherapy should be further explored.

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Efficacy of fulvestrant-based therapies in treating HR-positive, HER2-negative breast cancer with liver metastasis

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Background: Hormone receptor-positive (HR+) metastatic breast cancer (MBC) contributes to nearly 70% of breast cancer-related deaths. The liver is the third most common site for metastasis in breast cancer, and liver involvement has been found to have a poor prognosis. One contributing factor is resistance to hormonal treatments. Furthermore, estrogen receptor alpha gene (ESR1) activating mutations, which are enriched in metastatic tumors of the viscera such as the liver, have been linked specifically to resistance against hormone-blocking therapies. We seek to characterize the efficacy of specific treatment modalities, including hormone therapy, immunomodulators, radiotherapy, chemotherapy, and the role of ESR1 mutations in poor treatment response of MBC with liver metastasis. Methods: We conducted a retrospective matched cohort study of 3388 adults with HR+/HER2- MBC with liver and non-liver involvement, who were treated at MD Anderson Cancer Center from 1997-2021. Patients with liver and non-liver metastasis were matched by age at breast cancer diagnosis, race, BMI, and stage. All patients underwent fulvestrant monotherapy or fulvestrant-based combination therapy with CDK4/6 inhibitors, mTOR kinase inhibitors (everolimus), or PI3K inhibitors (alpelisib). We compared the overall and metastatic survival of patients with liver vs. non-liver metastasis on different treatment regimens. We also evaluated the impact of chemotherapy administered for metastasis. Results: Patients with liver metastasis experienced shorter overall and metastatic survival across all treatment regimens (HR, 1.44; 95% CI 1.34-1.57; P<.001). The addition of targeted therapies to fulvestrant offered a survival benefit over fulvestrant alone in patients with non-liver metastasis. However, this benefit did not extend to the liver metastasis
group. Independent of chemotherapy, liver metastasis was found to be a negative prognostic factor. Patients with first metastasis to the liver did not significantly differ in survival when compared to those who developed liver metastasis at a later stage. ESR1 mutations were identified in only a minority of the cohort (4%), but a higher prevalence of liver metastasis was found in patients with ESR1 mutations (49%) vs. the wild type group (45%). Independent of ESR1 status, patients with liver metastasis were found to have worse survival. Conclusion: We found liver metastasis to be a negative prognostic factor in patients with MBC independent of ESR1 status. While novel fulvestrant-based combination therapies have been promising for MBC, similar survival benefits are not seen in those with liver metastasis. Liver metastasis proves to be aggressive and difficult to treat, and current therapies are insufficient.

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Anthracycline improves the outcome of neoadjuvant trastuzumab-treated breast cancer patients with FcγRIIA F/F genotype by decreasing the ratios of CD8+PD1+ and CD68+PDL1+ cells

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Background:
Antibody-dependent cell-mediated cytotoxicity (ADCC) is one of the most important mechanisms of trastuzumab. Fragment C Gamma receptor (FcγR) IIA and IIIA polymorphisms influence the affinity of immunoglobin G (IgG). Recently, FcγRIIA and FcγRIIIA polymorphisms have identified with the efficacy of trastuzumab. However, whether FcγR polymorphisms are associated with the efficacy of trastuzumab in the neoadjuvant setting was unclear.

Patients and methods:
We retrospectively enrolled 101 patients with HER2-positive breast cancer receiving chemotherapy plus trastuzumab at least four cycles as neoadjuvant therapy and mastectomy in Sun Yat-sen university cancer center from May 2015 to March 2021. Among them, twenty patients were excluded because lacking of blood samples. Polymorphisms of FcγRIIA(rs1801274) and FcγRIIIA(rs396991) were examined by nested polymerase chain reaction (PCR) and sanger sequencing. Lastly, we performed multiple immunohistochemistry (mIHC) to examine the expressions of CD8, CD68, CD57, PD1 and PDL1.

Results:
Blood samples (n=81) were successfully detected. No significant differences between menstrual status, molecular subtyping, treatment and pathological complete response (pCR) rate. In paclitaxel-correlated with pCR rate (P< 0.05,Table1), moreover, the disease-free survivals (DFS) in 158 F/F genotype group (low affinity) (P=0.036), while that was not significant difference in patients with anthracycline-based treatment (n=47, P=0.248), indicating that anthracycline affinity. So far, there is no recurrence events in paclitaxel-based treatment group with -158V carriers genotype. The mIHC showed that the ratios of stroma CD8+PD1+ and CD68+PDL1+ cells were significantly higher in anthracycline-based treatment group (Table2), respectively, indicating that anthracycline improved the efficacy of neoadjuvant targeted therapy.
by decreasing the ratios of exhausted immune cells.

Conclusions:

-158V genotype is associated with better outcome in HER2-positive breast cancer patients who received paclitaxel combined with trastuzumab as neoadjuvant therapy.

Anthracycline improves the outcome of neoadjuvant trastuzumab-treated breast cancer patients population.

### Ratios of immune cells

<table>
<thead>
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<th>Characteristics</th>
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<td>V carriers (n=34)</td>
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<tr>
<td>Total population</td>
<td>pCR</td>
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<td>16</td>
<td>0.112</td>
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<tr>
<td></td>
<td>non pCR</td>
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</table>

### Ratios of immune cells in anthracycline-based and paclitaxel-based treatment group.

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UBE2E3 promotes the progression of HER2-positive breast cancer and influences the efficacy of targeted therapy via EGFR stabilization

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Background: In the past 20 years, the efficacy and prognosis of HER2-positive breast cancer have significantly improved. However, nearly 50% of patients still have residual invasive tumors after chemotherapy combined with dual-targeted neoadjuvant therapy, especially for those with disease progression during treatment. A lack of effective therapeutic regimens results from the failure of targeted therapy, whose heterogeneity is especially worthy of our attention. The aim of this study was to look for efficacy markers and investigate new drug-resistance mechanisms.

Methods: Firstly, the high-throughput sequencing data from 81 patients who received neoadjuvant chemotherapy TCbH (paclitaxel + carboplatin + trastuzumab) was analyzed by the efficacy outcomes. They were divided into 8 patients with stable or progressive disease (SD/PD), 35 with partial response (PR), and 38 with pathological complete remission (pCR). Then, UBE2E3 was chosen from the different expression genes between SD/PD and pCR based on efficacy results and the weighted gene co-expression network (WGCNA). UBE2E3 clinical correlations were investigated using publicly available data from The Cancer Genome Atlas (TCGA) and the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), and UBE2E3 was validated using immunohistochemistry (IHC) on 200 HER2-positive breast cancer tissue chips. Further, the UBE2E3 knockdown and overexpression stable transfer cell lines were constructed, and the effects of UBE2E3 on cell proliferation, clone formation, and drug sensitivity were verified by live cell imaging, the CCK8 assay, plate cloning, and IC50 assays, respectively. The tumor growth of UBE2E3 in vivo was investigated by an in situ transplantation tumor assay in nude mice. Meanwhile, the p-RB assay of mouse tissues by IHC was used to explore the effect of UBE2E3 on cell proliferation. RNA-seq was used to screen the downstream molecules of UBE2E3. Western blotting was used to verify the results of bioinformatics analysis and to explore the downstream key molecules. The protease inhibitor MG132 and actinomycin CHX were used to look at the effect on the stability of the target protein. Immunoprecipitation and silver staining assays were used to find interacting proteins with the UBE2E3. Results: Ten hub-genes which were efficacy-related were identified by WGCNA analysis, in which UBE2E3 was highly expressed in the SD/PD group (p < 0.05). In HER2-positive breast cancer, high expression of UBE2E3 was associated with poor prognosis and decreased disease-free survival both in public data and Fudan University Shanghai Cancer Center (FUSCC) data [HR 2.36, (1.25–4.47), p < 0.05]. The experimental results demonstrated that UBE2E3 promoted the proliferation of HER2-positive breast cancer cells, enhanced clone formation, and drug sensitivity; and that UBE2E3 promoted tumor growth in vivo and upregulated the expression of p-RB. The differentially expressed genes' sets of the RNA-seq between overexpressed cell lines and control showed that overexpressing UBE2E3 activated the EGFR pathway. Further, an immunoblot assay confirmed that UBE2E3 positively regulated EGFR levels and activated the downstream MAPK pathway. The proteasome inhibitor MG132 and CHX assays showed that UBE2E3 could stabilize EGFR proteins. The co-immunoprecipitation and silver staining assays showed that UBE2E3 stabilized EGFR proteins by interacting with c-Cbl. Conclusion: UBE2E3 could negatively affect the efficacy of HER2-positive breast cancer therapy and is significantly associated with poor prognosis. UBE2E3 may serve as a potential marker of efficacy and prognosis for HER2-positive breast cancer in the future. Therapeutic efficacy is affected by UBE2E3, which binds to c-Cbl and causes upregulation of EGFR expression in vivo, which in turn causes the MAPK pathway to be activated and tumor growth to be pushed up.

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Soluble CD163 may be a predictive biomarker of the efficacy of nivolumab plus chemotherapy in patients with HER2-negative metastatic breast cancer (WJOG9917BTR).

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Background: We have conducted a phase II trial (WJOG9917B) to evaluate efficacy of triple therapy with nivolumab, paclitaxel and bevacizumab in patients (pts) with HER2-negative metastatic breast cancer (MBC). Although soluble CD163 has been reported as a potential biomarker for predicting the efficacy of nivolumab in melanoma, however the data is limited in breast cancer. In an ancillary study (WJOG9917BTR), serum level of soluble CD163 were evaluated to elucidate this question. Methods: The main study enrolled 57 pts and showed that median Progression-free survival (PFS) and overall survival (OS) was 14.0 months and 32.5 months, respectively, with a median follow-up of 29.5 months. We have collected blood samples from consenting patients. Serum samples were collected at pretreatment, cycle 1 day 8 and other time points, which were used to measure the concentrations of cytokines, chemokines, and other surrogate proteins. PFS, OS, and response were analyzed in association with the biomarker data using the Kaplan–Meier method, log-rank tests as appropriate. Results: Biomarker study included 50 pts (36 with recurrent BC and 14 with de novo stage IV BC). The median amount of soluble CD163 before treatment was 562.3 (pg/ml) (range: 158.7-1518.0), and the baseline CD163 levels were higher in pts with recurrent than de novo stage IV (p = 0.0099). Other clinical factors including tumor subtypes, liver metastasis, response, PFS or OS were not significantly associated with the baseline CD163 levels. The kinetic changes in serum soluble CD163 after treatment were divided into two groups; one group (30 patients, CD163 increased group) had increased soluble CD163 immediately after administration (Cycle 1 Day 8), with a median PFS of 18.2; the other group (20 patients, CD163 decreased group) had decreased CD163 immediately after administration, with a median PFS of 13.6. There was a significantly difference in PFS between these two groups (hazard ratio 0.50 [0.26-0.93], log-rank test, p = 0.0263), but not in OS (p = 0.0548). These results suggested that the early change of serum soluble CD163 may be a predictive biomarker of efficacy of nivolumab plus chemotherapy in pts with HER2-negative MBC. Conclusions: Soluble CD163 may be a predictive biomarker for early detection of the efficacy of nivolumab plus chemotherapy in pts with HER2-negative MBC. (UMIN000029590)
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Approximately half of primary breast cancers exhibit low levels of human epidermal growth factor receptor 2 (HER2), defined as a score of 1+ on immunohistochemical (IHC) analysis or a score of 2+ on IHC and lack of HER2 gene amplification on in situ hybridization (ISH). Tumors classified as HER2-low represent a target for novel antibody-drug conjugates. In addition, HER2-low expression accounts for about 60% of HER2-negative breast cancers (BC). Real-world studies noted that HER2-low represents 47-54% of hormone positive (HR-positive) HER2-negative breast cancers, a percentage higher than in the triple negative subgroup, reported at 35%.

The goal of this study was to determine the frequency of HER2-low expression in patients with HR-positive/HER2-negative and triple-negative breast cancers (TNBCs) in the real-world and compare it with the published literature. The IntegraConnect (IC) real-world database of 330 thousand breast cancer patients was used for this analysis. Within the IC database, a subgroup of 387 patients with HR-positive/HER2-negative breast cancer and 618 patients with TNBC were abstracted with medical chart curation. The mean age at diagnosis for each group was 56 years and most patients had an ECOG performance status of 0-1. The statistical tests used were the Mann-Whitney test for age at diagnosis and the Chi-squared test for race, major stage, and ECOG at diagnosis. Differences were considered significant at P < .05.

In the HR-positive/HER2-negative subgroup (n=387), 327 patients were tested by IHC and ISH. Sixty patients were tested by ISH only and were removed as they did not fit the definition of HER2-low. Of the 327 HER2-negative patients, 199 patients exhibited low HER2 expression (IHC1+, n=138 patients; IHC2+/ISH-negative, n=61), accounting for 61% (199/327) of HR-positive/HER2-negative breast cancers. In this group, numerically more patients were HER2-low than HER2-negative across all race subgroups.

In the TNBC patient group (n=618), 546 patients tested HER2-negative by ICH and ISH. Patients testing HER2-negative by ISH only were removed (n=72) from the analysis. Of 546 patients with TNBC, HER2-low expression accounted for 42% (227/546) [IHC1+, n=168; IHC2+/ISH-negative, n=59].
In the Black or AA patients with TNBC subgroup, 37.2% (N=129) were HER2-low compared with 44% (N=353) in White patients. In all TNBC race subgroups, numerically more patients were HER2-negative compared with HER2-low.

In conclusion, analysis of the IC database showed HER2-low expression in 61% of HR-positive/HER2-negative breast cancers and in 42% of TNBC patients. Approximately 37% of Black or African Americans (AA) patients with TNBC expressed low levels of HER2. The frequency of HER2-low expression in TNBC in the IC database at 42% is slightly higher than previous studies that estimate HER2-low expression at 35% of TNBC. The percentage of HER2-low in HR+/HER2-negative breast cancers at 61% is higher than previous reports, which estimate low HER2 expression in patients with primary and recurrent HR+/HER2-negative breast cancers at 47 and 54%, respectively.

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Efficacy analysis of CDK4/6 inhibitors in combination with endocrine therapy treatment in HR+/HER2- breast cancer according to PAM50 intrinsic subtype: primary results of SOLTI-1801_CDK-PREDICT study

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Background: First-line treatment with cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) plus endocrine therapy (ET) has demonstrated efficacy in improving progression-free survival (PFS), overall response rate (ORR) and, more recently, ribociclib was also improve overall survival (OS) in hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer (aBC). Unfortunately, most patients eventually progress and develop secondary or primary endocrine resistance. To date, no clinical or molecular markers have shown clinical utility in this setting. However, data from retrospective analysis suggest that intrinsic subtypes (IS) are prognostic and predict benefit from CDK4/6i+ET (Finn SABCS 2017, Prat. JCO 2021). Here, we have evaluated the impact of IS in PFS and ORR.

Methods: This study prospectively evaluated patients with HR+/HER2- aBC treated in the first-line setting with CDK4/6i + ET from February 2015 to January 2022 across 5 hospitals in Spain. Tumor biopsies had been performed within 90 days prior the patient started the CDK4/6i + ET. RNA from FFPE tumors was analyzed at the nCounter® (Nanostring Technologies) using a 72 custom gene panel including the PAM50 genes. The primary objective is to correlate the baseline PAM50 IS with PFS. The Kaplan-Meier method and multivariable cox model PFS analyses were performed adjusting for previous endocrine sensitivity, visceral disease, and metastatic onset disease. Secondary objectives were to estimate the ORR based on RECIST1.1 and its association with IS and the development of a prognostic algorithm that includes clinical and genomic data.

Results: From May 2020 to May 2022, 113 patients with PAM50 results who met all eligibility criteria, including sample quality, were included. IS distribution was 42.5% Luminal A, 46.9% luminal B, 7.1% HER2-enriched, 0.9% basal-like and 2.6% Normal-like (89.4% luminal vs 10.6% non-luminal). Baseline patient characteristics are shown in table 1. The median follow-up
for PFS was 18.5 m (interquartile range 10.0 – 31.7m). Median PFS for Luminal vs no-luminal subtypes was 26.8 m (95% CI: 18.9 - 43.8 m) and 10.0 m (95% CI: 5.8 - 26.0 m) (adjusted hazard ratio [aHR]= 2.44 95% IC: 1.17 - 5.07). Median PFS by all IS was not reached (NR) for Luminal A (95% CI: 23.0 – NR); 19.5 m luminal B (95% CI: 15.7 - 27.3 m, aHR vs Luminal A= 1.98 95% IC: 1.09 - 3.62), 10.0 m HER2-E (95% CI: 4.4 - NR, aHR vs Luminal A= 2.75 95% IC: 1.05 - 7.18), 12.4 m Normal-like (95% CI: 5.8 - NR, aHR vs Luminal A= 19.35 95% IC: 2.32 - 160.89) and not estimable for basal-like (aHR vs Luminal A= 5.44 95% IC: 1.44 - 20.60). ORR was not significantly higher in Luminal B (55.1%) and HER2-E (57.1%) subtype versus luminal A (46.3%) (p=0.677). OS follow-up is still immature.

Conclusions: We confirmed the independent prognostic value of the PAM50 IS in first-line HR+/HER2- breast cancer treated with CDK4/6i+ET. Further gene expression analysis and development of a prognostic composite score is ongoing and will be presented at the conference.

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Baseline patient characteristics
Baseline patient characteristics (n=113)

<table>
<thead>
<tr>
<th>Median age, years [range]</th>
<th>50 (28-80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK4/6i n, %:</td>
<td></td>
</tr>
<tr>
<td>Palbociclib</td>
<td>61, 54.0%</td>
</tr>
<tr>
<td>Ribociclib</td>
<td>36, 31.9%</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>16, 14.1%</td>
</tr>
<tr>
<td>Endocrine sensitivity n, %:</td>
<td></td>
</tr>
<tr>
<td>Hormone-sensitive</td>
<td>83, 73.4%</td>
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<tr>
<td>Hormone-resistant</td>
<td>30, 26.6%</td>
</tr>
<tr>
<td>Metastatic onset n, %:</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>55, 48.7%</td>
</tr>
<tr>
<td>Yes</td>
<td>58, 51.3%</td>
</tr>
<tr>
<td>ECOG PS n, %:</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>70, 61.9%</td>
</tr>
<tr>
<td>1</td>
<td>41, 36.3%</td>
</tr>
<tr>
<td>2</td>
<td>2, 1.8%</td>
</tr>
<tr>
<td>Disease location n, %:</td>
<td></td>
</tr>
<tr>
<td>Visceral disease n, %</td>
<td>49, 43.4%</td>
</tr>
<tr>
<td>Bone only disease n, %</td>
<td>25, 22.1%</td>
</tr>
<tr>
<td>Hepatic disease n, %</td>
<td>28, 24.8%</td>
</tr>
<tr>
<td>Menopausal status n, %: *Male patients not included (n=3)</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>83, 75.5%</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>27, 24.5%</td>
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<tr>
<td>Grade n, %:</td>
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<tr>
<td>1</td>
<td>6, 5.9%</td>
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<tr>
<td>2</td>
<td>74, 72.5%</td>
</tr>
<tr>
<td>3</td>
<td>22, 21.6%</td>
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<tr>
<td>Histologic type n, %:</td>
<td></td>
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<tr>
<td>Non-special type (IDC)</td>
<td>93, 83.0%</td>
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<tr>
<td>Infiltrating lobular carcinoma (ILC)</td>
<td>7, 6.2%</td>
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<tr>
<td>Other</td>
<td>12, 10.7%</td>
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<tr>
<td>HER2 IHQ n, %:</td>
<td></td>
</tr>
<tr>
<td>HER2-0</td>
<td>49, 43.7%</td>
</tr>
<tr>
<td>HER2-low (1+ or 2+ with ISH negative)</td>
<td>63, 56.25</td>
</tr>
</tbody>
</table>

Disclosure(s):
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An HRD scoring system based on long-focal copy number alterations predictive of PARP inhibitor response

Homologous recombination deficiency (HRD) is characterized by a defective double-stranded DNA repair mechanism due to alterations in the homologous recombination (HR) pathway. Deleterious mutations in HR pathway genes can help identify potential responders to platinum-based chemotherapies and PARP inhibitors (PARPi), which promote apoptosis in HRD cells. Until recently, the use of PARPi in breast cancer (BC) was limited to advanced or metastatic disease with pathogenic or likely pathogenic germline BRCA (gBRCA) mutations. However, the use of PARPi has expanded to treat early-stage HER2-negative BC with a high risk of recurrence and gBRCA mutations, HER2-negative BC with somatic BRCA mutations, and triple-negative BC. To date, no universal method for HRD scoring is accepted; therefore, biomarkers are needed to stratify patients into PARPi responders and nonresponders more effectively. Because PARPi are used to treat HRD-driven cancers, we aimed to identify genomic consequences of HRD. For HRD-specific features, we calculated the proportion of long-focal total copy number alterations (LF-tCNA), which estimates amplification events for long-focal segments. Aneuploidy is especially prevalent in medullary, metaplastic, and invasive micropapillary BCs. These copy number variations are not necessarily consequences of HRD but can influence HRD scores. Genome-wide loss of heterozygosity (gwLOH) can be a result of HRD and used as a biomarker for HRD. We developed several scoring methods based on LF-tCNA, gwLOH, and aneuploidy scores. These scores were tested as predictors of HRD, defined as known loss-of-function germline mutations in BRCA1, BRCA2, PALB2, or BARD1 (TCGA-BRCA cohort, n = 1,032). To calculate the optimal HRD score, we used multivariate logistic regression analysis with HRD as an outcome and LF-tCNA, LOH, and ploidy as predictors. Based on the results of logistic regression, LF-tCNA and ploidy were selected to calculate HRD status. The positive and negative predictive values (PPV, NPV) were used to set the upper and lower thresholds, respectively. Samples with HRD scores above 7 (PPV) have the greatest potential for PARPi and platinum-based therapy response, while scores below -1 (NPV) were considered HRD wild type (WT). To validate the developed HRD score, we tested the score by
combining BC cohorts (MSK_NCI and MET500 cohorts, n = 164) and used gBRCA1/2 pathogenic mutations as an outcome. Our HRD scoring system distinguished HRD WT from HRD-positive samples (AUC = 0.81) more effectively than a previously reported score based on LOH, telomeric-allelic imbalance (TAI), and large-scale state transitions (LST) (AUC = 0.72). We tested our HRD scoring system across tumor microenvironment molecular subtypes. The median HRD score in the basal-like subtype was increased compared to other subtypes, supporting the prevalence of gBRCA1/2 pathogenic mutations in this subtype. Moreover, the number of HRD-positive patients and the percent positive agreement, defined as the proportion of positive test results from our HRD also positive for HR mutations, were calculated for each BC subtype. Only 22% of basal-like HRD-positive samples also carried germline HR pathway mutations, which indicates 78% of HRD-positive patients who might benefit from PARPi or platinum treatment would have been missed by germline HR gene panels. This BC HRD scoring method is a promising tool for identifying HRD patients who may respond to PARPi and platinum-based therapies, but additional studies are required for clinical validation.

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Targeted capture sequencing allows sensitive genomic profiling of circulating tumor DNA in advanced HR+/HER- breast cancer patients

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Introduction: CDK4/6 inhibitors provide substantial benefits as 1st or 2nd line treatments and are now the standard of care for patients with advanced HR-positive, HER2-negative breast cancer. Recently, we demonstrated that a high-resolution SiMSen-seq assay (SSS) provides a sensitive and robust method for detecting 11 PIK3CA hotspot mutations in cell-free circulating DNA, allowing the identification of patients eligible for alpelisib treatment. Unfortunately, all patients progress at some time point due to intrinsic or acquired resistance. Therefore, detecting additional genomic biomarkers for treatment resistance beyond PIK3CA mutations is crucial. Targeted panel sequencing offers a promising strategy to profile circulating tumor DNA (ctDNA) for genetic alterations in multiple genes associated with treatment response and disease progression. This ongoing study aims to show that a commercial NGS assay (AVENIO ctDNA Expanded Kit, Roche Diagnostics) can (1) detect PIK3CA mutations with similar sensitivity as our high-resolution SSS assay and can (2) simultaneously identify additional genetic alterations in multiple genes, possibly associated with treatment resistance or disease progression. Material and Methods: To this end, we collected plasma samples from 46 metastatic HR+/HER2- breast cancer patients before starting 1st (32 patients) or 2nd (14
patients) line treatment. Samples were analyzed using SSS and the AVENIO ctDNA Expanded Kit, enriching for 77 clinically relevant cancer genes. PIK3CA mutation detection and variant allele frequencies (VAF) were compared between the two methods. Additionally, mFAST-SeqS was used to estimate the tumor fractions in plasma samples. Results: The median z-score from mFAST-SeqS analyses was 2.38 [25–75th percentile: 1.23–4.5], and 17/46 (37%) patients had z-scores \( \geq 3 \), indicating elevated tumor fractions (>5%). Patients starting 2nd line treatment had significantly higher z-scores than those starting 1st line treatment (median 2.2 vs. 3.8, rank-sum p-value 0.042). One sample repeatedly failed with the SSS assay, leaving 45 samples for a head-to-head comparison. Considering only PIK3CA hotspot mutations covered by both assays, 16 alterations were detected in 14 patients (31%) by the SSS assay and 19 alterations in 17 patients (38%) by the AVENIO ctDNA Expanded Kit. Both assays detected the identical co-occurrence of two PIK3CA mutations in two samples. Two of three mutations only detected with the AVENIO ctDNA Expanded Kit were also observed with the SSS assay but below the pre-defined detection limit. One mutation was only detected by the AVENIO ctDNA Expanded Kit. Overall, we found an excellent concordance rate of 94% between the two assays, confirming the high sensitivity of the panel sequencing assay. Moreover, the VAF of SSS and AVENIO kit were highly correlated (Spearman’s rho = 0.97, p < 0.001). Using the AVENIO kit, a large number of additional mutations in 40 genes could be identified in 42/46 (91%) patients with a median of 2.0 variants (range 1-13) per sample. The most frequently mutated genes included PIK3CA (43%), followed by ESR1 (20%), TP53 (20%), MET (17%), SMAD4 (17%), ERBB2 (11%), and BRCA2 (11%). The median VAF was 0.64% (range 0.1-29.8). Further analyses are still ongoing. Conclusion: The AVENIO ctDNA Expanded Kit revealed a high sensitivity and concordance rate for detecting PIK3CA hotspot mutations in plasma samples compared with the high-resolution SSS assay. A major advantage of panel sequencing over a single gene approach is that the interrogation of multiple genes can indicate a true negative PIK3CA result if other variants are present with a high VAF. Moreover, other actionable targets or mechanisms of resistance can be captured simultaneously, thus improving the effective precision treatment of metastatic breast cancer patients.

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Quantitative proteomic analysis of plasma exosomes from patients with advanced hormone receptor-positive/HER2-negative breast cancer receiving palbociclib and tamoxifen

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Background: A CDK4/6 inhibitor (CDK4/6i) in combination with endocrine therapy (ET) is standard first-line therapy for advanced, hormone receptor (HR)-positive, HER2-negative breast cancer (BC). However, not all patients respond and responders eventually develop drug resistance and disease progression. Exosomes are small extracellular vesicles that are secreted by both normal and tumor cells as a mechanism for intercellular communication. The protein cargo of exosomes reflects biological processes activated in cancer cells and may serve as predictive biomarkers to select patients most likely to benefit from treatment and to identify mechanisms of resistance. Methods: Whole blood was collected in Streck tubes at baseline and at time points during treatment from patients with advanced, HR+/HER2- BC enrolled in a single arm, phase 2 trial of first line therapy with palbociclib plus tamoxifen that was conducted by The Big Ten Cancer Research Consortium (NCT02668666). Plasma was separated and stored at -80°C within 48 hours of collection. Different exosome protein isolation methods were evaluated and optimized to maximize protein recovery. Exosome and plasma proteins were extracted, purified, and digested with trypsin. Tryptic peptides were isotopically labeled with Tandem Mass Tag (TMT) 10plex for protein expression level quantitation. Triplicate samples from each patient were analyzed by LC-MS/MS with QExactive HF Orbitrap mass spectrometer. An unsupervised clustering method was used to classify patients based on exosomal proteomic profiles. Results: We developed a sensitive and efficient exosome extraction method to obtain exosome protein from minimal volumes of patient plasma. The optimized exosome isolation method quantitatively identified 800 proteins from a 100 µl plasma sample. Significant enrichment of exosome-specific markers was observed when comparing patient samples with healthy donor samples. A network model was developed to differentiate responders/stable disease patients from non-responders using exosome proteomics data generated from pretreatment plasma samples. Preliminary data from the first 22 patients analyzed (responders, n= 6; stable disease, n=12, and non-responder, n=4) identified a network of 45 proteins that predicted response/stable disease vs progressive disease with high specificity (95%) and sensitivity (89%). We also noted significant differences in the exosome proteomic profiles of patients with de novo vs. recurrent metastatic disease. A network of 22 proteins differentiated de novo vs recurrent metastatic disease with > 85% sensitivity and 78% specificity, providing molecular evidence differentiating the two disease states. This finding is relevant in light of the higher response rate and improved PFS in patients with de novo metastatic disease in this trial, and confirms that this approach may provide molecular insight into mechanisms of primary resistance to CDK4/6i. Results for the entire trial cohort of 46 patients will be presented, along with analysis of serial samples collected at various time points during treatment. Conclusion: This proof-of-concept study demonstrates that an ultrasensitive exosome proteomics platform combined with deep learning methods is ideally suited for developing predictive protein biomarkers and for exploring molecular mechanisms of drug resistance. If results are confirmed, this novel approach holds great promise for identifying protein biomarkers that could be used to select patients unlikely to respond to ET and CDK4/6i in order to spare them ineffective treatment and for selecting participants for clinical trials of novel agents. Additionally, exosome proteomics data generated from serially collected
specimens can be used to identify mechanisms of resistance that emerge during therapy. This approach can be widely applied to other treatment regimens and disease sites. This study was funded by Pfizer.

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Identifying immune-related predictive factors for paclitaxel + bevacizumab therapy in patients with HER2-negative advanced breast cancer- A multicenter retrospective study

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Background: In IMpassion 130 trial, programmed death-ligand 1 (PD-L1) expression was seen in about 40% of participated patients with triple negative advanced breast cancer (TN-ABC) [Schmid, 2018, N Engl J Med], however, actual situation of PD-L1 expression in patients HER2-negative ABC patients including with TN-ABC has not been well studied. Furthermore, no biomarker related to chemotherapy for HER2-negative ABC patients except for PD-L1 in TN-ABC has been identified. Recently, several reports regarding the relationship between peripheral immune-related markers; such as absolute lymphocyte count (ALC) or neutrophil-to-lymphocyte ratio (NLR), and efficacy of eribulin therapy [Miyoshi, 2020, Breast Cancer; Watanabe, 2020, Breast Cancer Res Treat] or paclitaxel plus bevacizumab (PB) therapy [Nakamoto, 2021, Sci Rep], however, the relationship between the efficacy of PB therapy and peripheral immune related markers including dynamic change during the therapy or local immune-related markers is unclear. Therefore, we conducted multi-institutional, retrospective study 1) to evaluate the actual situation of PD-L1 expression and other immune-related markers of the primary site by central review, and 2) to explore biomarkers for first-line PB therapy using
peripheral and local immune-related markers. Patients and methods: We retrospectively
reviewed medical records of HER2-negative ABC patients who received PB therapy as first-line
(1L) or second-line chemotherapy for ABC. Clinical data including ALC, NLR and serum
albumin (Alb) were extracted from medical records, and the pathology of archived tissues of
primary and metastatic site (if available) were centrally reviewed including PD-L1 (VentanaR
SP142). Statistical analyses were performed using Kaplan-Meier method, log-rank test,
Wilcoxon’s test, and Cox hazard model. Mixed-effects model for repeated measures (MMRM)
to evaluate the relationships between dynamic change in immune-related markers and time-to
treatment termination (TTT) of PB therapy. Results: We identified 156 HER2-negative ABC
patients who underwent PB therapy, and 114 out of 156 patients were eligible for analyses. Of
114 patients, 63 patients (55.3%) had recurrent disease, and 65 (57.0%) patients had visceral
disease. Eighty-seven out of 114 (76.3%) patients received PB therapy as 1L chemotherapy.
Eighty-four specimens (73.7%) were diagnosed as estrogen-receptor (ER) positive, and PD-L1
positivity rate were 3.6% (1/84) in ER+ subgroup and 30.0% (6/20) in ER- subgroup,
respectively. Paired biopsy specimens were eligible in 14 patients, and significant elevation of
Ki67 labeling index was noted. In patients who received 1L PB (n = 87), there was no positive
3) at the initiation of 1L PB therapy and TTTs. However, low NLR (cut-off at 2.5 and 3) at the
initiation of second cycle of PB therapy reduced the risk for treatment-termination as; hazard
ratio [HR], 0.427; 95% CI 0.218-0.843; P = 0.0147 and HR, 0.344; 95% CI 0.170-0.731; P =
0.0066, respectively. PD-L1 positive patients (n = 5) showed numerically increased risk of
treatment-termination (HR, 2.68; 95% CI, 0.922-6.196; P = 0.0674) for 1L PB therapy, however,
there was no significant difference in mortality risk regarding PD-L1 statuses. Multivariate
analysis using MMRM disclosed that increase of Alb level was predictive factor for 1L PB
therapy (HR, 0.41; 95%CI, 0.18-0.93; P = 0.0338). Conclusion: According to our real-world
study, 1) PD-L1 positive rate was lower than that of previous reports, 2) low NLR at the initiation
of second cycle of PB therapy and dynamic change in albumin level were identified as
predictive factors and 3) PD-L1 overexpression was not a prognostic or a predictive factor for
PB therapy in patients with HER2-negative ABC. Funding: Chugai Pharmaceutical CO., LTD.

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Efficacy of subsequent-abemaciclib treatment after disease progression on palbociclib combined with endocrine therapy in patients with ER-positive HER2-negative metastatic breast cancer

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Purpose: Currently, CDK4/6i combined with ET has become the standard of care as first- or second-line treatment for ER+ human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). However, at present, there are no guidelines for the selection of appropriate treatments after disease progression on prior CDK4/6i treatment combined with ET. Therefore, this retrospective study aimed to verify the efficacy and evaluate predictive factors of clinical outcomes in the patients with ER+/HER2- MBC during subsequent-abemaciclib treatment after disease progression on prior-palbociclib combined with ET.

Methods: In total, 81 patients with ER+/HER2- MBC were treated with palbociclib and ET at our medical center between December 2017 and November 2020. Among them, 25 patients who received subsequent-abemaciclib after disease progression on prior-palbociclib were included. All patients provided informed consent for the indicated treatment. Clinicopathological variables were compared using Fisher’s exact test. The Mann–Whitney U test was used to compare categorical variables. PFS and time to chemotherapy (TTC) were estimated using Kaplan–Meier analysis with 95%CIs.

Results: The median age was 69 years, and four women were premenopausal. Stage IV disease occurred in 28.0% (7/25) and visceral metastases were observed in 68.0% (17/25) of the patients. The treatment line of prior-palbociclib was the first-line in 3 (12.0%), second-line in 11 (44.0%), and third- and late-line in 11 patients (44.0%). The median PFS of prior-palbociclib plus ET was 6.3 months (95%CI=5.814–6.786). Subsequent-abemaciclib combined with fulvestrant after disease progression on prior-palbociclib was administered in 64.0% (16/25) of the patients. Median numbers of previous ET and chemotherapy of subsequent-abemaciclib were 2 and 0, respectively. Subsequent-abemaciclib after disease progression on prior-palbociclib resulted in an ORR and clinical benefit rate (CBR) of 16.0% (4/25) and 44.0% (11/25), respectively (Table 1). Kaplan–Meier curve analysis showed that the median PFS was 5.3 months (95%CI=3.082–7.518). Univariate analysis revealed that the best overall response (BOR) to prior-palbociclib was the only independent predictive factor for PFS (HR=0.190; 95%CI=0.050–0.722; p=0.015) (Table 2). With regard to grade ≥3 TRAEs in the subsequent-abemaciclib, neutropenia and diarrhea were observed in 16.0% (4/25); appetite loss and fatigue in 12.0% (3/25); leukopenia and anemia in 8.0% (2/25); and thrombocytopenia and liver dysfunction in 4.0% (1/25) of patients. Of them, 10 patients required one dose-level reduction and 2 needed two dose-level reductions. Three patients (12.0%) required dose discontinuation: two had uncontrollable...
appetite loss and nausea and one had pneumonia. Of the 25 patients, 12 were not administered any prior chemotherapy and the median TTC in those treated with subsequent-abemaciclib was 33.9 months (95%CI=11.3–56.1). Next-line treatment after disease progression on subsequent-abemaciclib in the patients who were not administered prior chemotherapy was performed in 2 (8.0%) who were treated with ET and in 12 (48.0%) who were treated with chemotherapy (1 taxane-based, 7 eribulin, and 4 oral 5-fluorouracil). The median PFS in patients treated with chemotherapy after disease progression on subsequent-abemaciclib treatment was 6.2 months (95%CI=3.4–8.9).

Table 1. Best overall response rate in patients with ER+/HER- MBC who were treated with subsequent-abemaciclib after disease progression on prior-palbociclib

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</tr>
<tr>
<td>CRR</td>
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<td>44.0</td>
</tr>
</tbody>
</table>

Table 2. Univariate and multivariate analyses of the progression-free survival in patients with ER+/HER2- MBC treated with subsequent-abemaciclib after progression on prior-palbociclib

Disclosure(s):
Hirohito Seki, MD.PhD: No financial relationships to disclose
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Do thymidine kinase 1 (TK1) plasma concentration and activity play a role in therapy management of metastatic breast cancer patients treated with CDK4/6 inhibitors?

Introduction: CDK4/6 is a checkpoint kinase, regulating the transition of the S into the G2 phase of the cell cycle. As a cell transverses through the cell cycle, thymidine kinase 1 (TK1) is expressed and represents a direct marker of proliferative activity, which might indicate therapy efficiency of CDK4/6 inhibitors (CDK4/6i), the first choice of therapy in case no sign of visceral crisis is detected in hormone receptor positive (HR+), HER2 negative (HER2-) metastatic breast cancer (MBC) patients. We here determined whether the activity and/or concentration of TK1 in plasma samples of MBC patients treated with CDK4/6i harbours predictive, monitoring or prognostic value.

Methods: Blood of 90 HR+/HER2-MBC patients drawn at baseline of CDK4/6i (Ribociclib/Palbociclib) plus endocrine treatment and 18 HR+/HER2-MBC patients drawn before initiation of endocrine monotherapy (control), as well as available matched blood samples of these patients after six months under TX (n=90), 12/24 months before progression (n=72/24) and at the time of progression (n=52) are available. TK1 concentration in plasma samples was measured by competitive ELISA (ABIN809094, Shanghai BlueGene Biotech Co., LTD, China) and TK1 activity of matched plasma samples by competitive, two-step chemiluminescence immunoassay (REF 310960, Diasorin, Stillwater, US). Statistical analysis was conducted via log-rank test and univariate or multivariate Cox regression.

Results: Currently, baseline samples were evaluated for TK1 concentration (n=106) and activity (n=90). The mean value for TK1 activity was 12.69 U/L and the median value was 8.37 U/L in the entire cohort. Values ranged from 0.89 to 79.50 U/L and the standard deviation was determined to be 12.64 U/L, which is similar to the mean value. In contrast to the control group, high TK1 activity
(Cut-off: mean or determined by ROC analysis and maximal Youden’s Index for PFS < six months) was significantly correlated with decreased progression free survival (PFS) in the CDK4/6i cohort (p-value < 0.05 in log rank test and univariate Cox regression). In addition, using multivariate Cox regression analysis including clinical parameters (e.g. therapy line, prior chemo- or endocrine therapies, type of CDK4/6i accompanying endocrine therapy, number of sites of metastases, visceral metastases, menopausal status), TK1 activity was found to be an independent marker for PFS. High TK1 activity (Cut-off: mean or determined by ROC analysis and maximal Youden’s Index for PFS < six months or already deceased patients) at baseline was significantly correlated with shorter time from baseline to death in the CDK4/6i cohort (p-value < 0.05 in log rank test and univariate Cox regression) but not in the control cohort. For TK1 concentration analysis, the mean value was 21.76 ng/ml and the median value was 18.57 ng/ml in the entire cohort. Values ranged from 7.35 ng/ml to 46.66 ng/ml and the standard deviation was determined to be 11.16 ng/ml, which is half of the mean value. In contrast to TK1 activity measurements, no significant association of TK1 concentration with PFS or overall survival (OS) was detected in the CDK4/6i cohort. Currently, all remaining samples during the course of treatment are evaluated for TK1 activity and concentration and final statistical analysis of the complete data set will be available at the meeting. Conclusion: Our preliminary results indicate that TK1 activity, in contrast to TK1 concentration, determined before starting CDK4/6 inhibition could be a suitable predictive and prognostic biomarker for estimating response to treatment. Our final analysis will clarify, whether TK1 could also serve as a monitoring marker during treatment.

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Background: Different immune cell states reflect distinct tumor microenvironment and led to various clinical outcomes for cancer patients. However, very few studies examined the contribution of peripheral blood (PB) immune landscapes to the treatment response due to the limited applications. This study aimed to explore the circulating immune cell landscapes associated the sensitivity to cytotoxic chemotherapy with trastuzumab in HER2 positive metastatic breast cancer patients. Methods: Whole blood were drawn at baseline and after 2 cycles of trastuzumab plus cytotoxic chemotherapy from six patients (3 responders and 3 non-responders). Approximately 3,500 to 10,000 peripheral blood mononuclear cells per patients were profiled using single-cell RNA sequencing (scRNA-seq). scRNA-seq data were further processed and analyzed using Seurat package version 3.1. Cell populations were clustered using the Louvain algorithm and subsequently annotated using known marker genes. Differential abundance in cell population was quantified using MiloR and differentially expressed genes were detected using MAST between responders and non-responders. Results: After removing low quality cells, a total of 65,295 cells were clustered into 18 clusters. CD8 Effector T, CD4 Naïve T, CD4 Effector T, Cytotoxic NK, Naïve B, Plasma B and Monocytes were significantly enriched in responders compared to non-responders. Especially, CD8 Effector T, NK, Plasma B and Classical Monocytes showed distinct patterns that those cells were enriched in pre-treatment than post-treatment of responder but not in non-responder. From the differentially expressed gene analysis, cytotoxic or costimulatory marker genes (GZMK, GZMA, GNLY, CCL5, NKG7, PRF1) were enriched in responders. While, exhausted or coinhibitory marker genes (DNAJB1, LGALS9, HAVCR2) were enriched in non-responders. Gene set enrichment analysis revealed four pathways associated with T cell, B cell receptor signaling, NK cell mediated cytotoxicity and Cytokine-cytokine receptor interaction which showed differences between responders and non-responders following chemotherapy. Finally, validation with flow cytometry using independent cohort showed that constant expression manner in HAVCR2, LGALS9 and LGALS3 genes. Conclusions: Single-cell transcriptome analysis identified distinct PB immune landscapes associated with treatment response in HER2-positive metastatic breast cancer patients. Differential abundance and unique gene expression programs of immune cell populations could serve as potential predictive biomarkers for anti-HER2 therapy.

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Predictive and prognosis value of PIK3CA mutations in HER2-positive breast cancer treated with tyrosine kinase inhibitors (TKIs): a systemic review and meta-analysis

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Background: PIK3CA mutations is one of the most frequent gene alterations in breast cancers, which was reported to be related to the treatment response of anti-HER2 regimens. However, the relationship between PIK3CA mutations and treatment response of a tyrosine kinase inhibitors (TKIs) is still unclear. We thus conducted a systemic review and meta-analysis to investigate the predictive and prognosis value of PIK3CA mutations in HER2-positive breast cancer treated with TKIs. Methods: The following databases were searched from inception to July 2022: Medline, Embase and the Cochrane Library. Abstracts from conferences were also reviewed for inclusion. The critical information was extracted from eligible studies. Results: A total of 16 reports including 17 studies were assessed for eligibility, enrolling 1706 patients. Ten studies including 902 patients were in the neoadjuvant setting, the pCR rate is significantly higher in PIK3CA wild-type (WT) patients than in mutated-type (MT) patients (OR = 0.45; 95% CI: 0.31-0.65; P< 0.001). Seven studies including 804 patients were in the metastatic setting, the pooled objective response rate (ORR) is significantly higher in PIK3CA WT patients than in MT patients (OR = 0.40; 95% CI: 0.23-0.70; P = 0.001), and similarly, the clinical benefit rate (CBR) in WT patients is also higher (OR = 0.43; 95% CI: 0.19-0.98; P=0.045). A total of 4 metastasis studies reported progression free survival (PFS), and 2 of them reported overall survival (OS), revealing a marginally significant relationship between PIK3CA mutation and worse PFS (HR = 0.82; 95% CI: 0.67-1.00; P=0.052) and OS (HR=0.63, 95%CI : 0.39-1.02; P=0.062). No evidence of publication bias was found in both the neoadjuvant setting and metastatic setting. Conclusion: Our findings indicate that PIK3CA mutations is significantly associated with a lower rate of pCR when treated with TKI-containing regimens in neoadjuvant chemotherapy of early-stage HER2-positive breast cancer, and is significantly associated with lower ORR and CBR in metastatic HER2-positive breast cancer.
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Background: HER2-positive breast cancer subtype accounted for around 15-20% of all breast cancer. The introduction of HER2-targeted therapy such as trastuzumab and pertuzumab has
remarkably increased the patients’ prognosis of HER2-positive breast cancer. However, resistance exists due to impaired drug binding to HER2 receptor and constitutive activation of HER2 downstream signaling pathways. P95HER2 isoform is a truncated form of HER2 that retains the C terminal domain but lacks an N terminal trastuzumab binding site, leading to trastuzumab resistance in HER2-positive breast cancer. A new P95HER2 antibody is developed to target the extracellular domain of p95HER2 in formalin-fixed paraffin-embedded (FFPE) HER2-positive breast cancer tissues by using hematoxylin and eosin (HE) staining method. Objectives: To evaluate the expression of P95HER2 and its clinicopathological characteristics in HER2-positive breast cancer. Methods: We assessed 68 HER2-positive patients (IHC 3+ or IHC 2+/in situ hybridization [ISH]+) from Fudan University Shanghai Cancer Center (FUSCC) who underwent breast cancer surgery and were treated with adjuvant chemotherapy (taxane or anthracycline or combination) plus trastuzumab from 2014 to 2016. P95HER2 HE antibody is provided by Simcere Pharma. In this study, we compared 27 patients with primary trastuzumab resistance with 41 non-relapse breast cancer patients. 14 patients have not received trastuzumab targeted therapy. P95HER2 staining of either 1+, 2+ or 3+ observed in any tumor area in HE slides was considered to be P95 HER2 positive. Chi-square test was used to determine the relationship between P95HER2 expression of patients’ characteristics. The main outcome measures were disease free-survival (DFS), distant disease-free survival (DDFS) and overall survival (OS) by using log-rank test. Univariable and multivariable Cox regression analyses were used to identify independent factors related to prognosis. Results: From 2014 to 2016, we assessed the expression of P95HER2 expression in 68 HER2 positive breast cancer patients from FUSCC. Median follow-up was 45 months. In our study, 19 (27.9%) were P95HER2 positive. P95HER2 positive expression rate is higher in premenopausal patients than in postmenopausal patients (68.4% vs 38.8%, P= 0.028). Univariable analysis showed that higher T-stage (P= 0.018), higher N-stage (P= 0.001) and P95HER2 positive expression (P= 0.033) were associated with worse DDFS. Multivariable analysis showed that higher T-stage (hazard ratio, 6.019; 95% CI, 1.205-30.078; P= 0.029) and P95HER2 positive (hazard ratio, 2.349; 95%CI, 1.03-5.358; P= 0.042) independently predicted worse DDFS. P95HER2 positive was significantly associated with shorter 5-year DDFS (42.1% vs 67.6%, P= 0.028), but has no significant difference in DFS (36.8% vs 59.5%, P= 0.072) and OS (74.8% vs 81.2%, P= 0.685). Conclusions: P95HER2 positive was found more in premenopausal patients and was associated with a higher metastasis rate, indicating that P95HER2 expression tends to be a more aggressive isoform type of HER2-positive breast cancer. P95HER2 may serve as a therapeutic target for anti-HER2 therapy.

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Background: Homologous recombination deficiency (HRD), broadly defined as a loss of the cellular mechanism underlying homologous recombination, is often observed in breast cancer. HRD causes distinctive perturbations to tumor genomic architecture that allow for its molecular identification, while also rendering HRD+ cancers vulnerable to specific chemotherapeutic interventions. This makes the molecular identification of HRD a promising avenue in precision medicine of breast cancer. Specific features of HRD include the presence of large-scale transitions (LST), telomeric allelic imbalance (TAI) and Loss of Heterozygosity (LOH). Each are
readily detectable via targeted next generation sequencing (tNGS) or via array-based genotyping. However, genome-wide approaches for HRD detection using cost-effective methods, such as low-pass sequencing (LP-WGS), remain relatively under-explored. Here, we investigated whether HRD signals can be successfully re-capitulated using LP-WGS technology and benchmarked our results against the current field standard (both tNGS and array genotyping). Methods: LP-WGS and tNGS was performed on 96 samples across a range of tumor types (including N=17 breast cancer samples). LP-WGS libraries were prepared using Nextera (Illumina) using 0.4ng DNA input, and sequenced to 0.5-1x coverage. tNGS libraries were prepared using TSO500 (Illumina) using 40-80ng input, and sequenced to >150x unique read coverage. Regions of CNV were estimated using CNVKit v0.9.6, and regions of LOH were estimated using a novel ancestry-aware method. Small variant detection was performed using the TSO500 v2.2.0.12 analysis pipeline. SNP array analysis of 12 tumor samples using Oncoscan (ThermoFisher) was also performed. CNV and LOH estimates derived from LP-WGS, TSO500 and SNP array data were calculated using Jaccard similarity, treating the SNP array data as the “ground truth”. Results: We benchmarked HRD signals derived from LP-WGS compared to the array-based calls and observed near perfect sensitivity for CNV gains across samples (Jaccard index=1.0), as well as for CNV losses between LP-WGS and SNP array (Jaccard index=1.0). We additionally noted that LPS-WGS calls captured both CNV loss and gains that were not detectable via the SNP array. For TAI, LP-WGS re-capitulated 7/10 unique signals also identified via array. We also observed high concordance between regions of the genome-wide, paving the way for a more affordable assay that may help to inform clinical decision making in the future treatment of breast cancer.

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Long-term oncologic outcome of unselected triple-negative breast cancer patients according to BRCA1/2 mutations: a comprehensive single institution study

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Background Triple-negative breast cancer (TNBC) is known to have a higher risk of early recurrence and relatively low risk of late recurrence compared to luminal type breast cancer. Among all subtypes of breast cancer, TNBC is more likely to have BRCA1/2 germline mutation which showed prevalence rate from about 10% to 20% in previous reports. To date, there are only few studies about the effect of BRCA1/2 mutations on the long-term oncologic prognosis in TNBC patients. We analyzed long-term oncologic outcome in unselected TNBC patients according to BRCA1/2 mutations in a comprehensive single institution. Methods Among 11,994 patients who underwent primary breast cancer surgery at Samsung Medical Center (SMC) between June 2008 and January 2016, 1,628 (13.6%) were TNBC patients. Of those, patients with inadequate and unavailable samples at SMC biobank and patients with follow-up duration less than 12 months and who had distant metastasis at presentation were excluded from the study, and 953 patients were enrolled. A retrospective study was conducted and BRCA1/2 genetic testing was done with SMC biobank samples through Next Generation Sequencing (NGS). Results Among 953 unselected TNBC patients, 122 patients (12.8%) had BRCA1/2 mutations: 91 (9.5%) were in BRCA1, and 32 (3.4%) were in BRCA2. One patient had both BRCA1/2 mutations. BRCA1/2 carriers were more likely to have personal history of ovarian cancer (9.0% vs. 0.5%, p < 0.0001), family history of breast cancer and/or ovarian cancer (40.2% vs. 9.4%, p < 0.0001), bilateral breast cancer (4.9% vs. 1.2%, p = 0.0105), and higher nuclear grade (86.0% vs. 74.0%, p = 0.0250). The median follow-up duration was 80.9 months. There were no significant differences in disease-free survival (DFS), distant metastasis-free survival (DMFS), overall survival (OS), and breast cancer-specific survival (BCSS) (p = 0.375, 0.268, 0.413, and 0.133, respectively) between BRCA1/2 carriers and non-carriers. However, BRCA1/2 carriers showed significantly worse contralateral breast cancer (CBC)-free survival than non-carriers (p < 0.0001). Sixty and 120-months cumulative recurrence rate were 18.5% and 31.2% for BRCA1/2 carriers versus 19.3% and 22.7% for non-carriers (p = 0.834 and 0.136, respectively). However, cumulative recurrence rate at 150 months showed absolute but not statistically significant difference between BRCA1/2 carriers and non-carriers (36.2% versus 23.5%, p = 0.080). Cumulative CBC recurrence rate on 60, 120- and 150-months estimates were 6.7%, 18.7% and 25.5% for BRCA1/2 carriers versus 1.1%, 2.7% and 5.2% for non-carriers which showed statistically meaningful difference (p = 0.025, 0.006 and 0.018, respectively). Sixty months, 120- and 150-months cumulative expire rate were 11.2%, 15.6% and 27.7% for BRCA1/2 carriers versus 14.3%, 20.7% and 20.7% for non-carriers (p = 0.319, 0.202 and 0.549, respectively). Discussion In this unselected cohort of patients with TNBC, we found 12.8% (122 patients among 953) prevalence of BRCA1/2 mutations. The median follow-up duration was 80.9 months. There was no significant difference in DFS, DMFS, OS and BCSS by BRCA1/2 mutation status in long-term follow up. However, BRCA1/2 carriers showed significantly worse CBC recurrence rate at 60, 120- and 150- months. And also, BRCA1/2 carriers had 12.7% higher risk of recurrence than non-carriers at 150 months, which was not statistically meaningful but showed absolute difference. Among patients with CBC recurrence, 41.3% (12 patients among 29) were BRCA1 carriers, over 85% had TNBC type of recurred CBC and approximately 80% underwent chemotherapy. In conclusion, we demonstrated that CBC recurrence risk is relatively high in TNBC patients with BRCA1 mutation and showed high chance to receive chemotherapy. Therefore, long-term follow up and appropriate genetic counseling, risk assessment should be done properly for BRCA1/2 mutation carriers in TNBC patients.

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Background: Extreme adiposity has been associated with tumor progression and increased mortality after a breast cancer diagnosis, but the underlying mechanisms remain unclear. Pre-clinical and in vitro analyses suggest that higher levels of adiposity impair anti-tumor immunity, but studies in human breast cancer patients are lacking. Previously, we found that higher levels of subcutaneous adiposity had stronger associations with breast cancer outcomes than did higher levels of visceral adiposity or overall obesity measured by BMI, underscoring the
importance of measuring adipose tissue distribution as well as overall body size to understand the adiposity-cancer link.

Methods: We identified women with a first-primary, stage 2 or 3 invasive breast cancer diagnosed and treated at Kaiser Permanente Northern California between 2005 and 2015. Using diagnostic computed tomography scans collected as part of routine clinical care, we measured subcutaneous (SAT) and visceral adipose tissue (VAT) areas in cm² at the third lumbar vertebra. We calculated body mass index (BMI) from clinically-collected height and weight. We isolated RNA from 251 FFPE breast tumors collected at biopsy or excision; these were a preliminary, random sample within each immunohistochemical subtype groups from an ongoing study that will analyze 1400 breast tumors. We verified RNA quality prior to performing NanoString BC 360™ assays to calculate the PAM50 molecular intrinsic subtype and measure the expression levels of genes related to immune cell abundance and anti-tumor immune activity. Using linear regression models, we examined the mean change in log2 gene expression (dependent variables) associated with each adiposity exposure (BMI, SAT and VAT as independent variables).

Results: Mean (SD) age at diagnosis was 56 (13); a majority of women were either overweight (BMI 25-<30-kg/m²: 30%) or obese (BMI>30-kg/m²: 35%), and most were diagnosed with stage 2 (61%) vs. stage 3 (39%) breast cancer with representation from each PAM50 subtype: n (%) Luminal A, 46 (18%) Luminal B, 56 (22%), HER2-overexpressing 26 (27%), and 82 (33%) basal-like. In unadjusted analyses, expression of genes related to macrophages, PD-1 and TIGIT increased with increasing subcutaneous adiposity, whereas expression of genes related to mast cells decreased (see Table 1). We found a similar (though non-significant) pattern for BMI. Associations with increasing visceral adiposity were closer to the null. After adjusting for PAM50 subtype, age and stage at diagnosis, only the association of increasing subcutaneous adiposity with increasing PD-1 expression remained statistically significant.

Conclusion: Excess subcutaneous adiposity was associated with increased PD-1 expression, whereas excess visceral adiposity or obesity defined by BMI were not. These results from the first 251 samples of an ongoing study of 1400 tumors provide evidence from human breast cancer patients to demonstrate the importance of measuring body composition to assess adipose tissue distribution and support the hypothesis that excess adiposity impairs anti-tumor immunity.

Association of Adiposity Measures with Immune-Related Gene Expression in the Breast Tumor Microenvironment (n=251 patients with stage 2-3 breast cancer at Kaiser Permanente Northern California)
<table>
<thead>
<tr>
<th>Outcomes:</th>
<th>Body Mass Index at diagnosis (per 5-kg increase)</th>
<th>Subcutaneous adipose tissue (per 1-SD [cm²] increase)</th>
<th>Visceral adipose tissue (per 1-SD [cm²] increase)</th>
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<tr>
<td>Immune-related signature</td>
<td>Beta</td>
<td>95% CI</td>
<td>p-value</td>
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<td>(-0.12, -0.08)</td>
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<tr>
<td>Major Histocompatibility Complex</td>
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<td>(-0.01, 0.01)</td>
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</tbody>
</table>

1 95% Confidence Interval
2 A 1-unit increase represents a doubling in the log expression level of the genes in the signature

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Variant Classification Discordance: A real-world experience of genetic test results in a community-based setting

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BACKGROUND Accurate interpretation of hereditary cancer germline genetic variants is critical to ensuring appropriate care. Myriad Genetics has developed tools that are instrumental in the accurate classification of variants, including a previously described history-weighting algorithm (Pheno), mutation co-occurrence statistical analysis (MCO), and in trans haplotype analysis. Differences in classification are known to occur among commercial testing laboratories, however the rate at which a single provider may observe variants with a different classification has not been reported. Here, we compared genetic test results from multiple laboratories ordered by a single surgical community-based practice with the classifications from Myriad’s testing laboratory. METHODS Variants initially reported as a “variant of uncertain significance” (VUS) on hereditary cancer test results from multiple commercial laboratories ordered by a single surgeon at a community-based, comprehensive breast center from June 2013 to May 2021 were evaluated and compared to the classifications from Myriad. In total, 212 variants were submitted for comparison. After review, 42 variants were excluded because they had not been observed previously in Myriad-tested patients. Therefore, 170 variants were eligible for comparison. Variants were classified as pathogenic/likely pathogenic, VUS, and benign/likely benign for comparison. Descriptive statistics were used for analysis. RESULTS Discordant classification was observed between Myriad and other testing laboratories for 28.2% (48/170) of the variants compared. Initially, all 170 variants were classified and reported by other testing laboratories as VUS, however, 15 variants (8.8%) were subsequently reclassified by other testing laboratories (N=13 were reclassified as benign/likely benign; N=2 were reclassified as pathogenic/likely pathogenic). Among all variants compared, 23.5% (40/170) were definitively classified by Myriad as benign/likely benign. For 90.0% (36/40) of these variants, evidence driving the classification relied upon Pheno (32 variants), MCO (4 variants), and in trans haplotype analysis (8 variants), with some variants having multiple lines of evidence. Other in-
house specific rules were used for the remaining classifications (4/40;10%). Fifty-five percent (22/40) of the discordant classifications were seen in high-risk genes including APC, BRCA1/2, MLH1, MSH2, MSH6, PMS2, PALB2 and STK11, and 45% (18/40) were in moderate-risk genes including ATM, BARD1, BRIP1, CHEK2, and RAD51C. Of the 13 variants reclassified by other testing laboratories as benign/likely benign, six were classified as VUS by Myriad. Notably, two variants classified by Myriad as VUS were reclassified by other laboratories as pathogenic/likely pathogenic. CONCLUSIONS These data indicate that even in a single practice, significant discordance in variant classification exists based on the chosen laboratory. Myriad definitively classified nearly one-quarter of variants classified as VUS by other laboratories, likely due to the use of Myriad’s laboratory-developed classification tools. The degree of discordance observed here reflects the need for continuous laboratory investment in variant classification tools and evaluation of genetic variants, enabling physicians and patients to receive accurate results to facilitate appropriate medical management decisions.

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PIK3CA mutation prevalence in hormone receptor positive breast cancer patients in United Arab Emirates

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Background: The Phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha (PIK3CA) gene is mutated in about 30-40% of hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2- ) breast cancer (BC) patients. For HR+/HER2-advanced breast cancer patients with disease progression following endocrine-based therapy, the NCCN guideline recommends testing for PIK3CA mutations with tumour or liquid biopsy to identify suitable patients -specific PI3K inhibitor in combination with fulvestrant. The primary objective of this study was to evaluate the proportion and distribution of PIK3CA mutational landscape of HR+ve BC patients at the largest cancer centre in the United Arab Emirates (UAE). Material and methods: Retrospective review of consecutive HR+ve BC patients at Tawam Hospital for whom PIK3CA testing was requested. DNA was extracted from the samples and a targeted resequencing assay was used for mutation detection in exons 7, 9 and 20 of the PIK3CA gene. Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio S5 Prime System with a detection limit of 2-5% of the mutant allelic content. Results: 124 patients with HR+ve BC were enrolled in the present study. The pathology samples were considered unsuitable/unsatisfactory in 18
cases. The median age was 51.5 years (range 31-90). All patients were female, 54% were post-menopausal and 49% presented with de-novo metastatic disease. Of the 106 eligible patients, PIK3CA mutations were detected in 33 (31%) patients, the most common being H1047R (45%) and E545K (30%) mutations in exons 20 and 9, respectively. Other less common mutations included C420R mutations (6%) in exon 7, E542 (6%) in exon 9 and H1047Y (3%) in exon 20. 9% of patients had more than one hotspot mutations, primarily in exons 9 and 20. Of the 12 HER2 +ve patients tested, 3 had PIK3CA mutations, most commonly the H1047R mutation in exon 20. Conclusion: The prevalence of PIK3CA mutations and the presence of most common hotspot mutations in exons 20 and 9 was consistent with prior published studies. The clinical relevance of PIK3CA mutations in HER2 +ve BC patients needs further assessment.

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Distinct molecular differences between African American/Black and White women with Triple Negative Breast Cancer

Introduction: Triple-negative breast cancer (TNBC) is an aggressive disease that lacks well-defined molecular targets. It accounts for 15-20% of all breast cancers and disproportionately affects women of color due to both limited access to treatment and genetic variation. Recent studies identified BRCA1(or 2) and the PIK3CA/AKT1/PTEN axis as targets for treatment, but these studies neglected to account for genetic variations between race. Here, we present molecular differences between African American/Black (AA) and White (W) women with TNBC to highlight the importance of accounting for race to develop effective therapy and improve long-term outcomes. Methods: This study utilized the TCGA Firehose Legacy Breast Carcinoma dataset on cBioPortal. Subjects with breast cancer and negative ER, PR, and HER2 scores were stratified into AA (n=32) and W (n=69) subgroups. Data was analyzed to compare the most altered genes, copy number variation (CNV), and survival rates between the subgroups. The logrank test was used to obtain the hazard rate. The GISTIC2 model was used to assess CNV and G-scores (G; amplitude of aberration x frequency of occurrence). Results: The main genetic differences were in PIK3CA and BRCA1(or 2) genes. PIK3CA was detected as one of the ten most altered genes in TNBC, but this alteration was found in less than 10% of the TNBC cases. Of the 10%, PIK3CA was altered in 19% of W and 9% of AA subgroup. BRCA1(2) were altered in 10%(7%) of W but 0%(3%) of AA. Additionally, structural differences in chromosomes contributed to different survival outcomes. Both groups had co-amplification in 8q, but a significant hazard rate difference (z = 5.32, p < 0.001) was found for the W compared to the AA for the MYC gene. Further, the W had significantly higher amplification at 3q (G = 0.8 in W; 0.45 in AA). It is important to note that the PIK3CA gene lies in the 3q.26 region, meaning this gene is amplified significantly in the W subgroup. The AA group had a significant deletion at 8p.23 (G=0.5 in W; 0.8 in AA). Deletion of 8p causes MYC amplification, a targetable alteration. Conclusion: Our analysis reveals critical differences between AA and W subgroups with TNBC. Thus, it is clear that targeting the PIK3CA or BRCA1(2) gene benefits the W more than the AA.
population. To alleviate the disproportionate burden that AA women with TNBC face, more effort must be geared to find solutions specific to the AA subgroup. A greater sample size will help determine whether MYC amplification is unique to the AA subgroup, and if so, it could be targeted to improve outcomes of AA women with TNBC. Nevertheless, more data and research is needed to understand causes and decrease the rate of disparate outcomes in patients with TNBC.

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Effect of Sleep Traits on Subtype Specific Breast Cancer Survival: a Mendelian Randomization Analysis

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Background

There is increasing interest in the relationship between sleep traits and both quality of life and survival in breast cancer. Recent work has found that oestrogen receptor positive (ER+) tumour cells are more likely to spread, via the circulation, at night than in the morning, providing support for a potential role of sleep characteristics influencing metastasis and therefore survival from breast cancer. The aim of this study was to investigate causal effects of sleep traits on subtype-specific breast cancer survival.

Methods

Single-nucleotide polymorphisms (SNPs) identified from GWAS associated with sleep traits were used as genetic instruments for Chronotype (N=697,828), Insomnia (N=1,331,010), Sleep Duration (N=446,118), Napping (N=452,633), Daytime sleepiness (N=452,071) and Ease of Getting up (N=461,658). All instruments were identified in data from UK Biobank, except chronotype and insomnia, which were identified in meta-analyses of UK Biobank and 23andme. For all instruments female-specific effect estimates were used. For these SNPs, summary statistics of their association with breast cancer survival were obtained from GWAS meta-analyses of European women from the Breast Cancer Association Consortium (BCAC), (N=91,686, with 7531 breast cancer specific deaths over a median follow-up of 8.1 years). To estimate the causal effect of the sleep traits on breast cancer survival, we applied two-sample MR for both overall and subtype-specific breast cancer (Luminal A-like, Luminal B-like, Human Epidermal Growth Factor 2 (Her2) positive, Her2 negative and triple negative (TNBC)). Further stratification by tumour characteristics at diagnosis and treatment received was also used.

Sensitivity analyses were used to assess the robustness of main analyses to MR assumptions. Results For every hour increase in sleep duration, we observed worsening 5-year breast cancer specific survival in patients with ER+ tumours who received endocrine therapy (HR: 2.55, 95% CI: 1.10, 5.82) and for all patients receiving aromatase inhibitors (HR: 9.57, 95% CI: 1.61, 57.10). Conversely, improved 5-year survival was observed in patients with ER- tumours who received chemotherapy (HR: 0.30, 95% CI: 0.10, 0.87) and all patients receiving taxanes (HR: 0.23, 95% CI: 0.05, 0.98). We also observed that an increase in daytime sleepiness improved 15-year survival in patients both overall (HR: 0.34, 95% CI: 0.14, 0.80) and with lymph node negative tumours at diagnosis (HR: 0.12, 95% CI: 0.02, 0.64). Detailed sensitivity analyses are ongoing.

Conclusions

The current study uses a causal approach to identify potential effects between sleep patterns and breast cancer survival and confirms the previously observed relationships with increased sleep duration and worse survival in ER+ breast cancer. The
reasons for opposite effects seen in those with ER- and those receiving taxanes needs further mechanistic work. Although the improved survival in relation to increased daytime sleepiness appears to be in-keeping with previous findings, this may largely reflect shorter sleep duration. Further work accurately characterising sleep quality, rather than duration in those with breast cancer, examining the effects on quality of life and survival and establishing mechanisms are needed.

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Prevalence of Pathogenic Variants in Cancer Predisposition Genes in Women with Young Onset Breast Cancer

Introduction: Approximately 5% of breast cancers are diagnosed in women 40 years of age or younger. Known risk factors for young-onset breast cancer are few and can only account for a very small proportion of cases. In this study, we evaluated the contribution of mutations in 24 breast cancer predisposition genes in unselected Canadian women diagnosed with breast cancer at age 40 or younger.

Methods: This study is a sub-study of the larger Reducing the bUrden of Breast cancer in Young women (RUBY) Study. In the RUBY study, women diagnosed with breast cancer at the age of 40 years or younger are recruited at the time of diagnosis from 33 centres across Canada. Participants in RUBY provided detailed demographic and clinical data, in addition to provision of serial biospecimens. Participants could elect to consent into the genetics substudy, and have genetic testing performed for pathogenic variants in 24 breast cancer predisposition genes, including ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FAM175A, MLH1, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, RECQL, STK11, TP53 and XRCC2. Sequencing was performed and all potentially pathogenic variants were confirmed with conventional Sanger sequencing. Pathogenic and likely pathogenic mutations were reported for all 24 genes.

CanRisk scores for likelihood of having a pathogenic variant in 8 cancer predisposition genes (BRCA1, BRCA2, PALB2, CHEK2, ATM, RAD51C, RAD51D, and BRIP1) were generated for each participant. Results: 714 women consented and genetic testing was performed on the
blood samples provided as a component of the RUBY study. The mean age of the participants was 35.8 years (range 23-40 years), and the mean CanRisk score was 13.7 (range 2.3-98.0). Overall, 150 pathogenic mutations (21.0%) were detected in 147 women (three participants had mutations in two genes). The most common pathogenic variants detected were in BRCA1 (48), BRCA2 (40), CHEK2 (24), ATM (10), and PALB2 (9), representing 87.3% of all pathogenic variants identified. The mean CanRisk score was 28.8% (range 3.2-98.0%) for those identified with a pathogenic variant compared to 9.6% (range 1.0-88.9%) for those with a negative result ($p < 0.0001$). The prevalence of pathogenic variants was 32.9% for women age 20-30 years, 27.5% for 31-35 years, and 16.7% for 36-40 years. Conclusions: Twenty-one percent of women with breast cancer at age 40 or younger had a pathogenic variant in a breast-cancer predisposition gene. The great majority of these pathogenic variants were found in genes (BRCA1, BRCA2, CHEK2, PALB2) for which there are validated breast cancer treatment recommendations. All women with young-onset breast cancer should be offered germline genetic testing at the time of breast cancer diagnosis to make informed surgical and medical treatment decisions.

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Background: Obesity is an established risk factor for postmenopausal breast cancer and is associated with poor outcomes. Accumulating evidence suggests crown-like structures in the breast adipose tissue (CLS-B), a marker of local inflammation, play a role in explaining the obesity-breast cancer association. However, it is unknown whether breast tissue composition (i.e., the amount of fibroglandular tissue in the breast relative to fat) is related to CLS-B.

Objective: We evaluated whether breast tissue composition, as reflected by mammographic breast density, is associated with breast adipose tissue inflammation, as indicated by the presence of CLS-B, and whether the combination of breast density and obesity increases the presence of CLS-B among newly diagnosed breast cancer patients.

Methods: We examined the presence of CLS-B, detected by CD68 immunohistochemistry, in breast adipose tissue obtained via mastectomy from a quadrant uninvolved by tumor among 254 women with stage I–III breast cancer treated at Emory University Hospitals (2007–2012). Patient characteristics, including mammographic breast density (assessed on a mammogram up to 5 years before breast surgery) and body mass index (BMI) at diagnosis, were abstracted from electronic medical records. Mammographic density was assessed using the Breast Imaging Reporting and Data System (BI-RADS) density classification (1=almost entirely fat; 2=scattered fibroglandular densities; 3=heterogeneously dense; and 4=extremely dense); density was further categorized as fatty (BI-RADS 1-2) and dense (BI-RADS 3-4). Age and multivariable (MV)-adjusted logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the independent and joint associations of breast density kg/m2 vs. < 30 kg/m2 on the presence of CLS-B. Multivariable models adjusted for age (continuous, years) and parity (nulliparous, parous) with mutual adjustment of BMI (continuous, kg/m2) or mammographic breast density (dense, fatty) depending on the model.

Results: Women with obesity were more likely to have fatty breasts than women without obesity.
Obesity was strongly associated with the presence of CLS-B in age-adjusted models (OR=3.11, 95% CI: 1.79, 5.48) and multivariable models (MV-OR=3.70, 95% CI: 1.96, 7.15). There was no apparent association between dense breast tissue and presence of CLS-B in the age-adjusted model (OR=1.04, 95% CI: 0.59, 1.85). After additional adjustment for BMI and parity, we noted that women with dense breasts had higher odds of having CLS-B compared to those with fatty breasts (MV-OR=2.13, 95% CI: 1.07, 4.41). MV-ORs from the joint model (common referent: not obese, fatty breasts) were 1.54 (95% CI: 0.62, 4.24) for women without obesity but with dense breasts, 3.18 (95% CI: 1.15, 9.56) for women with obesity and fatty breasts, and 6.24 (95% CI: 2.23, 19.2) for women with obesity and dense breasts.

Conclusions: Our findings suggest that dense rather than fatty breast tissue is associated with breast adipose tissue inflammation among women with breast cancer. Results of the joint analyses suggest obesity is more strongly predictive of CLS-B presence than breast density. However, density may be an important risk factor for CLS-B among women without obesity while patients with obesity and dense breast tissue are the most likely to have CLS-B present. Future studies may consider the mechanisms by which density leads to increased presence of CLS-B.

## Joint Associations Table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N</th>
<th>N with CLS-B</th>
<th>Unadjusted OR (95% CI)</th>
<th>+Age OR (95% CI)</th>
<th>+Age, Parity OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined MD &amp; BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty &amp; not obese</td>
<td>44</td>
<td>8</td>
<td>1.00 (---)</td>
<td>1.00 (---)</td>
<td>1.00 (---)</td>
</tr>
<tr>
<td>Dense &amp; not obese</td>
<td>121</td>
<td>28</td>
<td>1.35 (0.96, 1.94)</td>
<td>1.46 (0.93, 2.29)</td>
<td>1.54 (0.62, 3.84)</td>
</tr>
<tr>
<td>Fatty &amp; obese</td>
<td>46</td>
<td>20</td>
<td>3.46 (1.96, 6.04)</td>
<td>3.51 (1.77, 6.20)</td>
<td>3.18 (1.53, 6.59)</td>
</tr>
<tr>
<td>Dense &amp; obese</td>
<td>45</td>
<td>22</td>
<td>4.71 (1.84, 13.10)</td>
<td>5.00 (1.94, 13.40)</td>
<td>6.24 (2.23, 19.2)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BM = body mass index; OR = odds ratio; CI = confidence interval; CLS-B = crown-like structures in breast adipose tissue; MD = mammographic density

**Note:** Categorizations are (1) almost entirely fat, (2) scattered heterogeneously dense, (3) scattered homogeneously dense, and (4) extremely dense.

**Formulas:**

- $\text{OR} = \frac{\text{Number of cases}}{\text{Number of controls}}$
- $\text{CI} = \text{Exp}(\text{OR} - 1.96 \sqrt{\text{Var}(\text{OR})})$ to $\text{Exp}(\text{OR} + 1.96 \sqrt{\text{Var}(\text{OR})})$

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Cell composition changes in healthy breast tissue is associated with advancing age and epigenetic age acceleration

Introduction: Risk factors for breast cancer include advancing age, lifetime estrogen exposure, and breast density. DNA methylation-based estimates of age are elevated in breast tissue of healthy women compared with paired blood samples, and the degree of age acceleration is associated with lifetime estrogen exposure. However, no prior work has examined cell compositional changes associated with breast epigenetic aging. In this study we estimated the abundance of different cell types in healthy breast, computed using gene expression data, and
Investigate cell composition changes that accompany advancing chronologic age and breast tissue specimens from 192 healthy women aged 19-90 years who donated breast tissue to the Susan G. Komen Tissue Bank at the Indiana University Simon Comprehensive Cancer Center. Methods: DNA/RNA were extracted (AllPrep, Qiagen) from breast tissue specimens from 192 healthy women aged 19-90 years who donated breast tissue to the Susan G. Komen Tissue Bank at the Indiana University Simon Comprehensive Cancer Center. Transcriptome analysis was performed using the QuantSeq 3′mRNA SeqFWD kit to generate RNA sequencing libraries. DNA methylation age was estimated using beta-values from Illumina EPIC 850K array platform. Age acceleration is defined using the residual of a linear regression of methylation age on chronologic age. Cell deconvolution was performed using CIBERSORTx to estimate the abundance of adipocytes, luminal epithelial cells, basal myoepithelial cells, vascular endothelial cells, lymphatic endothelial cells, immune cells (dendritic cells & macrophages), pericytes & smooth muscle cells, and fibroblasts. We examined cell composition changes with chronologic age, and with age-adjusted measures of acceleration in 6 epigenetic clocks: the Horvath Pan-tissue, Hannum, Phenotypic, Grim, Skin & Blood, and Epigenetic Pacemaker clocks, as well as the DNA methylation-based estimate of telomere length, DNAmTL. Results: Advancing chronologic age was associated with an increase in the imputed proportion of adipocytes (R=0.40, p< 0.0001), vascular endothelial cells (R=0.23, p=0.0033), and immune cells (dendritic cells & macrophages) (R=0.29, p=0.00016), and a decrease in the proportion of luminal epithelial cells (R=-0.43, p< 0.0001), and basal myoepithelial cells (R=-0.27, p=0.00047). Epigenetic age acceleration was significantly associated with increases in proportions of luminal epithelial cells (p< 0.0001 for age-adjusted Hannum, Phenotypic, Grim, and Skin & Blood clocks, p< 0.05 for Pan-tissue) and basal myoepithelial cells (p< 0.0001 for Phenotypic and Skin & Blood clocks), and decreased proportions of adipocytes and vascular endothelial cells (p< 0.0001 for Hannum, Phenotypic, Grim, and Skin & Blood clocks, p< 0.05 for Pan-tissue). Conclusion: Using gene expression data in healthy female breast tissue, we identified significant changes in cell-type-specific abundance that accompany advancing chronologic age, with an increase in adipocytes and immune cells, and a decline in luminal epithelial cells and basal myoepithelial cells. By contrast, epigenetic age acceleration in breast tissue is associated with decreasing proportions of adipocytes and vascular endothelial cells and a rise in basal myoepithelial cells and luminal epithelial cells. Our findings suggest distinct patterns of cellular composition changes that accompany normal aging compared with accelerated aging in breast tissue.

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The impact of single nucleotide polymorphisms on return-to-work after taxane-based chemotherapy in breast cancer

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Background Return-to-work (RTW) after breast cancer may be challenging for breast cancer survivors, especially those who experience adverse effects. Neuropathies are common adverse effect of taxane-based chemotherapy. Single nucleotide polymorphisms (SNPs) in genes related to taxane metabolism and transport, neural function, and neural- or DNA-repair may influence the risk of taxane-induced adverse effects, potentially impacting patient recovery and RTW. We examined the association of such SNPs with RTW in premenopausal breast cancer survivors. Methods We used Denmark’s nationwide population-based health registries to
metastatic breast cancer during 2007‒2011, who were candidates for adjuvant combination chemotherapy including cyclophosphamide and docetaxel. Only women employed at diagnosis were included. We collected archived tumor tissue from nationwide pathology departments and genotyped 26 SNPs in 20 genes using TaqMan assays. For each SNP, we categorized the women as wildtype, homozygote or heterozygote. Follow-up continued from the date of primary surgery to the first of RTW (defined as 4 consecutive weeks of work), recurrence, maternity leave/childbirth, other malignancy, retirement, death, emigration or 25th September 2017. We computed the cumulative incidence of RTW and used Cox regression models to calculate unadjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of RTW. Results We included 1,963 women. Women who were homozygotes for the phase 1 metabolizer CYP3A5 rs776746 (n=15) had lower cumulative incidence of RTW than wildtypes (n=1,600) and heterozygotes (n=249), 7%, 25% and 17% at six months, 57%, 87% and 88% at two years, and 82%, 94% and 94% at end of follow-up, respectively. Compared with wildtypes, CYP3A5 rs776746 homozygotes had delayed RTW throughout follow-up (HR 0-10 years: 0.48, 95% CI: 0.26, 0.86). No other SNPs were associated with RTW. Conclusions Among 26 SNPs, CYP3A5 rs776746 was associated with delayed RTW after breast cancer among premenopausal women. Our findings may help identify women at risk of a poor clinical course, who may benefit from enhanced supportive care during treatment and follow-up.

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DNA repair genes are more frequently mutated in non-white populations of metastatic breast cancer (MBC) patients

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Background: Although improvements in detection, therapeutic development and molecular profiling have decreased MBC mortality over the last twenty years, clinical outcomes are not being equally realized among all patients. Representation and enrollment into clinical trials are often not reflective of the general MBC population in terms of race and ethnicity, with Black and Hispanic patients being largely and often underrepresented. Not only does this imbalance translate into overall access to novel agents, but the lack of understanding of therapeutic efficacy in minority populations and tumor-based molecular differences reduce the use of truly personalized treatments for these groups. There is an opportunity to improve clinical outcomes for all patients with MBC, starting with a better understanding of the degree of any potential differences in underlying tumor molecular biology between racial groups. Methods: We utilized data from two cohorts of patients whose tumors underwent molecular profiling to examine differences in the frequency of genetic mutations across racial groups with MBC. The first cohort included 856 MBCs whose genomic profiles were retrieved from the AACR Genomics Evidence Neoplasia Information Exchange (GENIE) publicly available database. The second cohort included a separate set of 91 patients with MBC from an ongoing precision medicine program sponsored by the Side-Out Foundation (SOF). While the GENIE data were collected at 19 large academic cancer centers, the SOF data are derived from patients treated in the community setting. We compared the relative distributions of age and reported ethnicity between datasets, and compared the 20 most frequently mutated genes in each racial group across datasets. The analysis across races included 73 genes that were examined for differences in mutation frequency using Fisher’s Exact test and Pearson Chi-Square test (p<
Results: Although the GENIE set was significantly larger, race distribution was not statistically significant across the two populations. The combined populations included 831 white patients (88.4%), 43 Black patients (4.6%), 30 Asian patients (3.2%), and 35 Hispanic patients (3.7%). The age of initial (59.61) and metastatic (61.19) diagnosis was older in the SOF population compared to the GENIE population (48.81, 53.14; p < 0.001). Hispanic patients (46.92) were diagnosed with MBC at a younger age compared to White patients (53.78; p < 0.001). Of the 73 genes analyzed, 11 genes were found less frequently mutated in whites compared to non-whites including, NTRK1, SDHA, MSH6, TCF3, FANCC, GNAS, COP1, RECQL4, WRN, BCL6, and U2AF1. When the same 73 genes were examined for differences across racial groups, alterations of 22 genes reached statistical significance. The gene(s) with differences across racial groups, alterations of 22 genes reached statistical significance. The gene(s) were more frequently altered in the non-white population, 6 have roles in DNA repair (RTKs), including NTRK2, RET, ERBB3, and ERBB2, and 3/22 have roles in immune function, including BCL6, CIITA, and TLR4.

Conclusion: Analysis of genomic alterations derived from 2 independent real-world molecular profiling-based cohorts identified in non-whites MBC patients a set of candidate “actionable” genes involved in DNA damage repair, RTK expression, and immune function. Although these results require further validation, considering the relatively small samples sizes of the non-white populations, these findings may provide actionable targets for non-white patients with MBC that could be utilized in future trials.

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Circular RNAs express heterogeneously across different breast cancer subtypes and correlate with invasive disease-free survival

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Background: Circular RNAs (circRNAs) are a large class of RNAs derived from back splicing and subsequent circularization of precursor mRNAs. Due to their circular structures, circRNAs are protected from exonuclease-induced degradation and are thereby comparatively more stable than linear RNAs. circRNAs have been implicated in the progression of multiple types of cancers but few studies have systematically examined how circRNAs associate with different subtypes of breast cancer and prognosis. Methods: We conducted a nested case-control study of prospectively ascertained participants in the Chicago Multiethnic Breast Cancer Cohort (ChiMEC), in which patients without recurrence were matched with patients with recurrence on time to recurrence, age of diagnosis, tumor stage, and clinical subtype. We performed whole exome capture RNA sequencing on tumor samples that passed quality control. We then used CIRIquant to identify circRNAs by aligning back-splice junction (BSJ) reads to pseudo-circular
reference sequences and retained circRNAs that had a BSJ read count of 2 or greater in at least 5 patients. After normalization using the trimmed mean of M-values method, we used edgeR to model circRNA expression via a negative binomial distribution and performed differential expression (DE) analyses of circRNAs by ER and HER2 status, as well as between Black (self-reported) and White patients. Furthermore, we conducted survival analyses for each circRNA using Cox proportional hazards models to assess how the expression of each circRNA associated with survival outcomes of invasive disease-free survival (IDFS) and overall survival, while adjusting for age at diagnosis, stage, and HER2 status. Results: A total of 123 of 126 sequenced patients were included in the analysis, including 56 Black patients, 59 White patients, and 8 patients from other racial groups. The mean age of diagnosis was 51.9 years of age (SD 13.2) with 68% ER+, 48% PR+, and 30% HER2+ patients. We identified 16,927 high-confidence circRNAs. In the crude DE analysis, we found 489 circRNAs differentially expressed between patients with ER+ compared to patients with ER- tumors and 33 circRNAs between HER2+ vs. HER2- at a false discovery rate of 0.05. After adjusting for race and grade, we discovered 187 circRNAs differentially expressed by ER status and 38 by HER2 status. In the DE analysis by race, we found 88 circRNAs that were differentially expressed between Blacks and Whites. After adjusting for grade, ER, PR, and HER2 status, 14 circRNAs remained significantly different between racial groups. After a median of follow up of 8 years, 41 patients died, 41 patients had invasive recurrent diseases, and 2 patients had second primary breast cancers, for a total of 57 events in the IDFS analysis. Because of the matching study design to limit the impact of known prognostic factors, none of known prognostic factors (stage, ER, PR, HER2, grade, and race) were statistically associated with IDFS. In the survival analyses, we discovered two circRNAs (hsa-GSK3B_0001 and hsa-CMPK1_0006) that met the Bonferroni threshold for significance for their associations with IDFS but did not detect any circRNAs that were significantly associated with overall survival after correction for multiple testing. Discussion: This preliminary study demonstrates that multiple candidate circRNAs were differentially expressed between BC subtypes and racial groups, and several circRNAs were associated with IDFS. Future studies are warranted to validate our findings and cement the portability of these circRNAs as prognostic biomarkers across populations.

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Prevalence of germline BRCA mutations in unselected Korean patients with HER2-negative breast cancer: A Prospective cohort study

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Backgrounds Since OlympiAD study, National Comprehensive Cancer Network guideline recommends assessment of germline BRCA1/2 mutation in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy, which is not always possible in clinical practice due to limited resources for testing. Data on the prevalence of gBRCA mutation is still lacking, especially in patients with non-high risk for hereditary breast and ovarian cancer syndrome. In this study, we investigated prevalence of gBRCA mutation in unselected Korean patients with HER2-negative advanced BC in a prospective cohort and analyzed oncologic outcome. Methods Eligible patients were diagnosed with HER2-negative advanced BC and had initiated palliative systemic treatment. Peripheral blood was prospectively drawn from each patient and gBRCA mutation status was assessed by next generation sequencing using NGeneBio BRCAaccuTest®. In 100 patients, somatic mutations including BRCA1/2 from tumor tissue were investigated using targeted panel sequencing. To estimate the prevalence of gBRCA mutation with margin of error to be no more than ±4% at the 95% confidence interval in a population size of 20,000, 583 patients were to be enrolled. Results A total of 583 patients were enrolled between Oct 2019 and Mar 2022, and the prevalence of gBRCA mutation was analyzed in 570 patients, excluding ineligible patients. Median age was 54 years old (range 26-87) and 567 patients were female. 475 patients had
HR+/HER2- BC and 94 patients had triple negative breast cancer (TNBC). The overall prevalence of gBRCA1/2 pathogenic mutation was 7.3% (42/570) in unselected patients. The prevalence of gBRCA1 mutation was 1.6% (9/570) overall, 0.8% (4/475) in HR+/HER2- BC, and 5.3% (5/94) in TNBC. The prevalence of gBRCA2 mutation was 5.8% (33/570) overall, 6.3% (30/475) in HR+/HER2- BC, 3.2% (3/94) in TNBC. Prevalence in low risk TNBC (>60 years at first BC diagnosis, no known family history of relevant cancer and unilateral breast cancer) was 10.5% (2/19, all 2 patients had gBRCA2 mutation). Prevalence in low risk HR+/HER2- (>40 years at first BC diagnosis, no known family history of relevant cancer and unilateral breast cancer) was 5.9% (18/307, 17 patients had gBRCA2 mutation). The overall prevalence of gBRCA1/2 pathogenic mutation in Korean patients with low risk HER2-negative advanced BC was 6.1%. The result of somatic mutation, treatment patterns and clinical outcome according to gBRCA1/2 mutation will be further analyzed. Conclusions The prevalence of gBRCA mutation among Korean patients with HER2-negative advanced BC classified as low risk (6.1%) in this study supports routine testing of gBRCA mutation in this population.

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Application of 21-gene Breast Recurrence Score® assay to evaluate prognosis and benefit of adjuvant chemotherapy in BRCA1 and BRCA2 pathogenic variant carriers with early stage, estrogen receptor positive breast cancer

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Background: Minimal data exists for the utilization of the Oncotype Dx® assay specifically in breast cancers associated with BRCA1/2 pathogenic variants (PVs). It is unknown whether estrogen receptor positive (ER+) breast cancer associated with an inherited BRCA1 or BRCA2 (BRCA1/2) PV is more aggressive than disease seen in patients who do not carry an inherited PV, and whether there are differences between BRCA1 and BRCA2. In prostate cancer patients with inherited cancer predisposition due to a BRCA2 PV, more aggressive cancers are observed, which influences first-line treatment. Limited data exists for the optimal management of early stage ER+ breast cancer in BRCA1/2 PV carriers. Comparing Recurrence Score® (RS) results in ER+ breast cancer patients with an inherited BRCA1/2 PV (cases) versus matched patients who test negative for a PV in BRCA1/2 (controls) may inform whether biologically more aggressive breast cancer is seen in BRCA1/2 carriers and optimal treatment approaches.

Methods: A retrospective case control study was performed to compare RS results in women with breast cancer with an inherited BRCA1/2 PV versus patients who tested negative for an inherited BRCA1/2 PV. Female breast cancer patients seen between 2005-2020 at NorthShore University Health System with ER+Her2- early stage invasive breast cancer with 0-3 lymph nodes who completed genetic testing for BRCA1/2 were eligible for enrollment. BRCA1/2 cases were defined as individuals with an inherited PV in BRCA1/2 and controls were negative for BRCA1/2 or other known breast cancer risk gene PVs tested. Subjects were excluded if they had neoadjuvant therapy (hormonal or cytotoxic chemotherapy). Eligible cases were matched to control patients by age, grade, and stage. The Recurrence Score result was obtained by
A chart review; if not previously evaluated, Oncotype Dx assay was performed by Exact Sciences. Statistical analysis of the primary outcome used the paired t-test to determine mean difference in RS results between BRCA1/2 PV carriers and patients negative for a PV in BRCA1/2 using a 1:1 matched pairs design. Results: A total of 46 matched cases and controls were analyzed. Median age was 50 with a range of 28-74. Of the cases, 18 had a BRCA1 PV and 28 had a BRCA2 PV. Cases and controls were well matched for age (> 50 and ≤ 50); race, grade, stage, and progesterone receptor status. As expected, a higher number of BRCA1/2 carriers were treated with mastectomy while more of the controls received breast-conserving surgery. Chemotherapy was utilized more frequently in the cases (67.4%) versus the controls (54.4%). The average RS result was higher in the cases (27) than the controls (21.3) by a mean difference of 5.7 (p = 0.0195). Using Oncotype Dx cutoffs of low < 18, intermediate 18-30, and high ≥ 31, a statistically significant difference in RS result was noted in the cases versus

also had a score in the highest risk group while 35% had a score in the lowest risk group. Subgroup analysis showed that the cases had the largest difference in RS result from their population. Conclusion We present one of the largest data sets available to date of a well-matched cohort of cases and controls which shows that BRCA1/2 PV carriers are more likely to have a higher Recurrence Score result than their matched controls when matched for age, grade, and stage. These findings suggest ER+ breast cancer in BRCA1/2 PV carriers is biologically more aggressive. Further investigation is warranted to evaluate how this important finding impacts adjuvant therapy recommendations for BRCA1/2 PV carriers.

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Changes in preferences for ovarian cancer prevention strategies during the COVID-19 pandemic: Results of a discrete choice experiment.

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Background: The COVID-19 pandemic influenced patient health care decisions, but there is little information about the pandemic's impact on decisions about cancer risk reduction. This includes women at elevated risk of breast or ovarian cancer considering risk-reducing salpingo-oophorectomy (RRSO), risk-reducing salpingectomy (RRS), or other preventive measures. During the pandemic patients needed to balance their concerns about cancer risk reduction with their risks associated with elective health procedures, a risk which changed as vaccines became available. Methods: To address the impact of the COVID-19 pandemic on cancer prevention decision making, we recruited N=396 pre-menopausal women with a personal history of breast cancer or familial history suggestive of increased breast and/or ovarian cancer risk between 4/2019 and 3/2022. We conducted a discrete choice experiment in which patients were asked to choose between two scenarios that specified type of surgery (RRSO, 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. Risk of ovarian cancer for the scenarios provided varied in discrete intervals from
0% to 40%. We examined temporal trends during the pandemic using interactions with time coinciding approximately with the beginning of pandemic, peak vaccination period, and the Omicron wave. Results: We identified significant temporal interactions on a woman’s prevention decisions. In 2019, women at higher risk of ovarian cancer were more likely to choose prevention scenarios that favored lower ovarian cancer risk (odds ratio [OR] = 0.48; 95% CI = 0.37, 0.69 per 10% increase in ovarian cancer risk difference). This association decreased through the pre-vaccine period of 2020 by OR=2.61/month (95% CI = 1.21, 5.65). By June 2020, the effect of a 10% increase in ovarian cancer risk on intervention choice had attenuated substantially (OR=0.84, 95% CI 0.67, 1.00). By January 2022, the effect strengthened (OR=0.69, 95% CI 0.49, 0.88), but had not reached pre-pandemic levels. Before 3/2020, natural age of menopause (versus immediate) had a strong impact on the choice of a scenario (OR=3.56, 95% CI 1.65-7.65). At the beginning of the pandemic, the effect was reduced by 0.47/month (95% CI 0.22-0.99). The rate of attenuation slowed over time, such that the effect of having a natural age of menopause on choice was OR= 1.56 (95% CI 0.65, 2.46) by January 2022. Tests for temporal interactions were statistically significant for both ovarian cancer risk and age of menopause. Conclusions: Our results suggest that over the course of the pandemic, women seemed more accepting of higher risks of ovarian cancer and immediate (post treatment) menopause when considering preventive options. There was an inverse U shape curve of the effect of ovarian cancer risk on choices over time (Figure A), but the strength of the relationship had not reached pre-pandemic levels by January 2022. This may reflect patient tolerance for side effects as the pandemic evolved. These results suggest that factors such as ovarian cancer risk and delay of menopause influenced personal prevention choices, but that these choices were influenced by events related to events that hallmarked the COVID-19 pandemic.

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BRCA1/2 gene mutations in patients with high-risk breast cancer in a tertiary-level hospital in Guatemala

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Objectives, to establish the frequency of BRCA1/2 mutation rate in high-penetrance breast cancer susceptibility population Methods Based on NCCN guidelines for testing criteria for high-penetrance breast cancer susceptibility genes genetic counseling was offered to 140 breast cancer patients in the hemato-oncology unit of Roosevelt Hospital at Guatemala City performing test with NGS and MLPA technology from 2019 to 2021. Results The overall BRCA1/2 mutation rate high-risk patients were 23% (33/140). Of the patients with mutations, 66.6% (22/33) had BRCA1 mutation, 33.3% (11/33) had BRCA2 mutation, of the mutated population the median age was 45 years. Regarding the phenotype in the mutated population, 75% were triple negative, 16% luminal and 9% with Her2 overexpression. Of the patients carrying the BRCA1 mutation, we identified the c.212+1G>A mutation in 40% of the patients, possibly a founder mutation. In the triple negative population and under 45 years of age, the percentage of patients with BRCA 1/2 mutation is 40.9 (88.8% BRCA1 and 11.1% BRCA2). Conclusions: we found a percentage of BRCA 1/2 mutations in the selected population (NCCN criteria) similar to that reported in other Latin American countries, highlighting the high percentage of BRCA mutations in women under 45 years with triple negative phenotype, previous reports have highlighted the frequency of the c.212+1G>A mutation of BRCA1 in breast cancer patient in Guatemala, in this study 40% of the BRCA1 mutations correspond to said mutation, considering it as a probable founder mutation.

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Co-occurring alterations in PALB2 germline carriers identified by liquid biopsy in patients with advanced breast cancer

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Introduction: PALB2 is a BRCA complex-interacting protein and has an essential role in homologous recombination and repair (HRR). PALB2 germline (gPALB2) mutations are found in 1 – 4% of breast cancer patients and can be incidentally identified by liquid biopsy testing. Recent data has shown the efficacy for PARP inhibitors (PARPi) in breast cancer gPALB2 carriers, highlighting the importance of understanding genomic drivers in this group of patients. Here we present the genomic landscape of patients with advanced breast cancer (aBC) with incidental gPALB2 mutations identified by liquid biopsy testing. Methods: Genomic results were queried for aBC patients who had Guardant360 (G360) testing as part of routine clinical care from October 2020 – March 2022. Eligible patients had must have a diagnosis of breast cancer and an incidental gPALB2 alteration identified on G360, defined by presence of ClinVar loss-of-function single nucleotide variant (SNV)/indel mutation. Co-occurring somatic alterations in these patients were then analyzed after removing synonymous and variants of uncertain
significance. Analysis of HRR-related alterations, such as loss of heterozygosity and/or copy number loss, was performed in a subset of patients. Clinical demographics and clinical status (newly diagnosed or progressing at the time of G360 testing), were extracted from test requisition forms. Results: A total of 48 patients had gPALB2 alterations: 60% had indels and 40% SNVs. gPALB2 variant allele frequencies (VAF) were >30% for all patients (median VAF: 49.7, range: 34.1-66.6). All patients were female with a median age of 59 years (range: 31-84); 29 (60%) were tested at progression whereas the rest were tested at diagnosis. 36 (75%) patients with gPALB2 had co-occurring somatic alterations across 23 genes. The most commonly mutated genes were TP53 (47%), ESR1 (23%), and PIK3CA (19%); other mutated genes had less than 7% frequency. Notably, 95% of patients with co-occurring ESR1 alterations and 70% found to harbor PIK3CA co-occurring alterations were tested at progression. Other clinically relevant findings include co-occurring somatic alterations in MTOR (4%) and HRR-related genes ATM, ARID1A, CHEK2, FANCA (4% each; one patient had both ATM and CHEK2 somatic alterations). No somatic BRCA1/BRCA2 alterations were identified in gPALB2 patients. For 33 (69%) patients with gPALB2, additional HRR-related biomarker analysis was performed resulting in identification of 3 (9%) patients with copy number loss, one who had CHEK2 and PALB2 single copy number loss, resulting in PALB2 biallelic loss. In the overall cohort, an additional 33 patients were identified with uniquely somatic PALB2 alterations. Conclusions: Carriers of gPALB2 alterations comprise a rare subset of aBC patients analyzed by liquid biopsy. These patients have co-occurring somatic alterations identified in genes that have been reported in published cohorts of aBC patients without gPALB2 alterations. Assessment of additional somatic HRR-related alterations may identify other patients with PALB2 findings who could benefit from PARPi. Clinical studies are needed to assess how patients with gPALB2 and co-occurring mutations may have altered response and/or resistance to therapies, including standard-of-care regimens and PARPi.

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Background: Breast Cancer (BC) is one of the most common cancers diagnosed in Li-Fraumeni Syndrome (LFS). Most studies about the frequency of germline pathogenic variant (PV) TP53 p.R337H have been conducted in the South and Southeastern regions of Brazil reaching rates as high as 8% of detection. There is a lack of data on the frequency of this germline PV in other Brazilian regions, especially among patients without access to genetic tests. Objective: This study aims to evaluate the detection rate of TP53 p.R337H in patients (pts) at risk of hereditary breast cancer (HBC) and describe the clinical and demographic profile of the study cohort. Methodology: Hereditary cancer risk assessment based on the National Comprehensive Cancer Network Criteria (NCCN), version 1.2020, was performed in women with BC who were being followed in a public hospital (DF, Brazil) between January 2021 and January 2022. All pts eligible for germline genetic testing according to HBC NCCN criteria were referred for genetic counseling and genetic testing. For those patients who could not afford a comprehensive genetic test, a real time PCR test specifically searching for TP53 p.R337H variant was performed. In case of TP53 p.R337H detection in the proband, genetic counseling and familial variant testing were offered to family members. Results: Among 221 pts eligible for this study,
180 pts performed germline testing, including 100 pts tested only for the TP53 p.R337H variant (real-time PCR) and 80 pts performed out of pocket BC multigene panel testing (including TP53 sequencing). This cohort was mostly represented by pts from Central-West (47%) and Northeast (35%) regions of Brazil. The median age of BC diagnosis was 44 y.o. (18 - 78). Invasive ductal carcinoma represented 92% (n=203) of the tumors, 50% were ER/PR+ HER2-, 25% HER2 +, 25% ER/PR- HER2- (triple negative). Regarding stage at diagnosis, 59% (n=130) were stages IIB-IIIC and 13% IV. The detection rate of TP53 p.R337H was 1.1% (2/180). Among the pts who met the revised Chompret criteria for LFS, this frequency was 5% (2/40). One of them was diagnosed with a stage IIIB IDC ER/PR+HER2- at 28 y.o. and had no relevant family history of cancer. The other pt was diagnosed with a stage IV IDC ER/PR+HER2- at 44 y.o. and the family history revealed four sisters and one niece with BC, and one nephew with brain tumor at 4 y.o. The family members from these two families received genetic counseling and genetic testing. Cascade testing was able to identify 12 additional carriers. All carriers were referred for post-testing follow-up. Conclusion: According to these results, we expect to identify at least one p.R337H carrier in each 90 BC pts treated in the Federal's District Public Health setting who fulfill HBC NCCN criteria. In a limited resources setting, in Brazil, testing the TP53 p.R337H variant with PCR is a low-cost test that should be considered at least for pts that meet the revised Chompret criteria. The overall detection rate of TP53 p.R337H carriers was lower in comparison to other Brazilian studies from the South/Southeast of the country. Both cases identified in this cohort had advanced local disease or metastatic disease at BC diagnosis, raising the concern about the importance of LFS diagnosis, and high-risk surveillance and risk reduction strategies in this subgroup of pts. Despite the low detection rate of TP53 p.R337H in this cohort, there was a high familial impact through cascade testing.

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Mutations of TP53 and genes related to homologous recombination repair in breast cancer with germline BRCA1/2 mutations

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Background
Germline mutations of breast cancer susceptibility gene BRCA1 and BRCA2 (gBRCA1/2) are associated with elevated risk of breast cancer in young women in Asia. BRCA1 and BRCA2 proteins contribute to genomic stability through homologous recombination (HR)-mediated double strand DNA break repair (DDR) in cooperation with other HR-related proteins. In this study, we analyzed the targeted sequencing data of the breast cancer patients with gBRCA1/2 mutations to investigate the landscape of HR-related gene mutations and their clinical implications. Materials and Methods Data of the breast cancer patients with pathogenic gBRCA1/2 mutations and qualified targeted next generation sequencing, SNUH FiRST cancer panel, were analyzed. Single nucleotide polymorphisms, small insertions and deletions were analyzed with functional annotations using ANNOVAR. HR-related genes were defined as ABL1, ATM, ATR, BARD1, BRCA1, BRCA2, CDKN1A, CDKN2A, CHEK1, CHEK2, FANCA, FANC D2, FANCG, FANCI, FANCL, KDR, MUTYH, PALB2, POLE, P RAD51D, RAD54L, and TP53. Mismatch-repair genes were MLH1, MSH2, and MSH6. Clinical data were analyzed with cox proportional hazard models and survival analyses. Results Fifty five Korean breast cancer patients with known gBRCA1/2 mutations and qualified targeted
NGS data were analyzed. Ethnically distinct mutations in gBRCA1/2 genes were noted, with higher frequencies of Val1833Ser (14.8%), Glu1210Arg (11.1%), and Tyr130Ter (11.1%) in gBRCA1 and Arg2494Ter (25.0%) and Lys467Ter (14.3%) in gBRCA2. Considering subtypes, gBRCA1 mutations were associated with triple-negative breast cancers (TNBC), while gBRCA2 mutations were more likely hormone receptor-positive breast cancers. At least one missense mutation of homologous recombination (HR)-related genes were observed in 44 cases (80.0%). The most frequently co-mutated gene was TP53 (38.1%). In patients with gBRCA1/2 mutations, however, genetic variations of TP53 occurred in locations different from the known hotspots of those with sporadic breast cancers. The patients with both gBRCA1/2 and TP53 mutations were more likely to have TNBC, high Ki-67 values, and increased genetic mutations, especially of HR-related genes. Survival benefit was observed in the TP53 mutants of patients with gBRCA2 mutations, compared to those with TP53 wildtypes. Conclusion Our study showed distinct genetic landscape of breast cancer patients with gBRCA1 and gBRCA2 mutations in the Asian populations. Further studies on precision medicine are needed for tailored treatments of patients with genetic diversity among different ethnic groups.

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A COMPARISON OF BREAST CANCER SURVIVAL ACROSS DIFFERENT TUMOUR BIOLOGY IN YOUNG WOMEN: A MULTICENTRIC DATABASE STUDY IN KLANG VALLEY, MALAYSIA

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Background: OBJECTIVE: This study aims to determine the 5-year overall survival of young breast cancer according to tumour biology in Malaysia. METHODOLOGY: Multicenter retrospective study with convenience sampling method used to recruit the patients. All young women aged 50 years and below with breast cancer who underwent surgery/under follow up from 1st January 2014 to 31st December 2017 in Hospital Tengku Ampuan Rahimah (HTAR), Klang, Hospital Selayang and Hospital Putrajaya were included. Categorical data were analyzed using Chi-Square analysis and Fisher's Exact Test. 5-year overall survival was calculated using Kaplan Meier. Cox Regression to estimate hazard ratio for mortality in patients with different tumour biology. Recurrence were analysed using Chi-Square analysis. RESULTS: A total of 360 patients were recruited predominantly within 41 years to 50 years of age (63.9%). The majority of the patients were Malays (66.4%). Most of the patients were in Stage II (39.4%) with a significant number of patients in Stage III and IV (25.0% & 26.4% respectively). 56.1% had tumour biology of Luminal A followed by Triple negative (21.7%), HER2 Enriched (12.2%) and Luminal B (10%). Kaplan Meier analysis showed that the 5-year overall survival was 58.3%. There were no statistical significance across the tumour biology subtypes. Among the tumour biology groups, Triple Negative had the highest probability of survival with 54.5%. CONCLUSION: We observed that Triple Negative had the highest probability of survival at 5 years while Luminal B (HER 2 Positive) had the lowest probability. The 5-years overall survival was not statistically significant with accordance to locoregional recurrence rate and in different tumour biology. Keywords: Breast cancer, young women, tumour biology, overall survival, locoregional recurrence

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Screening Patterns of Mammography and Breast Magnetic Resonance Imaging Following Cancer Genetic Testing in an Integrated Health Care System

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Background
Patients at high-risk for breast cancer with genetic mutations are recommended to receive annual breast MRI in adjunct to annual mammography. Despite 15 years of clinical guidelines, uptake of annual breast MRI remains low. Further, little is known about screening patterns across genetic test results in patients tested for hereditary cancer susceptibility as part of usual care.

Methods
We conducted a retrospective cohort study in an integrated health system among women aged hereditary cancer susceptibility genes between January 1, 2010 and December 31, 2018. Genetic test orders and results (pathogenic or likely pathogenic (P/LP) variant(s), negative, or variant of uncertain significance (VUS)) were obtained from health system administrative and laboratory data. Mammogram and breast MRI use data were extracted from electronic health records and claims data. To characterize screening patterns, we calculated average proportion of time covered (PTC) as the number of days covered by mammography and/or breast MRI divided by the number of days from screening eligibility until the earliest censoring event: end of observation period, reached age 75 years, breast cancer diagnosis, death, bilateral mastectomy, or disenrollment in the health system. Per National Comprehensive Cancer Network (NCCN) guidelines, women with P/LP variants in BRCA1/2, TP53, PALB2, CHEK2, ATM, and NF1 became eligible for screening on either the day they received their genetic test result or reached age eligibility and received one year of covered time for each mammogram or MRI imaging procedure received. Per Healthcare Effectiveness Data and Information Set (HEDIS) performance measures, all other women became eligible for screening at age 50 years and received two years of covered time for each mammogram received. Average PTC was calculated overall, by genetic test results, and by screening type. Poisson regression was used to determine the association between average PTC and patient-level factors (age at test, race/ethnicity, and genetic mutations) and guideline factors (recommended screening age state).

Results
Of 1,167 women meeting the inclusion criteria, 140 (12%) had P/LP in high penetrance breast cancer susceptibility genes (Table 1). Average PTC for individuals with a high penetrance susceptibility gene was 34.4% for MRI, 47.6% for mammogram, 63.2% for either MRI or
mammogram, and 19.0% for both screening tests. The average PTC for those who tested negative, had VUS only, and had P/LP variants in genes unrelated to breast cancer was 50.3%, 44.4%, and 40.6%, respectively. Poisson regression model showed that among those with P/LP variants in high penetrance breast cancer genes, average PTC for annual MRI was positively

95% confidence interval [CI]: 1.94-2.20), higher absolute lifetime risk of breast cancer (IRR=1.38, 95% CI: 1.31-1.49), being 40-59 years old at genetic testing (IRR=1.04, 95% CI: 1.01-1.06), and non-Hispanic White race/ethnicity (IRR=1.10, 95% CI: 1.06-1.14).

Conclusions
Use of breast screening in women who had a P/LP variant(s) in high penetrance breast cancer susceptibility genes was low and not consistent with clinical guidelines, but comparable to the use of screening in women with negative and VUS results. Our findings suggest the need to improve screening in high-risk women with known genetic mutations and women at average risk.

Table 1. Average PTC by NCCN and HEDIS recommendation.

<table>
<thead>
<tr>
<th></th>
<th>MRI PTC (Range)</th>
<th>Mammogram PTC (Range)</th>
<th>MRI or mammogram PTC (Range)</th>
<th>MRI and mammogram PTC (Range)</th>
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<tbody>
<tr>
<td>NCCN</td>
<td>Overall</td>
<td>129</td>
<td>64.4 (0-100.0)</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>BRCA1</td>
<td>55</td>
<td>64.7 (0-100.0)</td>
<td>49</td>
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<tr>
<td></td>
<td>TP53</td>
<td>4</td>
<td>6.4 (0-19.1)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>14</td>
<td>53.0 (0-85.0)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>CREST1</td>
<td>14</td>
<td>53.6 (0-100.0)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>ATM</td>
<td>4</td>
<td>25.6 (0-62.8)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>NF1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HEDIS</td>
<td>Overall</td>
<td>-</td>
<td>688</td>
<td>48.9 (0-100.0)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>-</td>
<td>475</td>
<td>50.3 (0-100.0)</td>
</tr>
<tr>
<td></td>
<td>VUS</td>
<td>-</td>
<td>104</td>
<td>44.4 (0-100.0)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>-</td>
<td>29</td>
<td>40.6 (0-100.0)</td>
</tr>
<tr>
<td></td>
<td>P/LP</td>
<td>-</td>
<td>-</td>
<td>-</td>
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Disclosure(s):
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Introduction: Breast cancer is currently considered a public health problem, being the most frequent in women in Brazil. In the past, and in places where screening programs are not very successful, the diagnosis was made during the clinical examination, being carried out late, which compromised the prognosis and survival of the patient. To avoid late diagnosis, an attempt is made to have the strategy of appropriate screening programs that make an early detection by applying the test to the asymptomatic population and identifying lesions in the pre-clinical stage. Objectives: To analyze the incidence of reports highly suggestive of malignancy in patients undergoing mammography in Brazil between 2013 and 2021. Methodology: A retrospective and analytical cross-sectional study of the notifications available in the cancer information system (SISCAN) was carried out. The incidence of report notifications by the Breast Imaging Reporting Data System (BI-RADS) classification system was compared between high-risk and normal-risk women for breast cancer. In addition to the information regarding the BI-RADS report, they were analyzed comparing epidemiological data between high-risk and normal-risk women. Other variables analyzed were the age group of the screened population and the size of the nodule according to the BI-RADS. Results: In the period analyzed from 2013 to 2021, 16,065,383 screening mammograms were performed and reported in Brazil. Of these, 13,167,259 mammograms were performed on women at normal
risk, while 2,898,124 mammograms were performed on women reported as high risk. To analyze the difference between the reports in women at usual risk and those at high risk, the relative risk between them and the number necessary to cause harm was calculated, having found a relative risk of 0.5412 (CI 95% 0.5341 - 0.5483) in B4 and a relative risk of 0.433 (95% CI 0.4203 - 0.4462). As for the number needed to deal damage, it was observed 203 (95% CI 198 - 209) for B4 and 788 (95% CI 754 - 825) for B5. Discussion: Although the need for breast cancer screening programs to reduce mortality is already well established, some aspects of screening do not have much consensus. In our study, as proposed in the literature, the incidence of reports suggestive of malignant breast lesions was higher in high-risk women. This finding may be consistent with the fact that women with risk factors are more likely to develop breast cancer than those with usual risk. Some studies show that exams from high-risk patients tend to be examined in greater detail, in order to have a higher false positive rate than low-risk patients, just as low-risk patients have a higher false negative rate. Conclusions: Our study showed an increased prevalence of reports suggestive of malignancy in high-risk patients when compared to usual-risk patients. Such findings may mean that high-risk patients have a higher prevalence of malignancy, but also that clinicians review the examinations of high-risk patients more carefully, increasing the rate of reports suggestive of malignancy in these patients.

Reports of mammograms performed in the target population and in high-risk women in Brazil between 2013 and 2021

<table>
<thead>
<tr>
<th></th>
<th>Populares</th>
<th>High-risk women</th>
<th>Relative risk (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B0</td>
<td>1,439,841 – 11%</td>
<td>373,683 – 13%</td>
<td>0.8481 (p &lt; 0.05)</td>
</tr>
<tr>
<td>B1</td>
<td>4,906,097 – 37%</td>
<td>1,009,350 – 35%</td>
<td>1.0698 (p &lt; 0.05)</td>
</tr>
<tr>
<td>B2</td>
<td>6,452,900 – 49%</td>
<td>1,409,596 – 49%</td>
<td>1.0076 (p &lt; 0.05)</td>
</tr>
<tr>
<td>B3</td>
<td>279,335 – 2,1%</td>
<td>67,966 – 2,3%</td>
<td>0.9046 (p &lt; 0.05)</td>
</tr>
<tr>
<td>B4</td>
<td>76,329 – 0,6%</td>
<td>31,045 – 1,1%</td>
<td>0.5412 (p &lt; 0.05)</td>
</tr>
<tr>
<td>B5</td>
<td>12,757 – 0,1%</td>
<td>6,484 – 0,2%</td>
<td>0.4330 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Total</td>
<td>13,167,259 – 100%</td>
<td>2,898,124 – 100%</td>
<td>0.8481 (p &lt; 0.05)</td>
</tr>
</tbody>
</table>

Risco relativo a depender do tamanho do nóculo e o laudo BI-RADS entre mulheres de alto risco e risco habitual

<table>
<thead>
<tr>
<th></th>
<th>&lt;=10mm</th>
<th>11-20mm</th>
<th>21-50mm</th>
<th>&gt;50mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 0</td>
<td>0.8886 (IC 95%: 0.8562 - 0.9056)</td>
<td>0.8725 (IC 95%: 0.8423 - 0.9037)</td>
<td>0.8315 (IC 95%: 0.7729 - 0.8946)</td>
<td>1.0341 (IC 95%: 0.8816 - 1.2129)</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>1.4464 (IC 95%: 1.2925 - 1.6186)</td>
<td>1.7870 (IC 95%: 1.5040 - 2.1223)</td>
<td>1.2183 (IC 95%: 0.6933 - 2.1408)</td>
<td>0 pacientes de risco habitual com &gt;50mm e B3</td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>2.281 (IC 95%: 1.8479 - 2.8156)</td>
<td>1.9252 (IC 95%: 1.5848 - 2.3387)</td>
<td>1.5548 (IC 95%: 1.2454 - 1.9409)</td>
<td>1.1081 (IC 95%: 0.6290 - 1.9521)</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>2.962 (IC 95%: 1.9727 - 4.5506)</td>
<td>1.4758 (IC 95%: 1.0655 - 2.0442)</td>
<td>1.7349 (IC 95%: 1.3405 - 2.2453)</td>
<td>0 pacientes de risco habitual com &gt;50mm e B5</td>
</tr>
</tbody>
</table>
Disclosure(s):
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JULIANA M. REAL, MSc, PhD: No financial relationships to disclose
Analyzing the performance of Thermalytix, an AI-based breast cancer screening solution, in a community setting

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Background: Despite improvements in treatment strategies, breast cancer survival rates remain low in India due to a lack of awareness and late stage of presentation. If diagnosed and treated early, breast cancer survival rates improve. Screening mammography, the gold standard in cancer diagnosis, is not feasible in a resource-constrained setting. Niramai’s novel breast cancer screening technology, Thermalytix™, applies Artificial Intelligence (AI) over thermography, to give an automated interpretation of the breast thermal images. The portable Thermalytix test has been so far used to screen 60000 women in community settings across India and Kenya. This study is a recent evaluation of the test in rural setting.

Methods: Women who provided written consent and who underwent Thermalytix tests in community-based screening camps at primary health centers (PHCs) in Afzalpur Taluk of Gulbarga District, Karnataka, India between 01 August 2021 to 15 June 2022 were included in this study. Five thermal images in multiple views were analyzed using Niramai’s patented algorithm. Automated analysis of the thermal images produced a screening report and triaged the participants for follow-up. In case of abnormal thermal activity, Thermalytix triaged women as ‘red’ and were referred to the district hospital for follow-up with breast ultrasound and/or other investigations and and were recorded into the following three categories: Normal (BI-RADS 1), Abnormal - benign (BI-RADS 2/3) and Abnormal - malignant (BI-RADS 4/5). If no abnormal thermal patterns were detected by Thermalytix, women would be recommended routine screening.

Findings: The analysis included 3531 women were included in the analysis and the median age in the cohort was 42 years. Of them, 97 (2.74%) women were triaged ‘red’ by Thermalytix indicating a suspicion of breast abnormality. As on 15 June 2022, 29 (30%) out of 97 women underwent standard follow-up investigations of which two cases of carcinoma breast, one case of phyllodes, one case of tuberculosis mastitis and seven other benign cases were identified, indicating that Thermalytix has a positive predictive value of 35.71% (11/29) in detecting benign...
and malignant breast lesions. Furthermore, a Patient experience questionnaire was used to assess their experience. 98.71% women were being screened for breast cancer for the first time in their lives. 93.9% women said they were very satisfied with Thermalytix screening experience and remaining 6.1% said they were satisfied, thus aiding in strong acceptability and adoption of the test.

Interpretation: In resource-constrained settings such as India, where less than 2% of the women in the country have ever got screening for breast cancer, the portable, no-radiation Thermalytix test is an accessible breast cancer screening solution. Thermalytix’s patient-friendly features - privacy-aware, painless, comfortable, and radiation-free make it favorable for population screening in India, and thus, can increase the uptake of breast cancer screening. With the device’s capacity to fit into a backpack, it can make breast cancer screening accessible to even remote areas with limited resources. However, following up on women who were found to be Thermalytix positive still remains a challenge. Future studies will ensure that follow-up after abnormal breast screening is part of the approved clinical protocol.

Results of the screening program

<table>
<thead>
<tr>
<th>Total no. of woman screened by Thermalytix between 01 August 2021 to 15 June 2022</th>
<th>3531</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women screened ‘red’ by Thermalytix - suspicious of breast abnormality</td>
<td>97</td>
</tr>
<tr>
<td>Women who underwent follow-up investigations</td>
<td>29</td>
</tr>
<tr>
<td>Women with abnormal findings as per Breast ultrasonography</td>
<td>11</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>7</td>
</tr>
<tr>
<td>Breast Tuberculosis</td>
<td>1</td>
</tr>
<tr>
<td>Invasive Ductal Carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Phyllodes</td>
<td>1</td>
</tr>
</tbody>
</table>

3 malignancies and 8 benign lesions found in 29 Thermalytix RED patients

Disclosure(s):
Geetha Manjunath, n/a: Niramai Health Analytix: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Receipt of Intellectual Property Rights / Patent Holder (Ongoing), Salary (Ongoing)
Lakshmi Krishnan, n/a: NIRAMAI Health Analytix: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Terminated, August 16, 2022), Salary (Terminated, August 16, 2022)
Gargi Deshpande, n/a: NIRAMAI Health Analytix: Salary (Terminated, July 8, 2022)
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Does reducing the frequency of regularly scheduled physical examinations affect recurrence detection in patients with early breast cancer?

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Purpose: Follow-up care of patients with early breast cancer (EBC) usually includes routinely scheduled physical examinations. While ASCO guidelines recommend a physical exam every three to six months for the first three years, there is little evidence to support this schedule. Health care systems continue to be challenged to meet the future growth in demand from
increasing numbers of diagnosed patients and long-term survivors, scarcity of health care workers, and the need to control health care costs. Despite recognition that new follow-up models are needed, there continues to be no generally accepted well follow-up strategy. We evaluated recurrence detection patterns of patients transferred into a single centre survivorship program that follows ASCO recommendations.

Methods: Consecutive patients with EBC referred to the Wellness Beyond Cancer Program (WBCP) between February 1, 2013, and January 1, 2019, who had breast cancer recurrence, were reviewed. Descriptive analyses were used to present patients and disease characteristics stratified by type of recurrence and mode of cancer detection.

Results: Of 206 recurrences, 135 were distant recurrences (65.5%), 41 were ipsilateral breast recurrences (19.9%), and 30 were contralateral new breast cancers (14.6%). Patient reported symptoms lead to the detection of the majority of distant recurrences (125/135, 92.6%). The most common symptoms of recurrence were bone pain (24.8%), dyspnea/cough (13.1%), abdominal pain (10.7%). Ipsilateral breast recurrences were both quite frequently detected by patients (22/41, 53.7) and by routine mammographic surveillance (17/21, 41.5%). Contralateral breast cancers were primarily detected by imaging 83.3% (25/30). Only 2/206 (1.14%) recurrences/new primaries were detected by a healthcare provider at routinely scheduled follow-up visits. There was a statistical difference in recurrence detection between image detected vs. self-detected in the following factors: grade 3 (26.5% vs 51%, p < 0.007), triple negative breast cancer (3.9% vs. 15.1%, p=0.03), and HER2 disease (18.4% vs. 9.8%, p=0.04).

Conclusions: Despite regularly scheduled in-person follow-up visits following ASCO guidelines, healthcare providers rarely detect recurrences. Our data suggests that 30,000 – 35,000 follow-up visits were required for the healthcare providers to detect these 2 recurrences. This leads to further need for proper survivorship programs with patient and provider education, and concentration on targeted surveillance. Provided patients attend regular screening tests, our data points to less frequent in-person follow-up being associated with non-inferior breast cancer-related outcomes. Future prospective studies are required looking at different models of follow-up.

SABCS Abstract Table

<table>
<thead>
<tr>
<th></th>
<th>Image Detected</th>
<th>Self-Detected</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=51, %)</td>
<td>(n=122, %)</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (41.2%)</td>
<td>20 (16.3%)</td>
<td>0.007</td>
</tr>
<tr>
<td>2</td>
<td>29 (59.0%)</td>
<td>51 (55.3%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>13 (25.5%)</td>
<td>74 (51.0%)</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer subtype</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ER Positive</td>
<td>45 (88.2%)</td>
<td>118 (77.6%)</td>
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<tr>
<td>HER2 Positive</td>
<td>5 (9.8%)</td>
<td>28 (18.4%)</td>
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<tr>
<td>HER2 Unknown</td>
<td>7 (13.7%)</td>
<td>7 (4.8%)</td>
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<tr>
<td>Type of Recurrence</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Distant</td>
<td>5 (17.7%)</td>
<td>125 (82.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local</td>
<td>17 (55.1%)</td>
<td>22 (14.5%)</td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>25 (49.0%)</td>
<td>25 (51.0%)</td>
<td></td>
</tr>
</tbody>
</table>

The categorical variables are presented in number and frequency (%), and the continuous variables presented in median and range. *P-value of Chi-squared tests or Mann-Whitney U Test

Disclosure(s):
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Mark Clemons, MD: No financial relationships to disclose

Gail Larocque, BHSc; MN; NP-PHC: No financial relationships to disclose
Predictors of guideline-incongruent breast cancer screening in an urban comprehensive cancer center

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Background: Guideline-congruent breast cancer (BC) screening is imperative to systematically curb BC mortality. This study was conducted to identify predictors of BC screening behaviors congruent with guidelines from various nationally recognized organizations (e.g., American Cancer Society, National Comprehensive Cancer Network, American College of Radiology) among high- and average-risk women, and to elucidate the alternative screening behaviors of women who were incongruently screened. Methods: Medical records of 6,090 women who received at least two screening mammograms from January 2016 to March 2018 at the Karmanos Cancer Institute were reviewed to determine breast cancer risk status (classified by the Tyrer-Cuzick model) and breast density status to determine whether breast cancer screening was concordant with risk-driven screening guidelines. Breast density was determined by BI-RADS density scoring, with non-dense breasts defined by a score of A or B, and dense breasts as C or D. For women at average-risk of breast cancer, incongruent screening was defined as receiving supplemental imaging in the interval between screening mammograms. For high-risk women, incongruent screening was defined as not having a recommended supplemental image in the interval between screening mammograms. Further, we examined BC risk, breast density, age, and race as predictors for guideline-concordant screening.

Results: The screening cohort included 73.3% Black and 26.7% White women of whom 86.5%...
were classified as average-risk, 7.7% intermediate risk and 5.8% high risk. Further analyses focused on women with average and high-risk of breast cancer. Among both average- and high-risk women, 390 (6.9%) were incongruently screened, however the rate of incongruent screening was much higher among high-risk vs. average risk women (97.7 vs. 0.9%, p< 0.01). Among average-risk women, incongruent screening was more likely among women with dense vs. non-dense breasts (2.0% vs 0.1%, p< .01). High-risk women were more likely to be incongruently screened if they had non-dense compared to dense breasts (99.5% vs 95.2%, p < .01). Younger women more likely to be incongruently screened among average-risk women (55.11 [SD = 10.24] vs 62.20 [SD = 9.73]; t5267 = 4.87, p < .01, d = 0.73), whereas older women were more likely to be incongruently screened among high-risk women, although this difference was not statistically significant (52.38 [SD = 7.27] vs 47.50 [SD = 8.57]; t351 = 1.87, p = .06, d = 0.67). There was no significant impact of race and incongruent screening for individual risk-level categories. With the exception of rendering the age effect non-significant, preliminary multivariable analyses did not significantly change the results. Further analyses will be conducted to assess the relationship between predictive factors and incongruent screening. Conclusions: An apparent lack of adherence to evidence-based screening guidelines for BC has led to underutilization of supplementary breast imaging for women at high-risk for BC. Further interventions are needed to promote increased supplemental imaging for this group of women.

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Breast Imaging Recommendations for Females <40 Years of Age with ≥20% Lifetime Breast Cancer Risk: Practice Patterns at a Specialized Clinic

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  Country: United States
Background—There are limited data to guide breast cancer screening recommendations among females < 40 yrs of age with elevated lifetime breast cancer risk not driven by a known germline mutation. The American Cancer Society recommends initiating screening at age 30, while the National Comprehensive Cancer Network (NCCN) recommends 10 yrs younger than the youngest affected relative (YAR). Both support screening MRI in addition to annual mammogram (MMG). This study describes practice patterns related to screening imaging recommendations and patient (pt) follow-up.

Methods—At the Brigham and Women’s Hospital high-risk breast clinic, specialized advanced practice providers, surgeons and oncologists perform risk assessment including use of the Tyrer-Cuzick (TC) risk model, and provide risk management recommendations. For this study, we identified pts age< 40 yrs with >20% lifetime breast cancer risk, no known genetic mutation or high-degree relatives (FDR or SDR) with breast cancer. We evaluated factors associated with recommendation for i) early screening initiation, defined as prior to age 40, and ii) use of supplemental imaging modalities.

Results—335 pts met study criteria: 20% were age< 30, 36% were 30-34, and 44% were 35-39. Mean lifetime risk by the TC model was 32% (SD: 10%). Early screening was recommended in 75%; these pts were more likely to have an affected FDR (71% vs. 48%, p< 0.001) and younger affected relatives (median age of YAR: 44 vs. 55, p< 0.001). Among pts whose YARs were age< 50, early screening was recommended in-line with NCCN guidelines for 99% of pts with FDRs< 50 vs. 80% of pts with only SDRs< 50 (p< 0.001). Among pts whose YARs were age≥50, early screening was recommended contrary to NCCN guidelines in 51%. Factors associated with an early screening recommendation in this subgroup were having received a prior MMG (62% recommended early screening vs. 33% with no prior MMG) as well as being older at time of risk discussion (median age 37 in early screening group vs. 34 in routine screening group) and having younger affected relatives (median age of YAR: 53 vs. 56) (all p≤0.01). Factors associated with offering supplemental screening with MRI/US included having heterogeneously or extremely dense breasts, normal BMI, greater extent of family history, younger affected relatives and higher TC scores (Table). All except extent of family history remained statistically significant in multivariable analysis. Among those offered supplemental MRI/US who were eligible to initiate screening, 48% had pursued MRI, 7% US +/- MRI, 27% MMG alone, and 18% had no screening imaging at a median follow-up of 17 months.

Conclusions—These data suggest that providers in our high-risk breast clinic are using nuanced clinical judgment related to screening recommendations in pts < 40 yrs with elevated lifetime risk. Those with affected FDRs at age< 50 were consistently recommended early screening initiation, while practice recommendations varied more for pts with only SDRs age< 50 yrs. Multiple factors impacted recommendations for screening MRI/US, most notably breast density.

Factors associated with offering supplemental screening with MRI/US
<table>
<thead>
<tr>
<th></th>
<th>Recommended MMG alone (row %)</th>
<th>Offered MRI/US (row %)</th>
<th>p-value</th>
<th>MVA Odds Ratio</th>
<th>MVA p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast density</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-dense</td>
<td>25 (66%)</td>
<td>13 (34%)</td>
<td>&lt;0.001</td>
<td>0.34 ref</td>
<td>0.02 ref</td>
</tr>
<tr>
<td>Heterogeneously dense</td>
<td>28 (30%)</td>
<td>65 (70%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely dense</td>
<td>16 (20%)</td>
<td>64 (80%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior MMG</td>
<td>47 (38%)</td>
<td>77 (62%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25.0</td>
<td>46 (25%)</td>
<td>137 (75%)</td>
<td>&lt;0.001</td>
<td>ref</td>
<td>--</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>29 (38%)</td>
<td>48 (62%)</td>
<td></td>
<td>0.52 ref</td>
<td>0.05 ref</td>
</tr>
<tr>
<td>≥30.0</td>
<td>41 (59%)</td>
<td>29 (41%)</td>
<td></td>
<td>0.28 ref</td>
<td>0.001 ref</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 FDR + 1 SDR</td>
<td>22 (54%)</td>
<td>19 (46%)</td>
<td>0.002</td>
<td>147 ref</td>
<td>0.39 ref</td>
</tr>
<tr>
<td>0 FDR + ≥2 SDR</td>
<td>29 (39%)</td>
<td>46 (61%)</td>
<td></td>
<td>1.55 ref</td>
<td>0.26 ref</td>
</tr>
<tr>
<td>1 FDR + 0 SDR</td>
<td>30 (42%)</td>
<td>42 (58%)</td>
<td></td>
<td>ref</td>
<td>--</td>
</tr>
<tr>
<td>1 FDR + ≥1 SDR</td>
<td>29 (26%)</td>
<td>81 (74%)</td>
<td></td>
<td>1.58 ref</td>
<td>0.24 ref</td>
</tr>
<tr>
<td>≥2 FDR + any SDR</td>
<td>6 (16%)</td>
<td>31 (64%)</td>
<td></td>
<td>1.39 ref</td>
<td>0.58 ref</td>
</tr>
<tr>
<td><strong>Median age of YAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IQR)</td>
<td>50 (44-55)</td>
<td>45 (39-50)</td>
<td>&lt;0.001</td>
<td>0.96 ref</td>
<td>0.006 ref</td>
</tr>
<tr>
<td><strong>Mean TC lifetime risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SD)</td>
<td>27 (7)</td>
<td>32 (10)</td>
<td>&lt;0.001</td>
<td>1.07 ref</td>
<td>0.001 ref</td>
</tr>
</tbody>
</table>

Disclosure(s):

Alexandra Wehbe, MPH: No financial relationships to disclose
Alison Laws, MD, MPH: No financial relationships to disclose
Fisher Katlin, BA: No financial relationships to disclose
Eshita Sharma, BA: No financial relationships to disclose
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Rochelle Scheib, MD: No financial relationships to disclose
Judy Garber, MD, MPH: Ambry Genetics: Consulting Fees (e.g., advisory boards) (Ongoing); Helix Genetics: Consulting Fees (e.g., advisory boards) (Ongoing); Invitae Genetics: Consulting Fees (e.g., advisory boards) (Ongoing); Myriad Genetics: Contracted Research (Ongoing)
Lydia Pace, MD, MPH: No financial relationships to disclose
Tari King, MD: Besins: Advisory board (Ongoing); Exact Sciences: Advisory board participation and speakers honoraria (Ongoing)
WITHDRAWN
Breast cancer screening using ultrasound increases recall, biopsy, and cancer detection rates

Background: Ultrasound is often used as an adjunct to mammography for breast cancer (BC) screening. Usage of screening ultrasound (US) varies by state, likely due to differences in state-specific breast density notification laws and mandates requiring insurance coverage of supplemental screening for women at elevated risk of breast cancer. Screening US can increase cancer detection rates among women with dense breasts, but may increase recalls
and benign biopsies. As more states adopt policies mandating insurance coverage for "medically necessary" breast cancer imaging, it is important to understand the impact to screening US utilization and subsequent service utilization. This analysis examines use of screening US by state as well as associated rates of recall, biopsy, and cancer detection.

Methods: We analyzed deidentified administrative claims. We included women aged 18-74 in 2018. First claim was index date. Continuous enrollment was required in a commercial (COM) or Medicare Advantage (MA) plan from 1/2016 to index date (baseline period) and from index date to 6 months after (follow-up period). Recall, biopsy, and cancer detection rates were calculated for the follow-up period. We used CPT/HCPCS codes to identify procedures. Screening US was identified by CPT 76641 (complete) with modifier 50 (bilateral) or LT/RT (left/right). Using ICD codes, cancer by insurance type, state, and age. Proportions were compared with chi-squared tests.

Results: 939,410 women met study criteria (70% COM, 30% MA; Tables 1-2). In the COM population, recall, biopsy, and cancer detection rates with screening US were approximately two-fold higher than without (recall: 26.1% vs. 11.8%; biopsy: 5.0% vs 1.6%; cancer detection: 1.0% vs. 0.4%). In the MA population, recall, biopsy, and cancer detection rates with screening US were roughly three-fold higher than without (recall: 23.6% vs 9.0%; biopsy: 5.2% vs 1.6%; cancer detection: 1.9% vs 0.7%). In NY, NJ, and CT, the rate of screening US usage was > 14 times higher than in all other states (29.1% vs 1.9%). These three states had higher recall and biopsy rates, but similar cancer detection rates compared to all other states (recall: 14.4% vs. 11.4%; biopsy: 2.5% vs 1.7%; cancer detection: 0.6% vs. 0.5%). All proportion differences reached statistical significance (p < 0.001).

Conclusion: Screening US was associated with increases in recall and biopsy, but modest increases in absolute cancer detection rates. Observed state by state variation of screening US is likely driven by laws requiring zero patient payment insurance coverage of "medically necessary" imaging which, as is the case with NY, NJ, and CT, is interpreted to include screening US. Our results demonstrate that screening US may lead to a large increase in recall rates and biopsies without consequentially improving the cancer detection rate.

Table 1: Recall, biopsy, and cancer detection rates by age with and without use of adjunctive breast screening ultrasound in a commercially insured U.S. population

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>35.5%</td>
<td>20.2%</td>
<td>8.2%</td>
<td>2.6%</td>
<td>N/A*</td>
<td>0.3%</td>
</tr>
<tr>
<td>40-44</td>
<td>29.5%</td>
<td>16.5%</td>
<td>5.9%</td>
<td>2.0%</td>
<td>0.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>45-49</td>
<td>26.6%</td>
<td>13.5%</td>
<td>5.1%</td>
<td>1.6%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>50-54</td>
<td>25.3%</td>
<td>11.5%</td>
<td>4.7%</td>
<td>1.5%</td>
<td>1.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>55-59</td>
<td>24.3%</td>
<td>9.9%</td>
<td>4.6%</td>
<td>1.4%</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>60-64</td>
<td>23.6%</td>
<td>9.5%</td>
<td>4.3%</td>
<td>1.4%</td>
<td>1.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>65-69</td>
<td>22.7%</td>
<td>9.6%</td>
<td>4.4%</td>
<td>1.5%</td>
<td>1.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td>70-74</td>
<td>22.6%</td>
<td>10.3%</td>
<td>5.0%</td>
<td>1.7%</td>
<td>N/A*</td>
<td>0.8%</td>
</tr>
<tr>
<td>Overall</td>
<td>26.1%</td>
<td>11.5%</td>
<td>5.0%</td>
<td>1.6%</td>
<td>1.0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

* values are suppressed to comply with requirements for data release
Table 2: Recall, biopsy, and cancer detection rates by age with and without use of adjunctive breast screening ultrasound in a Medicare Advantage (MA) U.S. population

<table>
<thead>
<tr>
<th>Age</th>
<th>Recall With Screening US (n=6,100)</th>
<th>Without Screening US (n=272,408)</th>
<th>Biopsy With Screening US (n=6,100)</th>
<th>Without Screening US (n=272,408)</th>
<th>Cancer Detection With Screening US (n=6,100)</th>
<th>Without Screening US (n=272,408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>N/A*</td>
<td>16.5%</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>40-44</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>45-49</td>
<td>31.2%</td>
<td>11.9%</td>
<td>N/A*</td>
<td>1.5%</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>50-54</td>
<td>19.3%</td>
<td>11.6%</td>
<td>N/A*</td>
<td>1.6%</td>
<td>N/A*</td>
<td>0.4%</td>
</tr>
<tr>
<td>55-59</td>
<td>28.9%</td>
<td>10.5%</td>
<td>7.4%</td>
<td>1.4%</td>
<td>N/A*</td>
<td>0.5%</td>
</tr>
<tr>
<td>60-64</td>
<td>25.3%</td>
<td>10.1%</td>
<td>6.8%</td>
<td>1.6%</td>
<td>N/A*</td>
<td>0.5%</td>
</tr>
<tr>
<td>65-69</td>
<td>25.4%</td>
<td>9.0%</td>
<td>5.3%</td>
<td>1.6%</td>
<td>2.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>70-74</td>
<td>22.4%</td>
<td>8.7%</td>
<td>4.9%</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Overall</td>
<td>23.6%</td>
<td>9.0%</td>
<td>5.2%</td>
<td>1.6%</td>
<td>1.9%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

* values are suppressed to comply with requirements for data release

Disclosure(s):

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Analysis of an update to a novel breast cancer screening web-app

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  Country: United States
Introduction

A minority of women with breast cancer in Mexico are diagnosed through a screening program with a low rate of national coverage of about 20%, which translates into late diagnosis and worse outcomes. The detection of high-risk groups through easy-access interventions is essential to increase the screening rate.

OBJECTIVE

To identify and analyze patients at high risk of breast cancer, through a web app specially designed for this purpose.

MATERIAL AND METHODS

The web app stratified respondents according to breast cancer risk into 4 categories: very high risk (symptomatic), high lifetime risk, average risk (usual screening recommendations), or low risk. The app was programmed to guide patients to a risk-based information page or urge them to seek medical advice if indicated (https://cuccuanl.com/tamiz_mama/). The web app also provided the contact information of our center, or an appointment could also be scheduled within the app. Distribution was made via social media.

An upgrade of the app was launched, which expanded the functionality with the inclusion of the Gail model to identify women with a high lifetime risk for developing breast cancer and the option for a simple interpretation of mammographic results. In version 2.0, the patients were divided into 2 populations, the first one which already had a breast imaging test but wished to know what the BIRADS score obtained meant and the other group were those who answered a simple survey similar to the one available on version 1.0, with added questions to calculate the Gail model risk.

RESULTS

The web app was originally released in October 2021 with a total number of 1,012 women answering the survey. The update was released in June 2022 with 406 new subjects. 281 patients wished for a risk calculation with no prior breast imaging tests and 124 patients already had a breast image diagnosis test that wanted a simple interpretation. Table 1 depicts the answers given between both versions.

Among the group of patients that had a mammography but had doubts about the result 12.9% (n=16) reported a BIRADS 0, 12.1% (n=15) BIRADS 1, 46% (n=57) BIRADS 2, 14.5% (n=18) BIRADS 3, and 14.4% (n=18) BIRADS 4 or 5.

To date 41 patients have booked an appointment at the cancer prevention clinic directly within the webapp for further evaluation.

DISCUSSION AND CONCLUSION

The changes in the criteria of high risk did not translate into changes in the proportion of patients considered at high lifetime risk of breast cancer, but these changes made might be more specific for subsequent screening and chemoprevention strategies. The app persisted with a high proportion of symptomatic patients.
The results of integration of the simple mammography interpretation were surprising, with a high proportion of subjects with indication for a biopsy founded. In the Mexican population there is a significant gap between the screening mammography and the first consultation with a specialist, averaging 113 days from an abnormal screening test to a diagnosis of breast cancer (1), which delays treatment initiation resulting on a worst outcome.

These kinds of apps may empower patients to seek earlier consultation if warranted or educate patients on their personal risk for developing cancer so they may have a closer adherence to early detection programs. These results and subsequent updates might help evolve the app into something more akin to a digital navigator for patients.

Bibliography

Table 1

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Version 1.0 (n=1003)</th>
<th>Version 2.0: Cohort that didn’t have a screening test to interpret (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk (Symptomatic Patient)</td>
<td>12.8% (n=128)</td>
<td>13.2% (n=37)</td>
</tr>
<tr>
<td>High lifetime risk (V1: Positive family history, ≥5-year OCP use; V2: ≥1.7% Gail Index, Prior radiotherapy, ≥5-year OCP use)</td>
<td>18.2% (n=183)</td>
<td>15.3% (n=43)</td>
</tr>
<tr>
<td>Normal screening recommendation (≥40 years without additional risk factors)</td>
<td>16.8% (n=169)</td>
<td>17.8% (n=50)</td>
</tr>
<tr>
<td>Low risk of breast cancer (&lt;40 years without additional risk factors)</td>
<td>52.1% (n=523)</td>
<td>53.7% (n=151)</td>
</tr>
</tbody>
</table>

Results stratified by risk groups between version 1.0 and 2.0

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Background: Breast cancer is the second most common cancer occurring during pregnancy with limited evidence for appropriate staging (1,2). A Delphi study was performed to develop consensus guidelines. Methods: Guideline recommendations were constructed based on available evidence and included statements targeting highlighted areas of uncertainty from a clinician-based survey. Statements were divided into two domains: one focused on indications for staging and the second addressed imaging selection. A two round Delphi study was performed. Medical, radiation and surgical oncologists from Australia and New Zealand were invited to participate. Participants who had worked in their field for >5 years were considered experts. Participants voted using a 9-point Likert scale selecting from 1 (strongly disagree) to 9 (strongly agree). Consensus was achieved when >75% participants selected < 3, or >7 for a statement. Statements that did not reach consensus in the first round were refined and re-presented for subsequent voting. Results: 15 Australian and New Zealand experts agreed to participate: 8 medical oncologists, 3 radiation oncologists and 4 breast surgeons. 87% (13/15) of participants completed round one. Of the 18 recommendations, six did not meet consensus. These were revised, with seven recommendations re-presented in round two. 11/13 (85%) participants completed round two, with one further recommendation achieving consensus. Consensus was achieved on indications for staging including women with locally advanced or inflammatory breast cancer and clinical suspicion of metastatic disease. Staging should be delayed until after pregnancy if it will not immediately change management decisions. Staging should not routinely be used in stage I and II breast cancers. Where staging is indicated, it was agreed that visceral disease should be screened for; however, consensus was not achieved for whether screening for bone metastases should be performed. There was consensus for liver ultrasound as the imaging modality of choice for liver metastases screening. Participants did not agree on whether chest x-ray or CT chest was best practice for pulmonary metastases nor optimal imaging for bone metastases. There was also discord as to whether there is a role for PET scan. Conclusion: Consensus guidelines have been developed to standardise breast cancer staging during pregnancy. Consensus was achieved for indications for staging and use of liver ultrasound to screen for liver metastases. Optimal staging practices for bone and

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Abigail Miller, MBBS: No financial relationships to disclose
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Personalized Cancer Monitoring (PCM): a novel ctDNA tool to detect molecular residual disease in patients with early-stage breast cancer

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  Country: United States
Introduction: Identification of Molecular Residual Disease (MRD) in patients with breast cancer with circulating tumor DNA (ctDNA) presents a strategy to identify patients at high risk of relapse. Approaches that detect ctDNA at lower concentrations are required to increase sensitivity and improve on the lead time between ctDNA detection and clinical relapse. Here we present results using novel highly sensitive tumor-informed sequencing assays for ctDNA detection of MRD based on detection of multiple patient specific mutations in ctDNA.

Methods: 62 stage II-III breast cancer patients (23 hormone receptor positive HER2 negative (HR+HER2-), 20 HER2+, 15 triple negative breast cancer (TNBC) and 4 unknown receptor status) enrolled in the ChemoNEAR sample collection study were included. All patients received neoadjuvant chemotherapy, followed up by surgery, with samples taken at diagnosis, and post-surgery every 3 months for the first two years, followed by every 6 months for up to five years. Tumor DNA from FFPE samples and germline was Whole Exome Sequenced to identify patient specific mutations and design anchored-multiplex PCR (AMP™) Personalized Cancer Monitoring (PCMTM) assays to track mutations in plasma. Cell free DNA was extracted from 613 plasma samples (median volume 4ml, range 0.5-4.5ml) and sequenced with PCMTM assays, with 37-177 variants (median 52) per panel, to a depth of 100,000x per locus. A proprietary algorithm was used to identify ctDNA. Results: At a median follow-up of 52.7 months post-surgery (range 15.3-96.4 months), ctDNA was detected in 25.8% (16/62) of patients, with detected ctDNA levels ranging from allele frequency (AF) of 0.01%, to 32.5% (median 0.24% AF). Detection of ctDNA was associated with a high risk of future relapse (HR 65.4, 95% CI 14.5-293.7), with a median lead-time from ctDNA detection to clinical relapse of 13.7 months (range 3.9-58.9). MRD was identified in 76.9% (10/13) of patients who relapsed. ctDNA was detected prior to relapse in both patients with brain only relapse, but with a reduced lead time over clinical relapse (5.73 and 3.90 months), which was previously not achievable with digital PCR MRD-detection assays. Of patients with assessable baseline samples, 81% (39/48) had ctDNA detected. No patients with undetected ctDNA, or detectable ctDNA with AF<0.1%, relapsed during follow-up, whereas ctDNA was detected at baseline in all 10 patients who relapsed during follow-up (p=0.1). Conclusions: PCMTM detected breast cancer relapse with a long lead-time over clinical relapse, and strong association with relapse free survival, an advancement over previously published data with digital PCR MRD detection. Prospective, interventional trials are now required to assess whether treatment on the basis of MRD detection improves outcome, including the TRAK ER Trial (NCT04985266).

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Fees (e.g., advisory boards) (Ongoing); Roche/Genentech: Consulting Fees (e.g., advisory boards) (Ongoing), Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing), Contracted Research (Ongoing); Zentalis pharmaceuticals: Consulting Fees (e.g., advisory boards) (Ongoing), Consulting Fees (e.g., advisory boards) (Ongoing)
Introduction: Use of long-term endocrine therapy (ET) for ER+ breast cancer often leads to acquired ESR1 mutations (mutESR1), causing endocrine resistance, tumor progression, and poor prognosis. An unmet clinical need exists for treating ER+ mBC patients with mutESR1, particularly after progression on CDK4/6 inhibitors (CDK4/6i). ELAINE 2 is an open-label, phase 2, multicenter trial evaluating safety and efficacy of lasofoxifene (LAS [selective estrogen receptor modulator]) plus abemaciclib (Abema [CDK4/6i], provided by Eli Lilly) in patients with ER+/HER2- and mutESR1 mBC who progressed after prior ET. Preliminary data with LAS plus Abema showed median progression-free survival of 55.7 wks, objective response rate of 50%, and 24-wk clinical benefit (CB) rate of 69%, with an acceptable safety and tolerability profile. Here, we report ESR1 ctDNA mutant allele frequency (MAF) and correlations of ESR1 MAF
Changes with CB.
Methods: ELAINE 2 patients with detectable ctDNA mutESR1 at baseline (BL) were analyzed. Oral LAS 5 mg/day and Abema 150 mg BID were taken until disease progression, death, unacceptable toxicity, or withdrawal from the study. ctDNA was assessed by the Sysmex-Inostics SafeSeq assay—which detects mutESR1 at low allele fractions—at BL, every 4 wks, and end of treatment. MAF changes from BL to wk 4 were characterized as decreased (decrease in ESR1 MAF or none detected [ND]), increased (increase in MAF), or equivocal (in polyclonal patients [>1 mutESR1] with some MAF increasing and decreasing trends). Correlations of MAF change at 4 wks with CB at 24 wks were explored.

Results: 29 patients (median of 2 prior metastatic therapies: 97% CDK4/6i, 79% fulvestrant, 48% chemotherapy) had BL mutESR1 of Y537S (66%), D538G (45%), Y537N (28%), and other less frequently detected mutations; 14 (48.3%) patients were polyclonal. 26 of 29 patients had evaluable BL and wk-4 ctDNA results: 21 patients had decreased MAF (81% [54% with ND]), 3 (12%) had increased, and 2 (8%) had equivocal ESR1 MAF changes (Table). CB at 24 wks was seen in 17 patients with a decrease, 2 with an increase, and 1 with equivocal MAF change. A sensitivity of 89.5% and specificity of 20% were calculated for predicting CB based on direction of ESR1 MAF change. The positive predictive value (PPV) for CB with decreased MAF was 81% and the negative predictive value (NPV) for an increased MAF was 33%. Of the 14 (54%) patients with ND ESR1 MAF, 13 had CB resulting in 87% sensitivity, 50% specificity, 93% PPV, and 33% NPV.

Conclusion: In ELAINE 2, 81% of patients had decrease/cleared (ND) mutESR1 after 4 wks of LAS plus Abema, which correlated with clinical benefit. All mutESR1 detected appear targeted with this therapy. High sensitivity and favorable PPV were observed in patients with decreased MAF, and even more so in those with ND MAF; however, increased MAF was less specific and not as predictive of treatment failure. Our results indicate that ESR1 liquid biopsy evaluation may be an adequate non-invasive surrogate marker for monitoring patients on treatment. Further study in a larger population of women with endocrine-resistant mBC and acquired mutESR1 is warranted to explore this potential for monitoring treatment response or resistance to this novel LAS-Abema combination.

Table. Change from baseline to week 4 in ESR1 MAF and clinical benefit at 24 weeks.
CI, confidence interval; MAF, mutant allele fraction; ND, none detected; NPV, negative predictive value; PPV, positive predictive value.

*Sensitivity and specificity analyses do not include equivocal results.

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<thead>
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<th>Clinical benefit at 24 weeks</th>
<th>MAF change at 4 weeks (n=26)</th>
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<tr>
<td></td>
<td>Decreased/ND</td>
<td>Increased</td>
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<tr>
<td>Yes</td>
<td>17 (85%)</td>
<td>2 (8%)</td>
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<td>No</td>
<td>4 (15%)</td>
<td>1 (4%)</td>
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<tr>
<td>Sensitivity*</td>
<td>89.3% (95% CI, 65.5–98.2)</td>
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<tr>
<td>Specificity*</td>
<td>20.0% (95% CI, 1.05–70.1)</td>
</tr>
<tr>
<td>PPV</td>
<td>81.0% (95% CI, 57.4–93.7)</td>
</tr>
<tr>
<td>NPV</td>
<td>33.3% (95% CI, 1.80–87.5)</td>
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<td>ND only (n=14)</td>
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<tr>
<td>Sensitivity*</td>
<td>86.7% (95% CI, 58.4–97.7)</td>
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<tr>
<td>Specificity*</td>
<td>50.0% (95% CI, 9.50–80.5)</td>
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<tr>
<td>PPV</td>
<td>92.9% (95% CI, 64.2–99.6)</td>
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<tr>
<td>NPV</td>
<td>33.3% (95% CI, 1.80–87.5)</td>
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Disclosure(s):

**Senthil Damodaran, MD, PhD**: EMD Serono: Grants or Contracts to Institution (Ongoing); Guardant Health: Grants or Contracts to Institution (Ongoing); Novartis: Grants or Contracts to Institution (Ongoing); Sermonix: Grants or Contracts to Institution (Ongoing); Taiho: Grants or Contracts to Institution (Ongoing)

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Background: NF1 (neurofibromin type 1) encodes neurofibromin, and is commonly altered in many cancers, including breast cancer. NF1 suppresses breast cancer by not only negatively regulating RAS signaling but also by independently acting as a transcriptional co-repressor of the estrogen receptor (ER). In this study, we analyzed the genomic landscape of patients with NF1 alterations from a large genomic database to define what unique patient characteristics were associated with NF1 alterations. Methods: Retrospective analysis of the Guardant Health database based on samples from the commercially available Guardant360® plasma-based circulating tumor DNA (ctDNA) assay. Samples were queried between June 2020-June 2022 for patients with any detected NF1 alteration and breast cancer diagnosis. NF1 synonymous alterations were excluded from this study. Statistics were conducted using a two-sided Fisher's exact test. Results: NF1 alterations were found in 895 patients with breast cancer over 1156 samples, typically in female patients (98.2%) diagnosed with breast carcinoma (99.4%). The average age of patients was 66 years old (23-93), with a median of 1.4 serial tests (1-19). The common nonsynonymous NF1 alterations are missense mutations (56.5%), nonsense mutations (23.5%), indels (22.3%), and aberrant splicing mutations (8.2%). There were significant differences in NF1 alteration frequency between younger (< 55 y/o) vs. older (≤55 y/o) patients, with older patients demonstrating an increase in NF1 alterations (p< 0.0001) across all mutation types except for splice mutations. There was also a significant difference in NF1 alterations between female vs. male patients, with male patients trending toward a higher frequency in NF1 missense alterations. Mutations affecting genes encoding the receptor tyrosine kinase (e.g., HER2) and the Ras-MAP kinase pathways (e.g., several RAS and RAF genes) co-occur with NF1 mutations. In contrast, there is no evidence of co-occurrence with mutations in the ESR1 gene, which encodes ER. The blood tumor mutational burden (bTMB) score was evaluable in 848 patients with an average score of 26.1 mut/Mb (range 1.16-447.7). In addition, mutations affecting genes controlling the cell cycle were also found to co-occur with NF1 mutations. Conclusions: Plasma-based liquid biopsy via G360 can efficiently identify NF1 alterations illustrating that such genetic alterations are common in this metastatic breast cancer cohort. Analysis of co-occurrence of mutations supports our model that a key role of NF1 is to act as an ER transcriptional co-repressor, such that its loss is functionally redundant with acquiring ESR1 mutations. Oncogenic activation of the RTK-Ras pathways is needed for efficient progression to metastasis by additional mutations in this pathway. Mutational co-occurrence may also identify collaborating molecular events that collaborate with NF1 loss to promote treatment relapse and metastasis.
Disclosure(s):

**Eric Chang, PhD**: No financial relationships to disclose

**Jill Tsai, PhD**: Guardant: Salary (Ongoing)

**Bora Lim, MD**: Astrazeneca: Consulting Fees (e.g., advisory boards) (Ongoing); Eli Lily: Consulting Fees (e.g., advisory boards) (Ongoing); Genentech: research funding (Ongoing); Merck: research funding (Ongoing); Natera: Consulting Fees (e.g., advisory boards) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing); Puma: Research Funding (Ongoing); Takeda Oncology: research funding (Ongoing)
Estrogen receptor 1 (ESR1) mutations in circulating tumor DNA (ctDNA) from patients with ER+/HER2- metastatic breast cancer (mBC) treated with lasofoxifene or fulvestrant in the ELAINE 1 study

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Introduction: Acquired ESR1 mutations (mutESR1) after long-term endocrine therapy drive treatment resistance, metastasis, and poor prognosis for patients (pts) with ER+/HER2-metastatic breast cancer (mBC). Lasofoxifene (LAS), a selective estrogen receptor modulator, alone or with a CDK4/6 inhibitor (CDK4/6i) reduced tumor growth better than fulvestrant (Fulv) in mutESR1 BC xenograft models. ELAINE 1 is a randomized trial of LAS vs Fulv in pts with mutESR1 and prior progression on aromatase inhibitor and CDK4/6i. Preliminary results (ESMO 2022) showed that LAS prolonged median progression-free survival (mPFS) compared with Fulv with a favorable safety profile. Here, we report changes in ESR1 ctDNA mutant allele frequency (MAF) from baseline to 8 wks and their associations with clinical benefit (CB) and mPFS.

Methods: ELAINE 1 pts were randomized to oral LAS 5 mg daily or IM Fulv 500 mg on days 1, 15, and 29, then every 4 wks, until disease progression or severe toxicity. ctDNA mutESR1 mutations (baseline and 8 wks) were assessed using the Sysmex Inostics OncoBeam or SafeSeq assays—which detect mutESR1 at low allele fractions. MAF changes from baseline to wk 8 were characterized as decreased (decrease in ESR1 MAF or fully cleared), increased (increase in MAF), or equivocal (polyclonal patients [>1 mutESR1] with some increasing and decreasing MAF trends); correlations with PFS and CB were explored. Efficacy measures included objective response rate (ORR), PFS, and CB at 24 wks (CB defined as response or polyclonal. Of the 61 pts with evaluable baseline and wk 8 ctDNA, LAS decreased mutESR1 MAF in 29/35 pts (83% [11 complete clearance]) while Fulv decreased mutESR1 MAF in 16/26 pts (61.5% [6 complete clearance]) (Table).

mPFS with LAS was 8 and 4 mos for pts with decreased/cleared MAF and increased MAF, respectively, and with Fulv was 4.5 and 2.8 mos, respectively (Table). LAS decreased the common mutESR1 variants more frequently than Fulv (median relative change -87.1% vs -14.7%). In pts with decreased MAF, CB was observed in 16/29 LAS pts (55%) and 4/16 Fulv pts (25%). The predictiveness of ESR1 MAF clearance for CB was also explored. Of 11 pts with ESR1 MAF clearance taking LAS, 10 achieved CB, yielding a positive predictive value (PPV) of 90.9%. In contrast, 2/6 pts with ESR1 MAF clearance taking Fulv had CB for a PPV of 33.3%. Sensitivity for predicting CB based on direction of ESR1 MAF change was 94% with LAS and 80% with Fulv. In pts with Y537S MAF (n=33), LAS decreased Y537S in 13/15 (87%), with a median relative MAF decrease of 89%. In marked contrast, Fulv increased Y537S MAF in 11/18 pts (61%), corresponding to an MAF relative increase of 82%. LAS and Fulv resulted in complete clearance of Y537S MAF in 33% and 6% of pts, respectively.

Conclusion: Our data demonstrate that LAS more effectively decreased or cleared mutESR1 than Fulv. Further, mutESR1 clearance was associated with prolonged PFS and more CB in LAS but not Fulv pts, suggesting that LAS results in robust mutESR1 target engagement. Taken together, our data suggest mutESR1 as a potential liquid biomarker for predicting response to LAS in mutESR1, endocrine-resistant mBC pts.

Table. Change from baseline to week 8 in ESR1 MAF and clinical benefit at 24 weeks.
<table>
<thead>
<tr>
<th>Clinical benefit at 24 weeks</th>
<th>Lansoprazole (n=50)</th>
<th>Fulvestrant (n=50)</th>
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<tbody>
<tr>
<td></td>
<td>Decreased/ND MAF</td>
<td>Increased MAF</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (45.7%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>No</td>
<td>13 (37.1%)</td>
<td>5 (14.3%)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>94.1 (95% CI, 69.2–99.7)</td>
<td>60.0 (95% CI, 29.9–80.9)</td>
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<tr>
<td>Specificity (%)</td>
<td>27.8 (95% CI, 10.7–53.6)</td>
<td>42.9 (95% CI, 22.6–66.6)</td>
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<tr>
<td>Median PFS (months)</td>
<td>Decreased/ND MAF</td>
<td>Increased MAF</td>
</tr>
<tr>
<td></td>
<td>6 (95% CI, 4–8)</td>
<td>4 (95% CI, 2–6)</td>
</tr>
</tbody>
</table>

CI, confidence interval; MAF, mutant allele fraction; ND, none detected; PFS, progression-free survival.

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Monitoring for response and recurrence in neoadjuvant-treated hormone receptor-positive HER2-negative breast cancer by personalized circulating tumor DNA testing

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Background: The detection of circulating tumor DNA (ctDNA) may serve as an early predictor of response and recurrence. In this study, we used a tumor-informed ctDNA test to monitor clinical outcomes in patients with high-risk hormone receptor-positive HER2-negative (HR+HER2-) tumors who received neoadjuvant chemotherapy (NAC) on the I-SPY 2 trial (NCT01042379).

Methods: We collected blood samples at pretreatment, during (at 3 and 12 weeks after initiation of paclitaxel-based treatment with or without an investigational drug), after NAC prior to surgery, 4 weeks after surgery, and annually until clinical diagnosis of recurrence. Cell-free DNA was isolated from plasma (N=329 samples) and ctDNA was detected using a personalized, tumor-informed multiplex polymerase chain reaction next generation sequencing-based test (SignateraTM). All patients were at high risk for recurrence by MammaPrint. The response endpoints were pathologic complete response (pCR) and residual cancer burden (RCB), and the survival endpoint was event-free survival (EFS). Results: This analysis included 66 patients with HR+HER2- breast cancer who had blood samples collected before, during, after NAC and had at least one blood sample after surgery with sufficient plasma for analysis. 57.1% (32/56) had grade III disease; 72.4% (42/58) were node-positive; 36.2% (21/58) had T3/T4 disease; and 33.3% (22/66) were MammaPrint High 2. The percent ctDNA positivity rates at pretreatment, after NAC prior to surgery, and 4 weeks after surgery were 79.7% (47/59), 6.5% (4/62), and 2% (1/50), respectively. Significantly higher ctDNA positivity rates at pretreatment were observed in patients with larger tumors (95% in T3/T4 vs. 69% in T1/T2, Fisher’s exact p=0.0387), higher grade tumors (94% in Grade III vs. 67% in Grade I/II, p=0.0147) and by MammaPrint score (100% in High 2 vs. 71% in High 1, p=0.0052). In this high-risk HR+/HER2- cohort, 10/66 (15.2%) achieved pCR/RCB 0, who were all ctDNA-negative at surgery. 56/66 (84.8%) had no-PCR, with RCB I (limited residual cancer), II (moderate) and III (extensive) in 7 (10.6%), 31 (47.0%) and 18 (27.3%), respectively. ctDNA-positivity after paclitaxel-based treatment was significantly associated with RCB II/III status (Fisher’s exact p=0.01). All patients in this cohort with persistent ctDNA subsequently had RCB II or III at surgery. 47 patients had paired samples collected after NAC prior to surgery and at 4 weeks after surgery. Of the 47, 91.5% (43/47) were ctDNA-negative at both time points and 8.5% (4/47) were discordant; 1 was ctDNA-negative and later tested ctDNA-positive, while 3 were ctDNA-positive and later tested ctDNA-negative. 61/66 patients had EFS data with a median of 1.6 years of follow up (range: 0.6 to 5.6). 5 tested ctDNA-positive in at least one time point after surgery. Of these, 2 experienced a recurrence (one local relapse and one distant metastasis) and both tested positive at the time of recurrence. For the patient who developed a distant recurrence it was the only blood sample available at a follow-up time point; for the patient who developed a local recurrence, blood from two earlier follow-up time points had tested negative. To date, no recurrences have been observed in those whose test(s) after surgery were negative for ctDNA. Conclusions: The persistence of ctDNA during neoadjuvant therapy is associated with the extent of residual disease in a cohort of patients with HR+HER2-breast cancer in the I-SPY 2 trial and thus may be useful in identifying patients who are not having an optimal response to therapy. I-SPY 2.2 will test whether ctDNA has utility in redirecting therapy to improve surgical outcome and subsequent prognosis.
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ctDNA detection in seven different types of body liquids in patients with metastatic breast cancer

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Background. Liquid biopsies represent a less invasive alternative to tissue biopsy to characterize and possibly monitor the disease in patients with metastatic breast cancer. So far, blood remains the most frequently investigated body liquid in this context and the investigations mainly focus on the detection, quantification and characterization of the circulating tumor DNA (ctDNA). However, since blood might not capture the full disease profile, other sources of body liquids may have the potential to complement the information obtained from blood. The aims of the present study are therefore to assess whether: (i) ctDNA can be detected in different types of body liquids, and, (ii) the levels of ctDNA in a given liquid are associated with metastases in specific organs.

Patients and methods. Twelve patients from the post-mortem tissue donation program UPTIDER (NCT04531696) were included in this study. The receptor status of their primary tumor was: estrogen receptor negative, HER2 non-amplified (ER+/HER2-) (n=9), ER-/HER2- (n=2) and ER+/HER2+ (n=1). Median time between inclusion and death of the patient was 1.6 months (Interquartile range: [0.4-3.4]). Seven types of liquids were collected: blood, saliva, ascites, pleural fluid (PFL), cerebrospinal fluid (CSF), pericardial fluid and urine. Fluids were collected at study inclusion (blood, as well as saliva, urine, and ascites whenever possible) and at autopsy (except for saliva). In total, 108 liquid samples were collected and immediately centrifuged according to standard protocols. Cell free DNA (cfDNA) was extracted from the supernatant. All extracted cfDNA as well as germline DNA extracted from the 12 matched buffy coat samples underwent shallow whole genome sequencing. Log2 ratios were computed with CNVkit, and co-segmented per patient using the copynumber R package. Purity and ploidy were assessed by ABSOLUTE. Associations between organ involvement and ctDNA yield were assessed by Wilcoxon rank-sum tests. Samples at study inclusion and at autopsy were considered together unless otherwise specified.

Results. At the sample level, ctDNA could be identified in 54% of the samples. At the patient level, the proportion of liquid types in which ctDNA was detected was highly variable (median: -77%, Table 1). CtDNA was detected in ascites of all patients when investigated, in 78% of PFL, 73% of CSF, 67% of blood and 37% of pericardial fluid. Only for one patient with invasive lobular carcinoma, ctDNA was detected in saliva and urine, the latter most likely explained by invasion of the bladder. Of note, in 4/12 patients ctDNA could not be identified in blood but was detected in at least one of the other fluids for 3 of these patients. At autopsy, ctDNA levels tended to be higher in PFL, ascites, and CSF in case of pleural, peritoneal, and central nervous system (CNS) metastases respectively, reaching statistical significance only for PFL. In CSF, two patients have CSF ctDNA detected with no documented involvement of the CNS. No brain autopsy was however performed for these patients.

Conclusion. We have shown that ctDNA can be detected in all 7 different body liquids that were investigated in this study. The ctDNA levels in a given liquid can be associated with the presence of metastases in specific organs. Since ctDNA was not detected in 4 of our patients in blood but detectable for 3 of them in other liquids, the evaluation of additional sources of body fluids should be further investigated in patients with metastatic breast cancer. These results therefore open new avenues for the clinical monitoring and characterization of the disease.
Table 1. Summary of ctDNA detection per liquid type at the patient level based on the 108 evaluated samples.

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<th>Nr of liquid types with ctDNA detected</th>
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<td>6/7 (86%)</td>
<td>5/6 (83%)</td>
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</table>

Histo. = Histological, ILC = Invasive lobular carcinoma, NA = not available, nr = number, NST = non-special type

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Background: Growing body of evidence highlights the role of the peripheral anti-tumor immune response in patients with solid tumors. Peripheral blood mononuclear cells (PBMCs) comprise all the key circulating immune cell subsets, and their analysis may inform on the peripheral anti-tumor immune response status in real-time. Programmed death-ligand 1 (PD-L1), toll-like receptor 4 (TLR4) and signal transducer and activator of transcription 3 (STAT3) hold a key role in the cancer-associated inflammation and tumor immune evasion. We herein aimed to investigate the distribution of these molecules on PBMCs and their prognostic value among patients with breast cancer (BC). Methods: Peripheral blood (PB) was obtained from patients with early (n=99) and metastatic (n=99) BC, prior to the initiation of adjuvant and first-line treatment, respectively. PBMCs were isolated through ficoll density gradient centrifugation and PBMC cytospins were immunofluorescently stained using PD-L1, TLR4 and phosphorylated STAT3 (pSTAT3) antibodies. MDA.MB.231 BC cells served as controls to define the positivity of PBMCs for the respective markers via fluorescence microscopy. Results: PD-L1, TLR4 and pSTAT3 expression was identified on PBMCs of 27.8%, 27.1%, and 83.9% of all patients, respectively. The mean (± standard error of mean, SEM) percentage of positive PBMCs per patient was 13.8% ±1.8%, 10.5% ±1.6% and 37.1% ±1.9, respectively. A positive correlation was shown between the PD-L1pos, TLR4pos and pSTAT3pos PBMC proportions (PD-L1*TLR4; p=0.000, PD-L1*pSTAT3; p=0.001, TLR4*pSTAT3; p=0.002, Spearman's rho analysis). Patients with metastatic disease displayed increased TLR4pos PBMC percentages as compared to early disease (mean: 15.8% versus 5.2%; p=0.008, Mann Whitney U test). In the early BC setting, the detection of TLR4pos PBMCs was associated with reduced disease-free survival (DFS; median: not reached; p=0.020), while PD-L1pos PBMCs were correlated to shorter overall survival (OS; median: not reached; p=0.009). Early BC patients with PD-L1pos/TLR4pos PBMCs showed significantly reduced survival times (median DFS: not
Conclusions: PD-L1, TLR4 and pSTAT3 molecules are frequently expressed on PBMCs of patients with BC and provide significant prognostic information for early-stage BC patients. The role of the immune-phenotyping of PBMCs as a source for biomarker discovery merits further investigation in BC.

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Dual ctDNA and tissue sequencing improves detection of actionable variants in breast cancer patients

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Background: Next-generation sequencing of circulating tumor DNA (ctDNA) and solid-tissue can identify clinically actionable genomic variants that may be used for both treatment selection and disease surveillance. Due to differences in tumor biology and assay design, ctDNA and solid biopsies may identify unique variants. Here, we investigate a real-world dataset of breast cancer patients to determine whether clinically actionable variant detection is enhanced by dual ctDNA and solid tissue testing. Methods: We used the deidentified Tempus Lens database to retrospectively analyze stage IV breast cancer patients with known hormonal subtype. Each patient had dual testing defined as Tempus xF (ctDNA) and Tempus xT (tumor tissue)—which resulted in clinical reports for both tests. Patients were further stratified according to the timing of ctDNA biopsy relative to tissue biopsy. Concurrent dual testing was defined as samples as liquid >30 days after solid.

Variants were included in analyses if they met the limit of detection criteria of both assays. Clinical actionability was defined by indication-matched OncoKB Level 1-3. Fisher exact test was used to calculate significance. Results: Of the 1,341 breast cancer patients with dual ctDNA and tissue sequencing, at least one actionable variant was identified in 61% (n=823) of patients. In the subset of concurrent tested patients (n=782), 60% (n=473) had one or more actionable findings: 54% (n=257/473) of patients with actionable variants had perfectly concordant variants, 29% (n=136/473) had at least one unique variant detected only by solid tumor testing, and 20% (n=93/473) had at least one unique variant detected only by ctDNA testing. Similarly, in the longitudinal set (n=559), 63% (n=350) had one or more actionable findings: 34% (n=118/350) were concordant, 43% (n=150/350) were unique to solid, and 27% (n=96/350) were unique to ctDNA. When stratifying concurrent patients by OncoKB levels of evidence, 72% (n=98/136) of patients with variants unique in solid had at least one level 1-2 variant, while 39% (n=53/136) contained unique level 3 variants. Level 1-2 variants in PIK3CA were the most frequent variants seen uniquely in solid tumors, occurring in 54% (n=73/136) of patients. In contrast, in patients with unique ctDNA variants, 37% (n=34/93) of patients had at
least one level 1-2 variants and 72% (n=67/93) had level 3 variants. Level 3 variants in ESR1 were the most frequent variants seen uniquely in ctDNA, occurring in 57% (n=53/93) of patients. The proportion of concurrent patients with actionable variants found exclusively in ctDNA significantly differed by subtype (p=0.04): Luminal A (22%) and Luminal B (23%) contained the most patients with unique ctDNA variants. This ability to detect additional variants in ctDNA remained true even if profiling occurred over time. Indeed, in patients with ESR1 variants tested with ctDNA > 1 year after tissue, 78% (n=43/55) had ESR1 variants only detected in blood. Conclusions: We show that dual testing in breast cancer patients improves the identification of clinically actionable variants which may be missed by either ctDNA or solid tissue biopsy alone. Adoption of dual testing should be considered as standard practice to provide a comprehensive view of actionable molecular alterations.

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Multianalyte liquid biopsy to aid the diagnostic workup of breast cancer

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Breast cancer (BC) affects 1 in every 8 women in the United States and is currently the most prevalent cancer worldwide. Precise staging at diagnosis and prognosis are essential components for the clinical management of BC patients. The liquid biopsy (LBx) has promising applications in cancer screening and early diagnosis ultimately leading to better survival results and less disease burden. In this study, we evaluated the feasibility of the high-definition single cell assay (HDSCA) LBx platform to stratify disease states (early- and late-stage BC) and normal donors using peripheral blood samples. In the HDSCA3.0 workflow, both common white blood cells (WBCs) and rare cells, including circulating tumor cells (CTCs), EMT and platelet-coated cells, plus acellular structures are identified and classified computationally from scanned immunofluorescent images. This comprehensive LBx approach provides a quantitative landscape view of each individual case. In a striking example of the insight provided by HDSCA, we compared LBx results for early-stage and late-stage BC patients with two independent cohorts of normal donors to show the utility of a blood draw as a source of biomarkers for early-stage cancer detection. As expected, CTCs were detected at a higher level in late-stage patients, compared to either the early-stage or normal donors. Surprisingly, however, we observed a significantly higher incidence of tumor-associated large extracellular vesicles (LEVs) in the early-stage patients, compared to the other two groups. A patient-level classification model was able to correctly classifying LBx profiles as normal, early, or late with LEV enumeration as the strongest predictor, followed by epi.CTC enumeration. We will present a reproducible LBx profile of rare cells and LEVs of early-stage disease compared to late-stage BC and normal donors with high accuracy, allowing for robust stratification. Our findings illustrate the feasibility of the LBx to assess early disease states prior to clinically defined metastasis, stratified from normal donors, highlighting the general consideration of the liquid biopsy for the diagnostic work-up and potentially screening.

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A Multi-center Clinical Study to Harvest and Characterize Circulating Tumor Cells from Patients with Metastatic Breast Cancer Using the Parsortix® PC1 System in support of FDA clearance

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Background: Circulating tumor cells (CTCs) captured from the blood of cancer patients may serve as a non-invasive surrogate source of tumor material to investigate tumor characteristics in real-time. However, the only FDA-cleared CTC assay is limited to the enumeration of surface marker-defined epithelial cells and not designed for further characterization of the CTCs identified. The Parsortix® PC1 system is a semi-automated microfluidic device capable of capturing and harvesting CTCs from peripheral blood based on cell size and deformability, making it cell-surface marker agnostic. Here, we demonstrate that the Parsortix® PC1 system enables the enrichment and capture of CTCs from the blood of patients with metastatic breast cancer (MBC) and their interrogation using evaluation techniques commonly available in clinical laboratories. Methods: As part of a multicenter clinical trial (NCT03427450), peripheral blood samples from 216 patients with MBC and 205 healthy volunteers (HVs) were prospectively collected at four different clinical sites located throughout the United States. Each subject provided two separate blood samples collected into K2EDTA Vacutainer® tubes to be processed using the Parsortix® PC1 system on the same day. The cells harvested from one of the blood samples collected from each subject by the Parsortix® PC1 system were deposited onto cytology slides using a cytocentrifugation method and stained with Wright-Giemsa reagents using an automated stainer. The stained slides were subjected to cytopathological evaluation by a board-certified pathologist to enumerate CTCs. As proof of principle, cells harvested from the second blood sample were evaluated using one of three additional techniques: molecular profiling by qRT-PCR, RNA sequencing, or cytogenetic analysis of HER2 amplification by FISH. Results: Cytologic examination identified one or more cells as a CTC in 48.5% (95% CI of 41.5 – 55.4%) of the 194 patients with MBC and 9.9% (95% CI of 6.4 – 14.9%) of the 192 HVs. The results from the qRT-PCR evaluation (102 HVs and 74 MBC patients) showed differential expression of cancer-related genes (KRT19, EPCAM, and TWIST1) in the patients with MBC compared to the HVs. Results from the RNA sequencing (53 HVs and 16 MBC patients) showed differential expression of several genes involved in the Kegg Cancer Pathway in the patients with MBC compared to the HVs. The results from the HER2 FISH evaluation (38 HVs and 101 MBC patients) showed that while the majority of the CTC identified had normal HER2/CEP17 ratios, detection of HER2 amplification was possible. Conclusions: The Parsortix PC1 system is capable of capturing and harvesting CTCs from the peripheral blood of patients with MBC. Harvested cells can be evaluated using standard orthogonal methodologies such as gene expression and FISH to identify and characterize
CTCs. Based in part on the above results, the FDA granted a De Novo classification request (DEN200062) for the Parsortix PC1 device in May of 2022.

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Circulating tumor cells in metastatic breast cancer highlight potential role of copy number evolution in late-stage cancer mutational profile

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Background: Structural variation is a hallmark of breast cancer. Previous single-cell genomic analysis of 10 untreated early-stage primary TNBC tumors identified only one or two subclones per tumor, found that copy number variation (CNV) occurs early in the evolution of the tumor, and asserted that CNV changes do not contribute to genomic variation at later time points of a tumor’s growth. This PCNE model (punctuated copy number evolution) is analogous to the big-bang theory of colorectal cancer. However, cancer exists in a dynamic environment, and systemic chemotherapy provides evolutionary pressure, making stasis quite unlikely. An investigation of late-stage cancers could shed light on CNV evolution. Methods: We performed a longitudinal, prospective observational study of over 130 patients with metastatic breast cancer, with regular follow-up and detailed treatment histories. CTCs were enumerated by CellSearch, and samples with >20 CTCs in 7.5ml of whole blood were further processed for single CTC isolation via DEPArray, single-cell library construction, and whole-genome sequencing. CNV counts for each cell were obtained using previously published binning methods (Ginkgo). Three mathematical models were used to evaluate the evolution of CNVs: a punctuated model, a gradual model, and a gradual-on-punctuated hybrid model. Results: In total, 150 patient-years of data were collected. Among samples with sufficient CTC counts for study inclusion, a total of nine patients and 376 cells were isolated for sequencing. A mean sequencing depth of 0.8× was achieved from each single cell. The degree of CNV heterogeneity varies from patient to patient. CNV changes occurred over time in a gradual manner on a background of punctuated changes. The adjusted R2 value for the punctuated model was 0.46, the adj R2 value for the gradual model was 0.76, and the hybrid model achieved an adj R2 of 0.99. Patient samples with large CNV heterogeneity across single cells tend to be from patients with longer treatment histories and from the last blood draw (i.e., the blood collection closest to patient’s point of death). We also identified multiple whole-genome duplication (WGD) events from the same patient, in contrast to previous findings that WGD events are usually early clonal events in most instances. Finally, X loss events are among the most frequent chromosomal aberrations identified in CTCs (in up to 80% of CTCs in some patients), which supports previous literature on the loss of the Barr body in hastening metastatic spread. Discussion and Conclusion: In contrast to the previous study, our findings support a gradual-on-punctuated hybrid model, and this model can explain how copy number changes can be a source from which tumors gain resistance to systemic therapies. The model explains how CNV heterogeneities are seen in patients with longer treatment histories, suggesting that CNV continues to be a source of genetic variation at the metastatic stage of the disease course.

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Analyzing the results of liquid biopsy in the identification of ERBB2 amplified and HER2 expressing metastatic breast cancer: comparison and combination of cell and cell-free platforms

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Background Liquid biopsies are a non-invasive diagnostic approach for detecting circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA) that may provide clinically actionable information for treatment decisions for metastatic breast cancer (MBC) patients when a conventional biopsy is otherwise infeasible. In addition, the development of quantitative, reproducible, and more sensitive HER2 assays is expected to enable the identification of patients with HER2-low MBC that may benefit from novel HER2-targeted therapies. Here we report a comprehensive liquid biopsy platform including immunofluorescent HER2 and ER quantitative protein expression in CTCs (ctcIF) coupled with the determination of ERBB2 amplification and the number of Large-scale State Transitions (LST+) by single-cell CTC genomics (ctcDNA), and ctDNA alterations in plasma. Methods Blood samples were collected for cell-based and cell-free analysis from 62 patients with documented MBC and from 24 blood donors (HD) with no known cancer history. After isolation, nucleated cells were plated, and slides and plasma were bio-banked. CTCs were identified using Epic Sciences digital imaging and machine learning algorithms, and ctcIF enables quantitation of HER2 and ER protein expression. ctcDNA was analyzed by low-pass whole-genome sequencing (WGS), allowing detection of ERBB2 amplification (ERBB2amp) and quantification of large-scale state transitions (LST+) in individual CTCs. ctDNA from plasma was analyzed using a validated NGS panel (56 genes of interest) to detect ctDNA alterations. Results Within this cohort of 62 MBC patients, the presence of CTCs, ctcDNA (LST+) and ctDNA alterations were detected in 87%, 70%, and 59%, respectively, while no CTCs and no ctDNA alterations were detected in the HD
cohort, suggesting high specificity. ctDNA genomics was more sensitive than ctDNA in detecting ERBB2amp in MBC patients (11%, and 2%, respectively). A variant allele frequency (VAF) of > 40%, which is required for detecting a two-fold ERBB2 amplification by ctDNA, was not present among 86% and 0% of MBC detected by the ctDNA and ctDNA platforms, respectively, suggesting that the ctDNA platform can identify ERBB2amp among patients with a low ctDNA fraction. HER2+ or ER+ expression by ctIF were detected in 37% and 58% of MBC patients, respectively. At the cellular level, across 62 patients, CTC with detectable ERBB2amp by ctDNA had a higher median expression of HER2 protein by ctIF compared to CTC with ERBB2nonamp (1772 MFI vs 122.5 MFI, respectively; p< 0.001). Similarly, at the patient level, among patients with circulating ERBB2amp, HER2 protein was detected by ctIF in 100% of MBC patients (p< 0.001), suggesting a very high positive correlation between the presence of ctDNA genomic ERBB2amp and ctIF HER2 protein expression. A liquid biopsy classification of HER2 status by combining the three platforms (ctIF, ctDNA, and ctDNA) identified that among MBC, 11% were ERBB2amp, 26% were HER2 expressing (HER2+ and ERBB2nonamp), and 60% were HER2 neg (HER2- and ERBB2nonamp). Combination models of the three individual platforms (ctIF, ctDNA, and ctDNA) were able to provide potentially clinically actionable biomarker data (LST+ CTC, ERBB2amp CTC, HER2+ CTC, ER+ CTC and 1A+ SNVs) to 79% of MBC patients while retaining 100% specificity. Conclusions Here we reported a comprehensive liquid biopsy profile combining ctIF, ctDNA, and ctDNA platforms with high sensitivity and specificity in determining clinically actionable HER2 and ER biomarker status that may impact therapeutic decision-making in late MBC patients. The comprehensive liquid biopsy platform’s combined utility can aid biomarker profiling of MBC among often biologically heterogeneous tumor sites of metastatic disease and those inaccessible by conventional tissue biopsy.

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[Background] As the development of endocrine resistance and late recurrences are the major clinical concerns in hormone receptor (HR)-positive/HER2-negative metastatic breast cancer (MBC) patients, biomarkers to predict the occurrence of endocrine resistance or disease progression are crucial for improving patient outcomes. Aberrant HGF/c-MET signaling pathway has been reported to play a role in various cellular processes in cancer. Estrogen Receptor 1 (ESR1) mutations, encoding estrogen receptor α, are associated with endocrine resistance in HR+ breast cancer. PIK3CA hotspot mutations that induce hyperactivation of the PI3K are found in 30-40% of HR+ advanced breast cancers. In this context, we evaluated the prognostic values of c-MET-enriched CTC, ESR1 mutations, PIK3CA mutations, and cfDNA concentrations detected in the blood of HR+HER2- MBC patients. [Methods] MBC patients were prospectively enrolled during standard treatments at Samsung Medical Center (IRB No.2019-08-119). Circulating tumor cells (CTCs) were isolated using the GenoCTC® with c-MET-enriched or EpCAM-enriched CTC isolation kits (Genobio Corp., South Korea) from 4mL of blood each. PIK3CA and ESR1 hotspot mutations were analyzed by droplet digital PCR kits (Gencurix Inc., South Korea). cfDNA concentrations were calculated using ESR1 gene copy.
numbers from plasma. To compare the proportion of c-MET overexpression between primary breast tumors and metastatic sites in HR+HER2-breast cancer patients, primary breast (n=358) and metastatic sites (n=27) were independently collected. c-MET expression was evaluated by an immunohistochemistry assay using an anti-total c-MET (SP44) antibody with a Ventana Discovery XY automated system according to the manufacturer's instruction. c-MET overexpression was defined if the staining was scored as 2+ or 3+. Progression-free survival (PFS) was defined as the time from blood draw to the first of either disease progression or death during standard therapy. [Results] Out of 93 patients with HR+ MBC, analysis was performed in 63 HR+HER2- MBC patients. Seventeen patients (27%) had one or more EpCAM-enriched CTCs, and fourteen patients (22%) had one or more c-MET-enriched CTCs detected in their blood. The median follow-up time and median time to censoring were 8.4 months and 18.7 months, respectively. According to the Kaplan-Meier survival analysis by log-rank test, c-MET-enriched CTCs, cfDNA concentrations, and ESR1 mutations were significantly associated with PFS (p=0.0026, 0.0064, and 0.011, respectively). However, PIK3CA mutations and EpCAM-enriched CTCs were not statistically significant with PFS (p=0.38 and 0.86, respectively). Multivariate analysis showed that both c-MET-enriched CTCs (HR=3.5, p=0.014) and cfDNA concentrations (HR=2.2, p=0.031) were independent predictors for PFS in HR+HER2- MBC. The proportion of c-MET overexpression was significantly higher in metastatic sites (22.2%) than in primary breast tumors (4.7%) in HR+HER2-breast cancer patients (p=0.00002). As c-MET-enriched CTCs and cfDNA concentrations were independent predictors of disease progression, patients were divided into two groups depending on the result of c-MET-enriched CTCs and cfDNA concentration. When patients with low c-MET-enriched CTC and cfDNA concentrations were classified as a low-risk group and other patients into a high-risk group, the high-risk group had a shorter PFS than the low-risk group (p=0.003). [Conclusion] This study provided c-MET-enriched CTCs and cfDNA concentrations calculated by ESR1 copy numbers in patient blood were significant independent predictors of disease progression in HR+HER2- MBC. The poor prognosis in the c-MET-enriched CTC-high group and the difference in the c-MET overexpression rate between the primary breast and metastatic sites suggested the importance of monitoring c-MET-enriched CTCs in the blood of HR+HER2- MBC patients.

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Whole-genome bisulfite sequencing of single circulating tumor cells identifies cellular methylation heterogeneity in metastatic breast cancer

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Background: Although different patterns and changes in DNA methylation play an important role in cancer progression and tumor subtype differentiation, methylation remains relatively less understood in the context of tumor heterogeneity. Intra-tumor heterogeneity influences chemotherapy response, resistance development, and metastatic progression, and can be identified with liquid biopsy, a non-invasive approach to monitor cancer progression and provide predictive information. In this study, we sequenced circulating tumor cells (CTCs) to interrogate whole-genome methylation at single-cell level and single-base resolution. Methods: We enumerated CTCs in 7.5ml of whole blood samples from over 130 metastatic breast cancer patients using CellSearch, and selected blood samples with more than 20 CTCs to be further processed by DEPArray. After single-cell library construction using the Swift Accel-NGS Adaptase Module, whole-genome bisulfite sequencing (WGBS) was performed. The sequencing data were then aligned to the reference genome, and the methylation information was extracted by Bismark. We compared methylation profiles between CTC and WBC samples from each patient to identify differentially methylated regions (DMRs) using Methylkit. Multiple-comparison was conducted by SMART2 to identify DMRs within CTCs. Heatmap was plotted based on the regional methylation rates of DMRs. CpG and genic annotations were performed by annotatr. The pathway and function enrichment analyses (KEGG and GO) were conducted using clusterProfiler. Genomic region-based enrichment was conducted using LOLA. t-SNE clustering was used to investigate intra-patient heterogeneity. Results: A total of 376 cells from nine patients that passed our selection criteria were isolated for WGBS. The mean sequencing depth of all single cells was 0.8×, and an average mapping rate of 54% was achieved. We first compared CTCs and WBCs, and observed a global hypo-methylation pattern in CTCs (average methylation rate 68.8% in CTCs vs. 76.7% in WBCs). Moreover, approximately 2,000 highly differentially methylated regions were found in each patient, with hundreds of hypo- or hyper-methylated genes related to these DMRs. Hypo-methylated DMRs showed genomic region-based enrichment in breast-, prostate-, and fibroblast-related region sets. Then, we investigated methylation heterogeneity within CTCs, where t-SNE clustering identified four different subgroups in one representative patient. About 1,500 hypo-methylated DMRs were found, differentiating those four subgroups. KEGG pathway analysis indicated enrichment in the Rap1 signaling pathway and focal adhesion. GO enrichment analysis highlighted the regulation of GTPase activity and membrane potential. Conclusions: Our study identified differentially methylated regions in CTCs of metastatic breast cancer patients, and demonstrated intra-patient heterogeneity based on cellular methylation information. Future studies are warranted to validate our findings and explore their biological mechanisms and clinical relevance.

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TROP2 and HER2 expression by liquid biopsy in women with mTNBC

Introduction

A blood-based biopsy can inform the prognosis for MBC patients when conventional tissue biopsies are not feasible within often biologically heterogeneous sites of metastatic disease. Several anti-Trophoblast cell-surface antigen 2 (TROP2) and HER2 targeted therapies are now available, either as approved therapy options or in clinical trials for MBC patients. Tumor expression of TROP2 is prominent in metastatic cancers, such as HER2-negative MBC and TNBC, with limited treatment options. Technical feasibility data of blood-based TROP2 and HER2 immunofluorescence assays demonstrate the utility of the Epic Sciences platform for this cohort of metastatic TNBC (mTNBC) patients. Methods Cultured cancer cells (expressing TROP2, HER2, or neither) were added to Healthy Donor (HD) blood, creating the model system used in assay development studies. Blood from 11 confirmed mTNBC patients was collected to analyze this clinically relevant population. Immunofluorescence staining and image analysis were performed on replicate blood-based biopsy slides to assess expression for TROP2 and HER2. CTCs were identified and characterized using Epic Sciences digital imaging and machine learning algorithms. Results Three cancer cell lines of various TROP2 expression levels (HEK293, low; MDA-MB-231, low; MDAMB-231, high) were added to Healthy Donor (HD) blood to create the model system used in assay development studies. Blood from 11 confirmed mTNBC patients was collected to analyze this clinically relevant population. Immunofluorescence staining and image analysis were performed on replicate blood-based biopsy slides to assess expression for TROP2 and HER2. CTCs were identified and characterized using Epic Sciences digital imaging and machine learning algorithms.
intermediate; and A431, high) exhibited immunofluorescence signal ranges of 168 MFI, 2147 MFI, and 2698 MFI, respectively. A fluorescence cutoff of 218 MFI was established following assay optimization to distinguish TROP2 positive CTCs based on a 95% confidence level. Within the cohort of 11 mTNBC patients, 100% of patients with mTNBC had detectable CTCs. 64% of mTNBC patients had TROP2 positivity (MFI, mean: 1328, range: 37-38281)). On the other hand, 0% of mTNBC patients had HER2 positivity (MFI, mean: 128, range: 40-361)). To date, studies with biomarker expression for these two drugs have been limited to tissue biopsy, which may not always yield contemporaneous sampling in the metastatic setting. These results offer a potential liquid biopsy test identifying pts more responsive to trop2 and her2 directed therapies. Discussion Here we report on a liquid biopsy profile combining protein expression of TROP2 and HER2. Blood-based assessment of TROP2 and HER2 expression is a potential marker for selecting MBC patients likely to respond to anti-TROP2 targeted therapies such as Sacituzumab, or Trastuzumab Deruxtecan has shown to improve survival in mTNBC in the ASCENT trial and DESTINY-04 studies. Recent data on the Destiny-04 trial, which allocated HER2 expressing MBC patients into T-DXd treatment, transformed the definition of TNBC. The development of quantitative, reproducible, and more sensitive immunofluorescence assays is becoming crucial for assigning patients whose disease continually evolves to targeted therapies by increasing clinical trial options. Analysis of the clinical utility of the blood-based cell analysis in guiding patient selection strategies for novel anti-TROP2, HER2, and other targeted therapies treatment in MBC is ongoing.

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Outcomes of multidisciplinary team approach and intensive patient education in young women with breast cancer to improve the rate of fertility preservation

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Background Young breast cancer patients of childbearing age often had to give up their opportunity as women or mothers for cancer treatment. As the survival rate of young breast cancer patients increases with advances in early detection and treatment of breast cancer, interest in issues such as fertility preservation, which have not been satisfied so far, is increasing. This study aims to report the experience of improvement of the fertility preservation rate through a multidisciplinary team approach and systematic patient education for young breast cancer patients. Methods Patients treated with multidisciplinary team approach including surgical, medical oncologist and fertility specialist were included for analysis. Patient were divided into two periods: before and after intensive patient education. Patient education included in-person counseling, hand-out materials, and audiovisual education about ovarian dysfunctions related to cancer treatment and fertility preservation methods. We compared the rate of fertility counseling, ovarian function preservation with gonadotropin releasing hormone antagonists (37.8% to 49.7%), and either embryo (0.9% to 5.6%) or oocyte preservation (0 to 7.5%) were significantly increased (all, p< 0.001) after intensive patient education. Pregnancy (9.5% vs 14.2%, p=0.034) and birth rate (7.7% vs 12.2%, p=0.043) were significantly higher with women with negative hormone receptor status. In hormone receptor positive patients, similar pregnancy rates were observed (13.3 ~ 15.4%) in patients who complete 5yearsd of endocrine therapy, stopped endocrine therapy due to side effects, and received no endocrine therapy. Patients with any type of recurrence were not pregnant during follow up period. Patients who stopped endocrine therapy for child plan showed highest rate of pregnancy (56.0%). Multivariable analysis revealed intensive education were highly associated with improved fertility outcomes (OR 3.843 95% CI 2.781–5.311, p=< 0.001) after adjusted for different stage and treatment modality. Conclusion Multidisciplinary team approach with intensive patient education of fertility preservation in young women breast cancer significantly improved fertility preservation attempt. Hormonal receptor status and recurrence were associated with impaired fertility outcomes

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Embryo utilization in young breast cancer patients who have undergone egg harvesting for fertility preservation

INTRODUCTION: Much progress has been made related to fertility preservation in women diagnosed with breast cancer. This includes heightened awareness of impaired fertility due to breast cancer treatment, increased referrals to fertility specialists and development of safe and expeditious means of egg harvesting. Nevertheless, there has been limited investigation of the ultimate issue in fertility preservation, namely the frequency with which women who have undergone egg harvesting actually pursue childbearing. We have retrospectively reviewed a single institution’s experience with egg and embryo utilization among patients who expressly desired childbearing and underwent egg harvesting after a diagnosis of breast cancer. These issues have also been analyzed relative to race and insurance coverage. METHODS: In an IRB approved study, breast cancer patients treated in our institution between 2010 and 2020 were identified and their post-diagnosis fertility and childbearing history was reviewed. Inclusion criteria were age at presentation ≤ 45 years and diagnosis of either invasive breast cancer or ductal carcinoma in situ. Race (self-reported on clinic intake form) and insurance coverage data were analyzed. In cases of incomplete medical record data, we interviewed patients by telephone. RESULTS: 316 breast cancer patients of reproductive age were identified (average age at diagnosis = 39 years, range: 23 - 45). Of these, 168 patients (53%) were offered fertility referral and 118 (38%) saw a fertility specialist. 91 patients (29%) pursued egg harvesting followed by cryopreservation of eggs in 49 cases and embryos in 41 with 1 case unknown. Over an average of 5 years of follow-up (range: 2 - 12 years), 28 women (31% of those who pursued egg harvesting) utilized the egg or embryo to pursue childbearing. 17 underwent embryo transfer to themselves and 11 used surrogate carriers. To date, this has resulted in 20 childbirths from 24 pregnancies. Four pregnancies are currently ongoing and 1 woman is awaiting embryo transfer. Four patients who had undergone egg harvesting conceived without fertility intervention. Of the 55 Medicaid patients of reproductive age diagnosed with breast
cancer, only 8 (15%) met with a fertility specialist, 4 harvested eggs, and none pursued childbirth. HMO/PPO insured patients were significantly more likely than Medicaid patients to pursue egg harvesting and embryo utilization ($X^2 = 7.320, df = 2, p = 0.026$). Of 260 HMO/PPO insured patients, 110 (42%) met with a fertility expert, 87 harvested eggs and 28 pursued embryo transfer. Due to the small sample size of patients who utilized embryos in each racial subgroup, analysis did not yield statistically significant differences across groups ($p=0.067$). Nevertheless, apparent racial disparities exist. Our data reveal that 5 of 17 (29%) Asian patients and 22 of 62 (36%) White patients utilized embryos as opposed to Black patients (1/4 or 25%), Hispanic patients (0/4 or 0%) and those who identified their race as “other” (1/4 or 25%).

CONCLUSIONS: These data demonstrate a low overall rate of cryopreserved egg and embryo utilization among women treated for breast cancer whose earlier pursuit of egg harvesting was evidence of a desire for childbirth. Furthermore, racial and insurance data demonstrate disparities in the pursuit of fertility treatment and utilization of preserved eggs and embryos. Further research will utilize interviews to analyze individual women’s decision-making process relevant to such issues as hormone therapy utilization, concerns about breast cancer recurrence, progression of disease and restraints imposed by relationship status and finances. Given the disparity findings reported here, finances will likely emerge as a significant barrier to childbearing in future qualitative research.

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The Association Between Symptom Severity and Physical Function among Participants in I-SPY2

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Title. The Association Between Symptom Severity and Physical Function among Participants in I-SPY2 Background. Patient-reported outcomes (PROs) are increasingly recognized as a valuable component to understand treatment tolerability and toxicity among patients on clinical trials. We have implemented a system for monitoring patient reported outcomes (PROs), ePRO instruments for patients enrolled in the I-SPY2 trial. I-SPY2 is a phase II multi-site clinical trial evaluating the effect of novel neoadjuvant therapies for locally advanced breast cancer. We correlated patient demographic factors with symptoms, investigated the trajectory of symptoms throughout treatment, and sought to characterize symptoms associated with decline in physical function (PF). Methods. Our study population included 259 I-SPY2 patients that completed surveys on one of 9 study arms (including novel oral taxane/immunotherapy combinations, IV paclitaxel, checkpoint inhibitor+//- LAG3 inhibitor, and control IV paclitaxel +/- trastuzumab/pertuzumab). After the 12 week period of investigational agents, most patients received standard adriamycin and cyclophosphamide (AC). Symptom severity, frequency, and interference was assessed weekly using 33 items from the PRO-CTCAE item bank. PF was assessed using the NIH PROMIS instrument and was evaluated at baseline, inter-regimen (after 12 weeks of treatment), pre-surgery, and 1 and 6 months at follow-up. An odds ratio was used to assess univariate associations between age and race, and symptoms. Regularized multi-variate regression was used to evaluate early symptoms (prior to week 6) predictive of a clinically significant (>5 point T-score) decline in PF from baseline to post-treatment follow-up among all races and age groups. Results. Of 259 patients (mean age (SD) = 46.8 (13.6)), 160 (58%) were White, 13 (5%) were Asian, 26 (10%) were African American (AA), 25 (9.3%) were Hispanic, and 35 (13.5%) self-reported “Other”. At baseline, AA patients had a higher severity of joint pain than White patients (OR = 14.9, P < 0.05). During study treatment with paclitaxel and/or novel agent within the first 12 weeks of treatment, AA patients and non-white (NW) patients were more likely to report severe vomiting than White patients (OR =13.22 and 12.72, P< 0.05 and P< 0.03 respectively). During treatment with AC, NW patients were more likely to report higher severity of neuropathy than White patients (OR = 5.43, P< 0.03). Among all patients, in analysis of early symptoms predictive of a clinically significant decline in PF between baseline and 1 month post treatment, predictors included high frequency of diarrhea, severity of itching, and severity of joint pain. Further analysis of symptom trajectories revealed that frequency of
diarrhea reported rose sharply between baseline and Cycle 2 with 9 patients (7%) reporting occasional or frequent diarrhea to 39 patients (28%) reporting occasional to almost constant diarrhea and remained stable at that proportion for the remainder of treatment. Frequency of diarrhea declined slightly during AC (17%) and dropped to baseline levels by follow-up. In contrast, severity of joint pain persisted post-treatment, rising consistently from baseline through follow-up with 3 patients (2%) reporting moderate to severe joint pain at baseline to 18 patients (35%) reporting moderate to severe joint pain at follow-up. Conclusion. Among I-SPY2 participants, when higher grade of diarrhea is persistent (or uncontrolled), it impacts physical function even after end of therapy. In some cases, race was also a determinant in symptom trajectory, although a higher enrollment of AA and NW patients will enable more robust estimates to be computed. While some of these early symptom predictors are transient and resolve by the time of follow-up, others persist long-term and contribute more directly towards impaired physical function at follow-up.

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Evaluation of Treatment Choices at Baseline Among Breast Cancer Patients Based on the Frailty Status of the Patients

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Background

Previous studies have shown that the frailty scores aid in better patient assessment and in advising treatment strategies. The objective of this study is to evaluate the impact of frailty status on the treatment choices among breast cancer patients.

Methods

Patient Reported Outcomes Mobile Platform (PROmpt®), an application for remote patient reporting, was used by breast cancer patients for completing surveys between September 2020 and April 2021.

Out of 317 breast cancer patients, there were 84 women for whom frailty assessment was done at baseline based on age, Activities of Daily living (ADLS), Instrumental Activities of Daily living (IADLS) and comorbidities. Frailty status was stratified based on frailty score into fit (score=0), intermediate fit (score = 1) and frail (score >=2). Treatment choices at baseline were stratified into targeted and cytotoxic monotherapy, hormone therapy, and systemic combined therapy. Role of chemotherapy treatment as adjuvant or neoadjuvant therapy was also assessed. Descriptive analysis was performed to assess the association of frailty status on the treatment choices at baseline.

Results: Around 24% of breast cancer patients were below 50 years of age and 76% patients were at least 50 years of age or older. The majority of the study population was White (84.15%) and non-Hispanic and Latino's (63.09%). Around 61% of patients had early-stage breast cancer and around 36% of the patients had late-stage breast cancer.

The majority of fit patients (70.59%) and intermediate fit patients (81.82%) receive systemic combined therapy at baseline. Out of fit patients, 67.80 % patients received adjuvant or neoadjuvant therapy, while 44.44 % of the intermediate fit patients received adjuvant or neoadjuvant therapy.

Discussion/Conclusion
Results demonstrate the feasibility of gathering fitness and frailty data as part of routine breast cancer care. Overall, the treatment choices among fit, intermediate fit and frail groups of patients appear consistent, although adjuvant/neoadjuvant therapy is directionally higher in fit patients. This similarity in regimen choice may be due to sample size, as the number of frail and intermediate fit patients is relatively small when compared to the fit patients. Further exploration related to treatment choices is recommended in a study population with higher levels of patients assessed as frail for comparative evaluation.

<table>
<thead>
<tr>
<th>Frailty Category</th>
<th>Targeted monotherapy</th>
<th>Cytotoxic monotherapy</th>
<th>Hormone therapy</th>
<th>Systemic combined</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT</td>
<td>5 (7.35%)</td>
<td>3 (4.41%)</td>
<td>12 (17.65%)</td>
<td>48 (70.59%)</td>
<td>68</td>
</tr>
<tr>
<td>INTERMEDIATE FIT</td>
<td>1 (9.09%)</td>
<td>0 (0%)</td>
<td>1 (9.09%)</td>
<td>9 (81.82%)</td>
<td>11</td>
</tr>
<tr>
<td>FRAIL</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>6</td>
<td>3</td>
<td>14</td>
<td>58</td>
<td>81</td>
</tr>
</tbody>
</table>

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Improving Health-Related Quality of Life with Outpatient High-Dose Methotrexate Regimen Among Solid Tumor Oncology Patients with Intracranial Metastases: A Qualitative Study

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Introduction: Breast cancer patients with intracranial (IC) metastases including leptomeningeal metastasis (LM) confer poor prognosis. Upon disease progression with standard lines of therapy, high-dose intravenous methotrexate (HD IV MTX) is offered to patients given its effective CNS penetrance. HD IV MTX is commonly administered inpatient, requiring extended hospitalization, rigorous leucovorin rescue, IV hydration, and urine alkalinization. Currently, outpatient regimens remain unknown. Methods: An outpatient MTX protocol with daily visits to outpatient infusion centers was institutionally developed. Study eligibility criteria included solid tumor diagnoses with IC±LM metastasis, disease progression on standard of care treatment, and transition from inpatient to outpatient regimen within the past 12 months. For eligible patients upon consent, qualitative semi-structured phone interviews were conducted with focus on physical functioning and symptom burden. Thematic analysis was utilized. Results: Of the 10 patients who were screened, three (breast=2, sarcoma=1) were eligible. Patient demographics included 2 Caucasians, 1 African American, mean age of 52 years, and s/p prior whole brain radiation. Among QoL measures, no differences in functional status were reported between the two regimens. Single sarcoma patient reported less nausea and emesis with the outpatient regimen. All patients agreed on convenience, autonomy, greater personal and family time, and stronger emotional support while undergoing the outpatient protocol. Despite honorable mentions of inpatient onsite staff inpatient. Conclusions: Interview analysis determined that patient autonomy and nonobligatory

Despite the small preliminary patient pool, this study delineates the feasibility in development of an institutionalized patient-centered outpatient MTX protocol. Future clinical trials will additionally be dedicated in conducting a cost-effective analysis comparing both MTX regimens.

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 Prospective cohort of breast cancer patients exposed to a navigation program for timely access to referral services in Mexico

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Background: Patient navigation (PN) is an essential component of cancer care that reduces barriers and enhances the provision of comprehensive, patient-centered care. PN programs and evidence regarding their effectiveness in low- and middle-income countries are limited. This study aimed to assess whether a PN program for the systematic identification of breast cancer (BC) patients' medical and support needs facilitated referral and timely access to the specialty and supportive care services they required.

Methods: This prospective cohort included women ≥18 years with a recent BC diagnosis (≤3 months [m]), treated at Hospital Zambrano Hellion TecSalud in Mexico, and who provided signed informed consent to participate in the PN program from Apr-21 to Jul-22. Participants completed a series of target questions and validated questionnaires to systematically identify their health needs at baseline, 3 m and 6 m since diagnosis. Subsequently, the navigator had a face-to-face or remote meeting with each patient to inform them about the needs detected at each timepoint. According to these needs, the navigator provided referral to the required services. However, it was each patient’s decision whether she attended to the recommended services. Patients’ attendance to referrals provided at baseline and 3 m were assessed at 3 m and 6 m, respectively. Descriptive statistics were employed.

Results: During the analyzed period, 263 patients were invited to participate in the study. Of these, 161 (61%) agreed to participate, 57 (22%) agreed but did not complete any survey, and 45 (17%) denied participation. At the time of the analysis, 148, 119 and 86 patients had completed baseline, 3 m and 6 m navigation, respectively. Median time from BC diagnosis to the baseline navigation meeting post survey-completion was 46 days (12-90). Patients’ median age at baseline was 48 years (24-88). As for medical insurance,
most had public (32%) or both public and private coverage (32%), while the rest had private (26%) or no insurance (9%).

Patients’ referrals according to their needs and the rate of attendance to those services are detailed in the Table. The main barriers that were qualitatively identified for non-attendance to referral services were time restrictions, patient-provider miscommunication, medical coverage limitations, and financial constraints.

Feedback regarding the PN program was provided in 72 cases. All respondents were very satisfied (97%) or satisfied (3%) with the program; affirmed the navigator had facilitated their referral to all (97%) or some (3%) of the services they believed they needed; and stated that the program aided to better cope with their illness (100%).

Conclusion: Patients experienced diverse health needs during their trajectory through BC, mainly in terms of psychological support, genetic counseling, maintenance of an adequate weight and access to support groups. However, a suboptimal proportion of patients received attention by the required services. This PN program effectively detected patients’ needs and provided referrals to specific services. Moreover, patients were highly satisfied with the program and believed it aided their coping process. Yet, several barriers that hinder attendance to the referral services might exist and should be identified to enhance the provision of timely, comprehensive care.

### Table. Patients’ referral and attendance to specialty and supportive care services.

<table>
<thead>
<tr>
<th>Referral services</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Referred patients (N=148 (100%))</td>
<td>Patients who attended (% of attendance)</td>
<td>Referred patients (N=119 (100%))</td>
</tr>
<tr>
<td>Psychology</td>
<td>92 (62%)</td>
<td>48 (52%)</td>
<td>69 (58%)</td>
</tr>
<tr>
<td>Genetics</td>
<td>80 (54%)</td>
<td>56 (70%)</td>
<td>40 (34%)</td>
</tr>
<tr>
<td>Nutritionist</td>
<td>80 (54%)</td>
<td>20 (25%)</td>
<td>42 (35%)</td>
</tr>
<tr>
<td>Support groups</td>
<td>77 (52%)</td>
<td>54 (70%)</td>
<td>68 (57%)</td>
</tr>
<tr>
<td>Wigs</td>
<td>56 (38%)</td>
<td>44 (29%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Fertility preservation</td>
<td>37 (25%)</td>
<td>6 (16%)</td>
<td>NA</td>
</tr>
<tr>
<td>External protheses</td>
<td>31 (21%)</td>
<td>3 (10%)</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Breast reconstruction</td>
<td>28 (19%)</td>
<td>21 (75%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td>24 (16%)</td>
<td>8 (33%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>6 (4%)</td>
<td>5 (83%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Pain clinic</td>
<td>4 (3%)</td>
<td>4 (100%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>4 (3%)</td>
<td>3 (75%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Palliative care</td>
<td>2 (1%)</td>
<td>2 (100%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Sexuality counseling</td>
<td>NA</td>
<td>NA</td>
<td>18 (15%)</td>
</tr>
</tbody>
</table>

Disclosure(s):

**Fernanda Mesa-Chavez, n/a:** No financial relationships to disclose

**Emmeline Rochelle-Palacios, n/a:** No financial relationships to disclose

**Mauricio Canavati-Marcos, n/a:** No financial relationships to disclose

**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)
Feasibility of a Whole-Food, Plant-Based Intervention Among Women with Metastatic Breast Cancer and its Effect on Patient-Reported Outcomes

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Background: Women diagnosed with breast cancer commonly gain weight during and after treatment; this other patient-reported outcomes (PROs) such as cognitive dysfunction. Whole-food, plant-based (WFPB) dietary interventions lead to weight loss and cardiometabolic improvements, but their feasibility among metastatic breast cancer patients and their effect on cancer-related PROs have not previously been studied.

Methods: Women with stage 4 breast cancer and stable disease were randomized 2:1 into: 1) a WFPB dietary intervention (N=21) or 2) usual care (N=11) for 8 weeks with assessments at baseline, 4 and 8 weeks. Our WFPB diet consisted of weekly educational visits and an ad libitum whole-food, plant-based diet. Three prepared meals a day were provided for the duration of the trial. The diet included fruits, vegetables, whole grains, legumes, nuts and seeds.
and excluded meat, dairy, eggs, and added oils/solid fats. Effects of the WFPB diet on the outcomes were assessed by comparing marginal means by arm estimated at 8 weeks from the analysis of covariance model controlling for baseline.

Results: Of 32 subjects randomized, 20 intervention subjects and 10 control subjects completed all 3 assessments. Baseline and week 8 dietary intake among the intervention subjects is shown in table 1. Cognitive function, as measured by the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-COG) questionnaire and a modified MD Anderson Symptom Inventory (MDASI), showed significant improvement within the intervention group as well as in comparison to the control group (Table 2). Overall quality of life, emotional and physical wellbeing, and breast cancer-specific symptoms, as measured by Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire improved significantly within the intervention group. Mean fatigue was lower at 8 weeks within the intervention group as measured by the Brief Fatigue Inventory (BFI), but this did not reach statistical significance (p=0.10). When intervention subjects were asked, “On a scale from 1 to 10 [1 being “would not recommend” and 10 being “highly recommend”], how strongly would you recommend that other cancer patients be given this type of nutrition and support intervention if they were able and willing to participate?” participants’ mean score was 9.5.

Conclusion: Our WFPB intervention was feasible and acceptable, with high compliance despite asking subjects to make major changes in dietary intake. Clinically and statistically significant improvements in several PROs, including cognitive fun

PROs, longer studies are required to demonstrate durability of behavior changes and outcomes.

Table 1: Nutrient Intake of the Intervention Group (n=19*)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 8 Final</th>
<th>Percent Change</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total grams (weight)</td>
<td>2702.8</td>
<td>3192.5</td>
<td>18.1%</td>
<td>0.03</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>1733.2</td>
<td>1321.3</td>
<td>-23.8%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Fat (% of total kcal)</td>
<td>35.4</td>
<td>20.4</td>
<td>-42.4%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Carbohydrate (% of total kcal)</td>
<td>48.8</td>
<td>66.2</td>
<td>35.7%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Protein (% of total kcal)</td>
<td>14.8</td>
<td>12.6</td>
<td>-15.1%</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>% total protein provided by plant sources</td>
<td>46.5</td>
<td>95.7</td>
<td>105.8%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Dietary Cholesterol (mg)</td>
<td>210.3</td>
<td>7.5</td>
<td>-95.4%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Dietary Fiber (g/1000 kcal)</td>
<td>21.4</td>
<td>40.8</td>
<td>90.7%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*One participant was missing one three-day food record

Table 2. Patient-Reported Outcomes
Disclosure(s):
Thomas Campbell, MD: Benbella Books: Royalty (Ongoing); Penguin Random House: Royalty (Ongoing)
Erin Campbell, MD, MPH: Benbella Books: Royalty (Ongoing); Penguin Random House: Royalty (Ongoing)
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Karen Mustian, PhD, MPH: No financial relationships to disclose
James Fetten, MD: No financial relationships to disclose
Luke Peppone, PhD: No financial relationships to disclose

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Between Group Difference</th>
<th>Between Group Effect Size</th>
<th>p value (between group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Baseline</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>FACT-COG</td>
<td>139.8</td>
<td>156.5*</td>
<td>146.4</td>
<td>145.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Problems Remembering Things</td>
<td>3.4</td>
<td>2.0*</td>
<td>1.6</td>
<td>2.9</td>
<td>-1.8</td>
</tr>
<tr>
<td>Problems Concentrating</td>
<td>3.0</td>
<td>1.9*</td>
<td>1.8</td>
<td>2.9</td>
<td>-1.5</td>
</tr>
<tr>
<td>Problems Paying Attention</td>
<td>2.4</td>
<td>1.5*</td>
<td>1.8</td>
<td>2.8</td>
<td>-1.5</td>
</tr>
<tr>
<td>FACT-B Total</td>
<td>100.9</td>
<td>111.0*</td>
<td>109.7</td>
<td>112.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Physical Well Being</td>
<td>21.1</td>
<td>22.8*</td>
<td>22.6</td>
<td>22.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Emotional Well Being</td>
<td>16.1</td>
<td>18.0*</td>
<td>18.1</td>
<td>16.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Breast Cancer Subscale</td>
<td>25.7</td>
<td>28.5*</td>
<td>27.0</td>
<td>28.2</td>
<td>1.7</td>
</tr>
<tr>
<td>RFI</td>
<td>3.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.3</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

*p<0.05 for within-group change
BACKGROUND:
HER2-positive breast cancers, which accounts for 20% of breast cancers, is associated with aggressive clinical behavior and inferior survival. The approval of HER2 targeted therapy has changed the landscape of this disease and has reduced disease recurrence by 50% and has improved survival by 33%. However, cardiotoxicity is a well-recognized adverse event associated with HER2-targeted therapies. Adjuvant trastuzumab emtansine (TDM1) is the current standard of care for patients with residual breast cancer after neoadjuvant HER2-targeted therapy. TDM1 is associated with a risk of cardiotoxicity defined as a decline in left ventricular ejection fraction (LVEF). In a pooled analysis of data from seven metastatic breast cancer trials with TDM1, the incidence of cardiac events such as congestive heart failure (CHF), cardiac ischemia, cardiac arrhythmia or grade 1/2 LVEF drop was 3.37%.
Adjuvant breast radiation (RT) is routinely offered for patients at high risk for recurrence. Breast RT is also associated with long-term increased risk of cardiac disease more than 10 years after RT. The HERA trial which studied use of adjuvant trastuzumab showed that rates of cardiotoxicity were higher in patients receiving concurrent RT with trastuzumab (left sided > right sided breast cancer) compared to those who did not receive adjuvant RT, although not statistically significant. In the multivariate analysis, no treatment or baseline cardiovascular risk factors were strongly correlated with LVEF, but radiation therapy showed a borderline correlation (adjusted HR, 1.258; 95% CI, 1.00-1.58; P = .049).

The risk of cardiotoxicity with concurrent TDM1 and RT has not been well studied. With increasing use of TDM1 in the adjuvant setting, it is important to understand the cardiotoxic effects of combination therapy in early-stage breast cancer.

METHODS:
We undertook a review of our clinical database to identify patients who received adjuvant TDM1 with concurrent RT for Stage I-III breast cancer from 1/2020 to 01/2022. Clinical parameters including age, date of diagnosis, history of cardiac disorders, echocardiogram findings, radiation dose, final pathologic stage and molecular subtypes of cancer were extracted. All patients had ejection fraction to monitor cardiac function. Global longitudinal strain (GLS), which is a more sensitive and reproducible indicator of cardiac dysfunction than LVEF, was also collected, if available.

RESULTS:
Of 32 patients identified in our retrospective analysis, two patients (6%) developed a drop in ejection fraction post radiation. Median age of patients was 57y. Majority of the patients were Caucasian (44%) followed by Hispanic (28%). 19 (60%) patients had right sided breast cancers and 13 (40%) patients had left sided cancers.
The mean pre-radiation ejection fraction was 60% and post radiation was 61%. Using paired t-testing, there was no statistically significant difference in ejection fraction after radiation (p=0.343). Comparative GLS measurements were available for 16 patients and there was no statistical difference with concurrent radiation (p=0.18). All patients tolerated radiation with mostly grade 2 skin dermatitis except four patients who had grade 3 skin dermatitis. One patient had to discontinue radiation early given grade 3 skin dermatitis.

CONCLUSION:
This institutional review of 32 patients suggests that adjuvant TDM1 with concurrent RT did not result in a significant change in ejection fraction or GLS. Most patients tolerated radiation without significant skin toxicities. One of the limitations of the study is the small sample size. A larger study should look at more broader conclusions; however this data has strong clinical implications.

Cardiac Parameters pre and post RT
<table>
<thead>
<tr>
<th>Median age</th>
<th>57</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype of breast cancer</strong></td>
<td></td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>HR-/HER2+</td>
<td>9 (28%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (44%)</td>
</tr>
<tr>
<td>African</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>American</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (19%)</td>
</tr>
<tr>
<td><strong>Laterality of breast cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>19 (60%)</td>
</tr>
<tr>
<td>Left</td>
<td>13 (40%)</td>
</tr>
<tr>
<td><strong>History of Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>No</td>
<td>17 (53%)</td>
</tr>
<tr>
<td><strong>Radiation Dermatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (12%)</td>
</tr>
<tr>
<td><strong>Mean Ejection Fraction</strong></td>
<td></td>
</tr>
<tr>
<td>Pre-radiation</td>
<td>60%</td>
</tr>
<tr>
<td>Post-radiation</td>
<td>61%</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.343</td>
</tr>
</tbody>
</table>

Disclosure(s):  
**Faheem Farooq, MD**: No financial relationships to disclose  
**Dillon Cason, MD**: No financial relationships to disclose  
**Nisha Ohri, MD**: No financial relationships to disclose  
**Shicha Kumar, MD**: No financial relationships to disclose  
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Introduction: Fatigue is a debilitating and persistent condition of exhaustion that interferes with usual functioning. It is the most reported symptom across all cancer patients, and when related to the malignancy itself or to the neoplastic treatment, is referred to as cancer-related fatigue (CRF). Fatigue occurs in nearly all patients with metastatic breast cancer and is associated with poor clinical outcomes and worse quality-of-life. It is subjective and can be assessed from patient self-reports, such as the FACIT-Fatigue scale or Brief Fatigue Inventory, with no current gold-standard, which may lead to under reporting and lack of treatment intervention. Only since
2016, fatigue has been considered as a syndrome and included in the International Statistical Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) according to specific criteria. The aim of this real-world data analysis was to describe the prevalence of fatigue, as reported by physicians using ICD-10-CM codes, in patients with locally advanced (Adv) or metastatic (Mtx) breast cancer (BC) undergoing single-agent taxane-based chemotherapy (CT), and to assess whether relapsed subjects had a higher prevalence versus those diagnosed de novo at an advanced stage.

Methods: Electronic health records (EHR) were analyzed from TriNetX, a global research network containing real-world data from approximately 150 million patients in 115 Health Care Organizations (72 in the United States and 42 in the European Union). Using ICD-10-CM codes and structured data only (no medical notes), subjects were identified with a diagnosis of Adv-Mtx BC who underwent CT with single-agent taxane in 2020, 2021 and 2022 (first quarter). After splitting the cohort based on “relapsed” (second- or further line treatment) vs “de novo” (first-line treatment), we assessed the prevalence of fatigue (any type, R53.x) and CRF (R53.0) within the first 3 months after initiation of taxanes.

Results: Among 379,880 BC patients under follow-up in 2021 across the 115 sites, 50,490 (13%) had Adv-Mtx BC, of whom 16,170 (32%) were diagnosed de novo and 34,330 (68%) experienced relapse. The proportion of patients undergoing single-agent taxane-based CT was 7.5% (1,220) and 13.4% (4,590), respectively. Almost one third (28%) of relapsed patients had previously received taxanes. The prevalence of fatigue (any type) and CRF was similar between the “de novo” and “relapsed” groups (24.6% vs 25.7% and 6.6% vs 5.4%, respectively). Overall, 27% and 21% of all fatigue was coded as CRF in the “de novo” and “relapsed” groups, respectively. No relevant differences were observed between 2020, 2021 and 2022 results.

Conclusions: This real-world analysis reveals that at least one in four patients with Adv-Mtx BC undergoing taxane based CT suffer from fatigue, independent of disease history and other factors. Fatigue is an unmet medical need in patients with BC, particularly in patients receiving taxanes.

Table: Fatigue prevalence (as per ICD-10-CM codes) within the first 3 months of single-agent taxane-based CT in patients with locally advanced or metastatic BC diagnosed “de novo” or relapsed in 2021

<table>
<thead>
<tr>
<th>Locally advanced or Metastatic BC patients undergoing Single-Agent Taxane-based CT (N=5,810)</th>
<th>FATIGUE PREVALENCE (within first 3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Novo diagnosis (1,220; 32%)</td>
<td>Any Fatigue (R53.x) 300 (24.6%)</td>
</tr>
<tr>
<td>Relapsed (4,590; 68%)</td>
<td>+ Cancer-related Fatigue (R53.0) 80 (6.6%)</td>
</tr>
<tr>
<td></td>
<td>Any Fatigue (R53.x) 1,180 (25.7%)</td>
</tr>
<tr>
<td></td>
<td>Cancer-related Fatigue (R53.0) 250 (5.4%)</td>
</tr>
</tbody>
</table>

Table. Fatigue prevalence (as per ICD-10-CM codes) within the first 3 months of single-agent taxane-based CT in patients with locally advanced or metastatic BC diagnosed “de novo” or relapsed in 2021
Disclosure(s):

Anne Blaes, MD: Dompe Pharmaceuticals: Support for research only (Ongoing)
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Renuka Wakade, n/a: Dompé US Inc: Salary (Ongoing)
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Flavio Mantelli, n/a: Dompé Farmaceutici SpA: Salary (Ongoing)
Marcello Allegretti, n/a: Dompé Farmaceutici SpA: Salary (Ongoing)

Alessandra Fabi, MD: Astra Zeneca: 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); Daiichi Sankyo: 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); Eisai: 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); Eli-Lilly: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Terminated, June 30, 2022); exact science: Consulting Fees (e.g., advisory boards) (Ongoing); MSD: 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); 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); Pierre Fabre: 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); Seagen: 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)
Symptom and Functional Status for Individuals with Triple Negative Breast Cancer and Palliative Care Utilization: Findings from the Cancer Experience Registry

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  Country: United States

Background: Triple negative breast cancer (TNBC) can spread quickly and has a higher rate of recurrence than other breast cancers. Due to TNBC's aggressive nature and treatment, patients can experience adverse symptoms and side effects. Palliative care (PC) is intended to improve health-related quality of life (HRQOL) for patients with serious disease at any stage of their illness. However, PC is often conflated with end-of-life care which can affect its rates of utilization. The goals of this study were to explore how TNBC patients characterize their providers for symptom and side effect management. Methods: Data was collected through Cancer Support Community’s Cancer Experience Registry® (CER). From Jan 2015 to Aug 2021, 209 individuals with TNBC enrolled in the CER and completed the Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29 v2.0) profile measure. Five domains assess symptoms with higher scores corresponding to worse symptomology (depression, anxiety, pain interference, fatigue, and sleep disturbance) and two domains assess function with lower scores corresponding to worse functioning (physical and social). Scale scores were converted to standardized T scores and compared against the U.S. population (M=50, SD=10) and reference values for newly diagnosed patients with all types of breast cancer. We considered a group score difference of 3 points clinically meaningful. Moderate to severe impairments are reported as percentages of the sample that have PROMIS scores >1SD from M=50. Of the 209 TNBC patients, 66 (32%) participated after Nov 2018 and
answered newer survey items about utilization of PC providers in the past year. Results: Participants were mainly Non-Hispanic White (81%); resided in suburban/urban areas (84%); reported household income >$40K (64%); Mean age=53y (SD=10; range 28-77). Median time since diagnosis was 2y. 25% reported advanced or metastatic disease; 41% were currently receiving treatment. TNBC patients reported elevated symptoms and deficits in functioning relative to the U.S. population (score difference>3) for all PROMIS subscales except depression (M=51.9) and social function (M=48.8). Fatigue and anxiety scores were highest (M=55.3 and M=56.2, respectively) exceeding the threshold for mild severity. About one-third of participants reported moderate to severe levels of symptom impairment for fatigue (36%), anxiety (36%), and pain interference (32%). Newly diagnosed participants reported higher levels of symptom severity and functional deficits which improved over time; however, survivors’ PROMIS scores remained worse than the U.S population for fatigue and anxiety.

Compared to reference values for breast cancer patients, newly diagnosed (< 2y) TNBC participants (n=83) reported elevated symptoms for fatigue, anxiety, and depression and worse social function (score differences, 4.0, 9.1, 5.3, and 3.9, respectively). In the past year, 69% saw an oncology provider for symptom and side effect support, 44% saw a primary care provider, and 9% a PC provider. Some participants sought care for symptom and side effect management from allied and psychosocial providers such as pharmacists (28%), counselors (25%), and physical therapists (24%). Conclusions: Among TNBC patients, we observed higher levels, on average, of fatigue, anxiety, and depression, and lower social function compared to reference values for breast cancer patients and the U.S. population. Symptom severity and functional deficits were highest among individuals newly diagnosed with TNBC suggesting the importance of incorporating PC into cancer care early in the disease course. TNBC patients and survivors most frequently rely on primary care and oncology care teams for management of symptoms. Future research should examine access barriers to PC providers.

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Referral patterns of metastatic breast cancer patients to Palliative Care team at a Cancer Center in Brazil

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Introduction: Breast cancer is the most common cancer in women and the leading cause of cancer-related death in women worldwide. The high prevalence of physical and psychosocial suffering among breast cancer patients and their families justifies the need for an early interdisciplinary approach by a palliative care team. The effectiveness of early palliative care for patients with advanced cancer has been demonstrated in many studies. Early referral to outpatient palliative care services improves symptom control, reduces suffering and improves quality of end-of-life care.

Aim: Evaluation of referral patterns of metastatic breast cancer patients to the outpatient embedded palliative care team.

Methods: We retrospectively retrieved data from electronic medical records of patients who were treated at a private community oncology practice in Brazil who died from metastatic breast cancer during the years of 2018 until 2021. We evaluated the patient's follow-up time by the palliative care team (follow-up > 12 weeks or not) and the year of referral to the service (pre-2020 vs 2020 and later) associated to the service referral type: Late referral (more than 8 weeks of metastatic diagnosis) or early referral. Each group was followed-up by cancer physicians and after referral was also followed-up by a palliative care multidisciplinary team who regularly evaluated cancer patients during their treatments at outpatient setting. During COVID-19 pandemic, some patients were evaluated by telemedicine appointments. We performed univariate comparisons analysis by Fisher's Exact Test. p < 0.1 was deemed as statistically significant.

Results: Of the 211 patients whose data were assessed, 99 patients were referred to Palliative Care team before 2020 and 112 patients after 2020. 13.1% of patients pre-2020 received early palliative care versus 33.9% of patients in the post-2020 referral group, resulting in a 3.37-fold odds of an early palliative care integration after 2020 (OR 3.37, CI95: 1.61 – 7.45; p< 0.001). Overall, 30.4% of longer follow-up patients were an early referral versus 19.3% of the shorter follow-up, resulting in an 82% greater chance (OR 1.82, CI: 0.92-3.63; p< 0.1) of prolonged assistance with early referral.

Conclusions: In this analysis, early palliative care integration for patients with metastatic breast cancer has increased after 2019 despite the COVID-19 pandemic, leading to prolonged time of accompaniment by the multidisciplinary palliative care team. This suggests that even in the face of this challenging moment, a mature and consolidated service is offered by the palliative care team. Also, according to previous data in literature, premature integration show signs of correlation with better quality of life and death, supporting early palliative care for this group of patients. However, further work is needed to examine the effect of this care model in our cohort.

<table>
<thead>
<tr>
<th>Table: Palliative Care Assistance by time-referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>Prolongued Assistance</td>
</tr>
<tr>
<td>Post-2020 referral</td>
</tr>
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</table>
Disclosure(s):
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Patient-Reported Symptom Burden in Women Undergoing Treatment for Early Stage and Metastatic Breast Cancer

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Background: Women undergoing treatment for breast cancer experience both disease- and treatment-related symptoms. Remote symptom management programs allow real-time symptom documentation, earlier intervention, and opportunities to improve quality of life and decrease symptom burden. This study describes patient-reported outcomes (PROs) in women undergoing treatment for early stage and metastatic breast cancer.

Methods: Women with breast cancer using Carevive’s remote symptom management (RSM) program completed weekly surveys to assess the presence of 14 common symptoms over 16 weeks. Symptoms assessed were anxiety, decreased appetite, fatigue, general pain, mouth sores, muscle pain, nausea, vomiting, numbness, sadness, shortness of breath, diarrhea, constipation, and insomnia. When a symptom was reported, additional questions were asked regarding symptom severity, frequency, and interference using the National Cancer Society’s Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE). The PRO-CTCAE produced composite scores, which classified each symptom reporting event as mild, moderate-severe, or severe. A mild symptom classification generates an electronic care plan with recommendations for symptom management; moderate-severe and severe classifications trigger an alert to the care team. Descriptive analyses summarize PROs for early stage and metastatic patients. Symptom burden was assessed by calculating the frequency distribution of each patient’s highest reported composite score for each symptom by month (Table 1).

Results: Between September 2020 and April 2022, 280 women enrolled in the RSM program; 201 of these women had complete staging information for analysis. 80% (n=160) had early stage (0-III) and 20% (n=41) had metastatic (IV) disease. 32% (n=64) were less than 50 years
old and 68% (n=137) were age 50 or older. 58% (n=116) were hormone receptor (HR) positive/HER2 negative, 22% (n=45) HR+ or -/HER2+ and 19% (n=39) HR-/HER2-. In Month 1, patients with metastatic disease most frequently reported moderate to severe symptoms for general pain (51%), nausea (32%), decreased appetite (22%), and diarrhea (29%). In Month 1, patients with early stage disease most frequently reported moderate to severe symptoms for general pain (32%) and diarrhea (28%). In Month 1, general pain was the most frequently reported symptom for both early stage (34%) and metastatic (51%) groups. In both groups over 16 weeks, nausea, diarrhea, and constipation were among the five most reported symptoms along with muscle pain for early stage patients and shortness of breath for metastatic patients. The frequency of all symptoms decreased over 16 weeks, but there remained cases of moderate-severe and severe symptom intensity through Week 16 for several symptoms. Conclusion: Women with metastatic and early stage breast cancer both report severe symptoms during treatment. Early stage patients may have different symptom profiles and unmet needs not captured by common PROs. Future work should further evaluate symptom profiles of early stage patients to understand how to best use PRO monitoring in the curative intent setting.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Early Stage</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% MO1</td>
<td>% MO2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>General Pain</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Numbness</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Sadness</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Constipation</td>
<td>26</td>
<td>15</td>
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</tbody>
</table>

MO=Month

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Effect of a 12 Week Virtual Supervised Exercise Program on Cardiorespiratory Fitness in Breast Cancer Patients Undergoing Chemotherapy: Results from the STRENGTH Trial

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Background: Chemotherapy (CTX) for breast cancer (BC) can have a detrimental effect on cardiopulmonary fitness (CRF), as measured by VO2max. This decline may be attenuated by

patients (pts) with BC. During the COVID-19 pandemic, many have pivoted to home-based exercise routines, which have been shown to be safe and feasible for pts with BC receiving CTX. We conducted the STRENGTH Trial to evaluate the effect of a 12-week virtual supervised exercise program in BC pts receiving CTX on CRF. Methods: This is a single-center, prospective, single-arm study designed to evaluate the effect of a 12-week virtual supervised

stage I-IV BC who were planned to receive at least 12 weeks of CTX of investigator’s choice were eligible for inclusion. Participants were asked to complete a total of 150 minutes (min) of moderate intensity physical activity/week, as a combination of a 45 min weekly virtual personal training session and workout classes streamed from the Peloton® Digital platform (i.e. walking, running, cardio, yoga, strength training, and cycling). The primary endpoint was the distance walked on a Six-Minute Walk Test (6MWT), an accepted surrogate marker for VO2max, at the start of the Functional Assessment of Cancer Therapy - General (FACT-G) and symptom assessment using the MD Anderson Symptom Inventory (MDASI) questionnaires at the beginning, middle and end of the study. Exploratory endpoints included treatment adherence, toxicities, completion and response. Results: 33 participants signed consent for the clinical trial and 2
withdrew voluntarily prior to beginning the program. 5 participants discontinued prematurely due to a diagnosis of COVID-19 (N=3) and pulmonary embolism (N=2) and were not included in the primary endpoint. One participant remains on study at this time. Median age 49 yrs; range 33-68. Mean BMI 29.55; range 18.1-46.5. 13 HR+/HER2-, 7 HR-/HER2-, 11 HER2+. 14 (45%) pts had Stage I, 11 (35%) pts had Stage 2, 5 (16%) pts had Stage 3, 1 (3%) pt had Stage 4. 23 pts (70%) received either an anthracycline or HER2-based therapy. 19 pts (61%) received neoadjuvant CTX on study, 11 pts (35%) received adjuvant CTX and 1 pt (3%) received treatment in metastatic setting. The average number of exercise min per week per participant was 123.2 min (95% CI, 104.1-142.2), with a relative dose intensity of 82%. In the pts that completed the study thus far (N=25), there was no statistically significant difference between the distance walked during the 6MWT at the start and end of the study (median difference= -10m, range: -129-150m, p= 0.67). There was no statistically significant difference in the FACT-G score at the start and end of the study (median difference= -1.0, range -17.83- 30.0, p=0.54). Pts scored higher on the MDASI (median difference= 0.33, range -1.55-4.62, p=0.04) at the end of the exercise program compared to the beginning. There were no new or unexpected treatment toxicities observed. Conclusion: Pts who participated in a 12-week virtual supervised exercise program during CTX for BC did not experience a statistically significant difference in the distance walked during the 6MWT between the beginning and end of the exercise program. Exercise may attenuate the decline in cardiorespiratory function that has historically been observed with CTX for BC. Some pts were not able to adhere to the recommended 150 min of exercise/week suggesting a potential need for modified exercise targets for pts with BC undergoing CTX. This study is limited by a small sample size and larger, randomized clinical trials are needed to further evaluate optimal exercise recommendations for patients with BC undergoing CTX in order to maintain and potentially, even improve, cardiorespiratory function.

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A pilot study of novel approach of intraneural facilitation versus standard physical therapy for prevention of chemotherapy induced peripheral neuropathy

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Background Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect of commonly used chemotherapy (CT) regimens and often results in dose reduction or cessation of treatment which can adversely affect cancer outcomes. Treatment options for CIPN are limited and no standard approaches exist to prevent CIPN. A novel therapy, Intraneural Facilitation (INF) has been developed by physical therapists at our institution’s neuropathy treatment center as a preventative and treatment modality for CIPN. INF therapy involves physical maneuvers and systematic application of pressure to improve peripheral microvascular circulation to the endoneurial capillaries of the extremities. We conducted a randomized pilot study evaluating INF versus standard physical therapy (PT) maneuvers as a non-invasive treatment modality for preventing CIPN during participants’ ongoing chemotherapy. This study was supported by an intramural (GRASP) grant and registered on clinicaltrials.gov (NCT0327919). Methods Newly diagnosed patients with breast cancer stages I to III and CT naive gynecologic cancers without preexisting peripheral neuropathy planning to receive treatment with platinum-based compounds and/or taxanes were eligible for this study. Participants were randomized into two treatment groups. Group one received INF and group two received a standardized program of PT including muscle stretching and strengthening exercises. Each group received two (45-minute) treatments twice a week for six weeks under the supervision of trained physical therapists. Participants were evaluated at baseline, week 3, week 6, and 3 months after the date of initiation of chemotherapy. The use of neuropathy medications, CT dose reductions, and treatment discontinuation was compared between the two treatment groups. Vascular perfusion was also evaluated at the same intervals using ultrasound to measure volume flow and pulsatility of the popliteal and posterior tibial arteries. Participants completed a survey at the end of treatment evaluating the effectiveness and satisfaction of the intervention. Results 44 out of 104 patients screened met the eligibility criteria and were randomized to either of the two therapy modalities from July 2017 to June 2022. A total of 38 participants received the allocated intervention and were included in the analysis (n=20 in the INF arm and n=18 in the PT arm). CT dose reduction due to CIPN grade 2 or higher occurred in 6/18 (33%) and 4/20 (20%) participants who received standard PT and INF, respectively. 2/18 (11%) participants required discontinuation of CT prematurely due to CIPN in the standard PT arm when compared to 1/20 (5.0%) in the INF arm. Pharmacologic interventions were required to manage CIPN in 4/18 (22%) participants in the standard PT arm vs 2/20 (10%) in the INF arm at the end of CT. Participants reported more control over their health (95.2% INF arm vs. 83.3% PT arm) and decreased nerve discomfort (75% in the INF arm vs. 61.1% in the PT arm). Participants reported high levels of satisfaction overall at the end of each intervention (95% in the INF arm vs. 83% in the PT arm). Conclusion Our pilot study evaluated the feasibility and potential for INF therapy compared to standard PT for the prevention of CIPN during ongoing chemotherapy. Based on the patient satisfaction survey, the burden and satisfaction with the assigned therapy modality between the two arms were favorable overall. Our results showed that CT dose reduction and early cessation in addition to pharmacologic interventions for CIPN were numerically less prevalent in the INF arm compared to the standard PT arm; however, further studies are needed to validate these findings.

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Impact of Integrative Therapies on Patients with Metastatic Breast Cancer

Background: Integrative therapies are shown to support cancer patients’ treatment plans, help with side effect management, and improve patients’ quality of life ([1-9]). In 2017, the American Society of Clinical Oncology endorsed the Association of Integrative Oncology’s Clinical Practice Guidelines highlighting their importance in breast cancer care. Recent studies suggest that more evidence is needed to bring attention to the role of integrative therapies in advanced breast cancer care [4, 7, 8, 10]. This analysis explores participants’ experiences with a wellness program implemented by Unite for HER (UFH), a non-profit organization that delivers integrative therapies and support services such as whole food nutrition services, medical acupuncture, oncology massage therapy, counseling, reiki, meditation, yoga, and fitness classes to patients with breast, metastatic breast, and ovarian cancer. As of April 2022, there were over 1,700 women diagnosed with metastatic breast cancer (MBC) participating in UFH locally and nationally.

Methods: UFH members completed a survey about the impact of the UFH Wellness Program on the overall quality of life, including measures on side-effect management, OTC/prescription drug utilization rate, stress reduction, changes to wellness habits, and the social and emotional challenges associated with living with MBC. In total, 119 unique UFH members with MBC answered online surveys distributed by email in 2020 and 2021. Survey questions were designed to evaluate the impact of the UFH Wellness Program. Descriptive analyses of survey questions and open-ended comments were conducted to
assess program impact.

Results: All respondents were MBC patients/survivors. No other demographic information was collected. While 2020 respondents received mostly in-person services for part of their program, all 2021 respondents received primarily virtual services due to the Covid-19 restrictions. Despite the inaccessibility of in-person services, the satisfaction levels with the wellness program did not drop significantly in 2021. More than two-thirds of respondents (80% in 2020, 67% in 2021) indicated that the therapies offered through UFH Wellness Program significantly improved the side effects of their treatment for MBC. Notably, more than a quarter of respondents (28% in 2020, 26% in 2021) specified that due to UFH integrative therapies they were able to reduce or eliminate one or more OTC/prescription drugs to manage side effects. At the same time, the majority reported experiencing reduced levels of stress after utilizing integrative therapies offered by UFH (93% in 2020, 81% in 2021), as well as improvements in their emotional wellbeing (95% in 2020, 83% in 2021), and quality of life during or after treatment for MBC (97% in 2020, 96% in 2021). Also, 86% of respondents in both years indicated that UFH services, such as nutrition counseling, cooking classes, and exercise classes, helped them adopt and maintain healthier habits in their life. Furthermore, a qualitative analysis of open-ended comments found that 1) respondents expressed deep gratitude and appreciation for UFH integrative therapies, 2) noted that they would otherwise not be able to access such therapies due to financial barriers, and 3) helped them feel better prepared to cope with the psychosocial aspects of their MBC experience.

Discussion: These results suggest that integrative therapies such as those offered by UFH can play a significant role in improving patients' outcomes by reducing stress and drug utilization to manage side effects and improving patients' well-being and quality of life during metastatic breast cancer treatment. These findings highlight the importance of choosing integrative oncology programs to support MBC patients' needs in managing the psychosocial and physical side effects of the disease.

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References


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Pilot study of a patient-reported outcome (PRO) measurement strategy to determine impact of screening for minimal residual disease (MRD) in high-risk breast cancer survivors

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Background: Patients treated for early stage breast cancer (BC) have a 30% lifetime risk of developing metastatic disease. Numerous studies have demonstrated that dormant bone marrow disseminated tumor cells (DTCs) are independently associated with risk of recurrence and death, yet interventions targeting these cells are lacking. The PENN-SURMOUNT (Surveillance Markers of Utility for Recurrence after (Neo)adjuvant Therapy) Screening Study was launched in 2016 to screen high risk BC survivors for DTCs using bone marrow aspirate (BMA) and identify eligible DTC positive patients for clinical trials. Given the novelty of this approach, we concurrently developed and pilot tested a PRO measurement strategy to study how the screening method of BMA and disclosure of DTC results impacts early-stage BC patients. Methods: PENN-SURMOUNT is a single center prospective, longitudinal cohort study examining BM and blood biomarkers of MRD among patients within 5 years of BC diagnosis who have high risk criteria (positive axillary nodes, triple negative biology, ER+ with Oncotype chemotherapy). From May 2019 – August 2021, we recruited patients on SURMOUNT to complete PRO surveys at baseline (T0), after BMA (T1), and after disclosure of DTC results.
(T2). Surveys were administered in paper form initially, then electronic form starting Feb 2021. PRO survey instruments were selected through literature review, followed by consensus among multidisciplinary clinical and research experts and patient advocates. PRO measures assess (Illness Intrusiveness Ratings Scale, IIRS), and decision making (Decision Regret Scale). Additional survey items assess tolerability of the BMA and patients’ risk perception and cognitive understanding after DTC results disclosure. Descriptive statistics summarize PRO survey compliance and responses at T0, T1, and T2 in the total population and the population who reported longitudinal data for T2. Results: 61 of 66 eligible patients on the SURMOUNT trial enrolled in the PRO pilot study and completed a baseline survey, of which 47 (77%) tested negative for DTCs. Mean completion rates were 0.92 at T0, 0.85 at T1, and 0.56 at T2. After electronic survey implementation, completion rates increased to 0.94 (T0), 0.97 (T1) and 0.81 (T2). At T0, 36 (59%) patients reported a high risk perception of developing BC recurrence at 5

subs of possible score 4-28, compared to an expected mean of 11.42 (SD 5.48) in a general survivorship population. Mean T0 illness intrusiveness was 27.3 (SD 13.9) out of possible score 13-91. At T1, approximately 85% of patients agreed that they correctly understood the purpose of the bone marrow procedure and what the procedure would entail. 44 (72%) of patients reported a maximum pain score <= 4 in the week post-procedure and 42 (69%) reported the BMA was same or better than expected tolerability. Exploratory subset analysis of patients with complete longitudinal data at T2 (n = 34) showed average scores of 13.4 (SD 6.0), 30.1 (SD 14.0), and 2.8 (SD 6.2) for recurrence distress, illness intrusive, and decision regret scores (scale 0-100), respectively. At T2, 26 (76%) of patients reported no decision regret for undergoing testing for DTCs; 27 (79%) reported feeling less anxious after DTC results disclosure. Conclusions: Participants of PENN-SURMOUNT perceived risk of recurrence as high. The BMA procedure was well-tolerated and better than expected among the majority of this cohort, and most did not regret having undergone BMA after DTC status disclosure. Longitudinal completion rates were low, limiting assessment of PROs at later time points, a major focus of future work in this setting.

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WITHDRAWN
Mammo-50: Mammographic surveillance in early breast cancer patients aged over 50 years – patient reported outcomes 3 years post diagnosis.

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Introduction: There is a lack of evidence or consensus on the optimum frequency and duration of mammographic surveillance and follow-up for breast cancer patients aged 50 years and older at diagnosis. Mammo-50 will provide clinicians with valuable, risk-adjusted information to guide their practice. It is due to report December 2023.

Quality of life (QoL) was assessed in a sub-study of the main trial. Methods: A multi-centre, randomised controlled, phase III trial of annual mammography versus 2-yearly for conservation surgery and 3-yearly for mastectomy patients with an observational cohort to explore reasons for non-participation. The trial randomised 5235 women between April 2014 and September 2018 and a further 915 registered in the cohort; 90% of women agreed to participate in the study. Questionnaires were completed at trial entry (3 years post-surgery) and then annually for up to 10 years. The distress thermometer was used as a patient reported measure of distress and concerns throughout the trial. The trial team contacted the patient’s clinical care team informing them of the reasons causing patients’ high levels of distress. Results: A total of 4521 (74%) women completed the distress thermometer at baseline. Of these, 289 (6.4%) reported high levels of distress (score 8-10), 825 (18.2%) medium levels of distress (score 5-7), 2033 (45.0%) low levels of distress (1-4) and 1374 (30.4%) reported no distress. Levels of distress were similar across clinical characteristics including surgery type, disease type and ER status, but differed for hormone therapy use (p=0.004). Women who had stopped hormone therapy tended to have higher levels of distress than those who had never had hormone therapy or for whom hormone therapy was ongoing. The most common reasons for causing high levels of distress (score, 8-10) in the 289 patients were sleep problems and/or nightmares (135 (47%)), fatigue, exhaustion or extreme tiredness (132 (46%)), worry, fear or anxiety (111 (38%)), hot flushes (94 (33%)), pain (89 (31%)), memory or concentration (84 (29%)) and sadness or depression (84 (29%)) of patients. Conclusions: Within the Mammo-50 trial, 6.4% of women reported high levels of distress upon trial entry. A quarter of women reported high/medium levels of distress with sleep, fatigue, worry, hot flushes, memory and sadness/depression being the main concerns. Levels of distress were highest in those women who had stopped hormone therapy. These results have been fed back to the UK NCRI breast cancer symptom management group whose remit it is to identify and provide guidelines for supporting women with unmet needs. Acknowledgement and disclaimer: This study is funded by the NIHR HTA programme (project ref. 11/25/03). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Conception and Pregnancy Among Young Breast Cancer Survivors

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Background: Breast cancer (BC) is the most common malignancy among women of reproductive age. Given limited data describing the conception and pregnancy experience of young BC survivors, we sought to explore these outcomes to inform counseling of women interested in future childbearing. Methods: Participants with stage 0-III BC in the Young Women's Breast Cancer Study (NCT01468246), a multi-center, prospective cohort of women diagnosed at age ≤ 40 from 2006-2016 who reported ≥ 1 live birth from a pregnancy after diagnosis were sent a survey with investigator-developed questions focused on their first post-diagnosis live birth. Women who had been diagnosed with BC during pregnancy were excluded from this analysis. The survey assessed conception, use of assisted reproductive technology (ART), pre-implantation genetic testing (PGT), endocrine therapy (ET), and peripartum complications. Summary statistics are presented. Results: 92/119 eligible women completed the survey (response rate: 77%). Median age at diagnosis was 32 (range: 17-40) years and at delivery was 37 (range: 29-47) years. Median time from diagnosis to delivery was 58 months (range: 11-154). Most women had stage 2 BC (43%, 40/92); 68% received chemotherapy (63/92); about half (51%, 47/92) were nulligravida at diagnosis. Overall, 61% of pregnancies were conceived naturally (56/92) and 39% with ART (36/92): 32% by in-vitro fertilization (IVF, 29/92), 7% with fertility medications only (6/92), and 1 with intrauterine insemination. 38% of IVF pregnancies were conceived using products from fertility preservation prior to BC treatment (11/29). Among women who used ART, 74% attempted to conceive naturally (25/36) for a median of 9 (range: 2-48) months prior to pursuing ART. The most common reasons for pursuing ART include infertility following BC treatment (33%, 12/36) and expediting conception to resume treatment (17%, 6/36). 11% of those with known inherited pathologic variant mutations underwent PGT (2/19). Reasons for not pursuing PGT included belief in more effective cancer risk reduction in the future (29%, 5/17), not being offered PGT (24%, 4/17), high cost (12%, 2/17), no interest in IVF (12%, 2/17), acceptable odds for inheriting the mutation (24%, 4/17), and belief in other risk reduction strategies (18%, 3/17); 1 woman reported ethical concerns. Of 57 women who took ET pre-pregnancy (63%), nearly all (96%, 55/57) discontinued ET > 3 months prior to attempting to conceive; 1 discontinued after awareness of pregnancy. Of those who had received prior ET, 60% resumed ET (34/57) a median of 3 (range: 1-50) months after pregnancy. Among 23 women who did not resume, 13 (23%) had completed the recommended duration; the remaining 10 reported one or more of the following reasons: felt better while off (28%, 6/23), desire for another child (22%, 5/23), and desire to breastfeed (17%, 4/23). Median time to delivery was 39 (range: 28-42) weeks with 12% delivering preterm < 37 weeks (11/92). 47% had a Caesarean section (43/92), with prolonged labor the most common indication (33%, 14/43). Hypertensive disorders of pregnancy (HDP, 20%, 18/92), gestational diabetes (7%, 6/92), small for gestational age (7%, 6/92), and postpartum hemorrhage (5%, 5/92) were the most common obstetrical complications. 9% of women had newborns requiring NICU admission (8/92) and 9% had low birth weight (8/92). Conclusion: Among young BC survivors with a live birth following diagnosis, most conceived naturally, with the majority who used ART first attempting natural conception. There was limited use of PGT among mutation carriers with ¼ not having been offered testing. Patient reported peripartum complications appear consistent with population norms, though the relatively higher rate of HDP bears further research. Among those yet to complete their ET, a notable proportion did not resume following delivery. This novel data may help to inform the care of young breast cancer survivors pursuing pregnancy.

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Background: Breast cancer (BC) is the most common malignancy in women of reproductive age, and the incidence of the disease is rising in this population. Many of these women are interested in childbearing after their BC treatment and a substantial minority will go on to have a live birth. Some will also want to breastfeed. However, there is only limited information available regarding the experience of young BC survivors breastfeeding following treatment. Methods: Participants in the Young Women’s Breast Cancer Study (YWS), a multi-center, prospective from 2006-2016, who reported at least one live birth following their diagnosis with stage 0-III BC were sent an additional survey including investigator-developed questions focused on breastfeeding after breast cancer treatment. Women who had been diagnosed with BC during pregnancy were excluded from this analysis. The survey assessed whether they breastfed, reasons for attempting and stopping breastfeeding, breastfeeding with the treated breast and untreated breast, and supports. Summary statistics, including medians and proportions, are presented. Results: Of 118 eligible women sent a survey, 92 completed the survey (78% response rate). Median age at diagnosis of BC was 32 (range: 17-40) years and at delivery was 37 (range: 29-47) years. 54% of women had attempted to breastfeed (50/92). Among those who had not, 93% noted a history of bilateral mastectomies (39/42). Additional reasons for not attempting to breastfeed included no interest regardless of BC history (5%, 2/42) and 1 woman underwent a unilateral mastectomy and did not think her supply would be sufficient. Among the women who did attempt breastfeeding, 68% had undergone lumpectomy and radiotherapy (34/50) with 85% of those women reporting that the treated breast did not produce milk (29/34). The 5 women who produced milk from the treated breast noted that the supply was substantially less than the untreated breast. To assist with breastfeeding, 76% used a pump only on the untreated breast (38/50) and 14% on both breasts (7/50). Women breastfed for a median of 5.5 (range:< 1-60) months and 64% were "somewhat"/"very much" satisfied with their ability to breastfeed (32/50). The most common reasons cited for stopping breastfeeding included having completed the planned duration (36%, 18/50), to start/resume endocrine therapy (22%, 11/50), and to resume breast imaging (8%, 4/50). Among patients who had not undergone a double mastectomy, 47% recalled receiving specific information about breastfeeding after a history of breast cancer (25/53), most commonly from the oncology team (56%, 14/25), lactation consultant (48%, 12/25), or online resources (44%, 11/25). Conclusion: In the largest series to date detailing the breastfeeding experiences of young BC survivors, approximately half of young BC survivors with a successful pregnancy attempted to breastfeed. Among those who had undergone prior lumpectomy and radiotherapy, women reported no milk production or only limited supply from the treated breast. Despite these limitations, most women who attempted to breastfeed were satisfied with their ability to do so. Specific resources to support the experience of breastfeeding in BC survivors are needed.

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Dietary patterns among women with early-stage breast cancer from the Healthy Living Program

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Background: Diet is a modifiable risk factor for breast cancer risk and mortality. Current guidelines recommend a diet that provides a diverse array of nutrients, comprised predominantly of fruits/vegetables and whole grains, with limited added sugar. The Healthy Living Program (HLP) is a clinical program at Memorial Sloan Kettering Cancer Center for patients with early-stage breast cancer that offers longitudinal, personalized lifestyle management starting at the time of diagnosis. Here, we report dietary patterns among the HLP cohort and association with baseline body mass index (BMI). Methods: We included all patients enrolled in the HLP from September 2020-February 2022. At the time of enrollment, participants complete a survey containing the National Cancer Institute (NCI) Dietary Screener of foods items over the past month. Total daily intake equivalents are calculated for foods from every diet of fruits/vegetables, which includes fruit, fruit juice, salad, potatoes, beans, other vegetables, tomato sauce, salsa, and pizza; 2) Total daily ounce equivalents of whole grains, which includes cereal, whole grain bread, whole grain rice, and popcorn; 3) Total teaspoon (tsp) equivalents of added sugars from candy, doughnuts, cookies/cake/pie, cereal, ice cream, and sugar-sweetened beverages including soda, fruit drinks, and sugar/honey in coffee/tea. Adherence to recommended daily intake of fruits/vegetables, whole grains, and added sugars was assessed as per the 2020-2025 Dietary Guidelines, the American Institute for Cancer Research, and the World Health Organization guidelines. Patient and tumor characteristics were abstracted from medical records. Results: Among the 399 patients included, the median age at diagnosis was 58 and median baseline BMI was 26.1 kg/m2. 45 patients had carcinoma in situ (11.3%), 296 had stage I disease (74.2%), 51 had stage II disease (12.8%), and 7 had stage III disease (1.8%). 316 had hormone-receptor positive disease (89.3%), 24 had HER2-positive disease (6.8%), and 26 had triple-negative disease (7.3%). 106 participants (27%) met the guideline recommendation of ≥4-5 cup equivalents of fruits/vegetables daily and 3 participants (0.8%) met the guideline recommendation of ≥3 ounces equivalents of whole grains daily. All patients in the cohort met the guideline recommendation of < 6 tsp equivalents of added sugars daily. Only 2 patients (0.5%) met guidelines for all three diet factors. Baseline BMI was significantly higher among patients who did not meet the recommended fruit/vegetable intake than among those who did (26.9 kg/m2 vs. 24.5 kg/m2, p=0.016). There were no significant differences in BMI between those who did and did not adhere to the other diet factor guidelines and no significant association between tumor stage or histology and dietary guideline adherence. Conclusion: Most patients with early-stage breast cancer did not meet the recommended daily intake of fruits/vegetables or whole grains. Participants who did not meet the fruit and vegetable intake guideline had significantly higher BMI at diagnosis. These findings indicate that lifestyle assessment near the time of breast cancer diagnosis identifies patients that could benefit from personalized dietary interventions to optimize prognostic factors such as BMI.

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Neil M. Iyengar, MD: Curio Science: Consulting Fees (e.g., advisory boards) (Ongoing); IntrisiQ Health: Consulting Fees (e.g., advisory boards) (Ongoing); MJH Life Sciences: Consulting Fees (e.g., advisory boards) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing), institution (Ongoing); OncLive: Consulting Fees (e.g., advisory boards) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing); Puma Biotechnology: Consulting Fees (e.g., advisory boards) (Ongoing); Seattle Genetics: Consulting Fees (e.g., advisory boards) (Ongoing); SynDevRx: Research funding to institution (Ongoing)
Ultrasound-guided injection with or without rehabilitation exercise in breast cancer survivors with sub-acromion-deltoid bursitis: a pilot randomized clinical study

BACKGROUND: Due to the increasing overall survival of breast cancer (BC) patients, a growing interest has been raised in the current literature on disabling consequences of cancer and its treatment [1,2]. In particular, after radical surgery for BC, patients might frequently be affected by functional limitation of the shoulder joint, potentially related to the immobilization, surgical scar tensions, axillary web syndrome, subpectoral prostheses or expanders, or peripheral nerve damage [3]. In this scenario, several challenges are still open in the therapeutic approach to this disabling condition and the optimal management of shoulder dysfunction in breast cancer patients is far from being fully characterized. Therefore, the aim of this study was to assess the effects of a comprehensive rehabilitation program including ultrasound-guided injection of the sub-acromion deltoid bursa (SAD) followed by a rehabilitation exercise protocol in terms of feasibility, pain relief, upper limb function, quality of life, and safety.

METHODS: In this study, we recruited consecutive breast cancer women referring to a Physical Medicine and Rehabilitation in Northern Italy and suffering from SAD bursitis in the absence of tendon lesions. Patients were assessed for eligibility and subsequently randomly assigned 1:1 to two groups. Group A received ultrasound-guided percutaneous injection of the SAD bursa (lidocaine and triamcinolone acetate) followed by a rehabilitation exercise program.
of 5 sessions lasting 1 hour each., while Group B received ultrasound-guided percutaneous injection only. Patients were assessed at baseline (T0), after a week (T1), and after 3 months (T2). The outcomes were numerical pain rating scale (NPRS), handgrip strength (HGS) test, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the Oxford Shoulder Score (OSS), Global Perceived Effect (GPE), and safety. RESULTS: Thirty-seven patients were enrolled and randomly assigned to Group A (n=19; mean age: 56.05 ± 10.30 years; body mass index (BMI): 23.58 ± 2.79 kg/m²) and Group B (n=18; mean age: 58.39 ± 12.09 years; BMI: 22.72 ± 3.16 kg/m²). No major or minor adverse events were reported after this multidisciplinary intervention. Statistically significant within-group differences were found in both groups in terms of NPRS after the treatment (p < 0.05) and after the follow-up (p < 0.05). The between-group analysis showed significant differences in pain intensity (NRS: 2.16 ± 1.39 vs 4.78 ± 1.77; p < 0.05), isometric muscle strength (25.11 ± 3.20 vs 20.33 ± 4.92; p< 0.001), shoulder function (OSS: 17.00 ± 3.27 vs 33.11 ± 6.471; p< 0.0001), and EORTC QLQ-C30 (Functional subscale: 88.74 ± 7.71 vs 77.67 ± 13.64; p=0.017; Symptom subscale: 11.43 ± 8.56 vs 19.61 ± 13.72; p=0.048; Global Health subscale: 79.36 ± 13.72 vs 70.56 ± 8.26; p=0.022) of the after the follow-up. However, no significant differences (p > 0.05) were reported at T1. CONCLUSION: Our findings showed that a comprehensive rehabilitation approach including ultrasound-guided injection combined with rehabilitation exercise might be safe, well-tolerated, and effective in breast cancer patients with SAD bursitis. These data emphasized the positive role of an interdisciplinary rehabilitation management in pain management and improving overall well-being of breast cancer patients. Further studies with larger samples and longer follow-ups are needed to confirm our data. REFERENCES: 1. 2020, 10, 864. 2. D'Egidio V et al. Counseling interventions delivered in women with breast cancer to improve health-related quality of life in young women with breast cancer: a systematic review. PLoS One. 2014 May 9;9(5):e96748. Disclosure(s): Lorenzo Lippi, n/a: No financial relationships to disclose. Alessandro de Sire, n/a: No financial relationships to disclose. Arianna Follì, n/a: No financial relationships to disclose. Francesco D'Abrosca, n/a: No financial relationships to disclose. Alessio Turco, n/a: No financial relationships to disclose. Giuseppina Bonizzi, n/a: No financial relationships to disclose. Nicola Fusco, n/a: AstraZeneca: Consulting Fees (e.g., advisory boards) (Ongoing); Boehringer Ingelheim: Consulting Fees (e.g., advisory boards) (Ongoing); Daiichi-Sankyo: Consulting Fees (e.g., advisory boards) (Ongoing); Gilead: Consulting Fees (e.g., advisory boards) (Ongoing); GlaxoSmithKline (GSK): Consulting Fees (e.g., advisory boards) (Ongoing); Merck Sharp & Dohme (MSD): Consulting Fees (e.g., advisory boards) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing). Marco Invernizzi, n/a: No financial relationships to disclose.
Does Breast Inflammation Contribute to Lymphedema Risk in Patients Treated with Axillary Lymph Node Dissection?

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Background
Chronic inflammatory responses initiated by lymphatic injury play a key role in the pathophysiology of secondary lymphedema. However, it is unclear if baseline inflammation or ethnic/racial variability in inflammatory responses increase lymphedema risk. Crown-like structures of the breast (CLS-B), consisting of macrophages engulfing necrotic adipocytes, are a marker of systemic inflammation and have been implicated in the pathogenesis of breast cancer, but their role in lymphedema development is unknown. Here we determine whether baseline differences in inflammation, characterized by the presence of CLS-B, contributed to lymphedema risk in a diverse cohort of patients treated with ALND.

Methods
A prospective lymphedema screening study. Body mass index (BMI) and volumetric arm measurements (perometer) were performed at baseline, postoperatively, and every 6 months. Breast tissue obtained at definitive surgery was assessed for CLS-B with CD-68 IHC stain in non-tumor breast tissue. Inflammation severity was determined by number of CLS-B/cm², with the median used to differentiate between mild and severe inflammation. Lymphedema was defined as a relative arm volume change of ≥10%. Lymphedema incidence was assessed using competing risk analysis and compared between patients with and without CLS-B. Uni- and multivariable analysis was
performed to identify factors associated with lymphedema development.

Results
Between 11/2016-03/2020, 304 ALND patients were enrolled; 281 had at least 6 months of follow-up and were included in the study. Eleven percent self-identified as Asian, 20% Black, 6% Hispanic, and 60% White. Median age was 48 years; median BMI was 26.3 kg/m², with higher BMI observed in Black and Hispanic women compared to Asian and White women (p < 0.001). Overall, 54% had CLS-B, with severe inflammation (> 0.4 CLS-B/cm²) identified in 71 (25%) patients. CLS-B presence correlated with BMI (36% [BMI < 25], 63% [BMI 25-30], 70% [BMI > 30], p < 0.001) and varied across racial/ethnic groups, with a higher prevalence in Black and Hispanic women (68% [Black], 69% [Hispanic] vs 59% [Asian], 46% [White], p = 0.03) (Table). Inflammation severity did not differ by race/ethnicity (p = 0.11). At 2.1 years median follow-up, 66 women developed lymphedema, with a 2-year lymphedema rate of 21.3% (95% CI 16.4-26.8). Lymphedema incidence was higher among Black and Hispanic women, compared to Asian and White women (2-year rate: 33.8% [Black], 31% [Hispanic], 17.4% [Asian], 18.2% [White], p = 0.002), and was higher among women with CLS-B (2-year rate: 28.2% [CLS-B] vs 12.9% [no CLS-B], p = 0.02). On multivariable analysis, Black race (White [referent]: HR 2.85, 95% CI 1.4-5.8; p = 0.03), receipt of NAC (upfront surgery [referent]: HR 2.46, 95% CI 1.04-5.8, p = 0.04) and older age (HR 1.03, 95% CI 1.01-1.06 per 1-year increase; p = 0.009) were independently associated with lymphedema development, while CLS-B was not (HR 1.37, 95% CI 0.81-2.34, p = 0.2).

Conclusions
In a prospective cohort of patients treated with ALND, Black race, receipt of NAC, and increasing age, but not CLS-B, were independently associated with lymphedema risk. However, the higher CLS-B prevalence in Black women suggests that they may have a propensity for increased inflammation, which may in part be contributing to the higher lymphedema risk observed, but is likely not the only inflammatory mechanism that modulates risk.

Table. Clinical characteristics of study cohort stratified by the presence of CLS-B
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n = 275)</th>
<th>Patients with CLS-B (n = 149)</th>
<th>Patients without CLS-B (n = 126)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>46 (40, 51)</td>
<td>45 (42, 57)</td>
<td>46 (39, 56)</td>
<td>0.2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3 (22.5, 31.1)</td>
<td>28.7 (24.2, 32.3)</td>
<td>23.4 (21.1, 29.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (11%)</td>
<td>17 (11%)</td>
<td>12 (10%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>57 (21%)</td>
<td>39 (26%)</td>
<td>18 (14%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>16 (6%)</td>
<td>11 (7%)</td>
<td>5 (4%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>164 (60%)</td>
<td>76 (51%)</td>
<td>68 (70%)</td>
<td></td>
</tr>
<tr>
<td>cT stage</td>
<td></td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>1</td>
<td>57 (21%)</td>
<td>39 (26%)</td>
<td>18 (14%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>125 (45%)</td>
<td>54 (36%)</td>
<td>71 (56%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>44 (16%)</td>
<td>28 (19%)</td>
<td>16 (13%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44 (16%)</td>
<td>24 (16%)</td>
<td>20 (16%)</td>
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</tr>
<tr>
<td>cN stage</td>
<td></td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>0</td>
<td>72 (26%)</td>
<td>37 (25%)</td>
<td>35 (28%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>180 (66%)</td>
<td>99 (65%)</td>
<td>81 (64%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (2%)</td>
<td>4 (3%)</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (6%)</td>
<td>9 (6%)</td>
<td>8 (6%)</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Ductal</td>
<td>232 (84%)</td>
<td>121 (81%)</td>
<td>111 (88%)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>35 (13%)</td>
<td>21 (14%)</td>
<td>14 (11%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (3%)</td>
<td>7 (5%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Receptor subtype</td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>HR+/HER2+</td>
<td>185 (67%)</td>
<td>100 (67%)</td>
<td>85 (67%)</td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>55 (20%)</td>
<td>25 (17%)</td>
<td>30 (24%)</td>
<td></td>
</tr>
<tr>
<td>HR-HER2-</td>
<td>35 (13%)</td>
<td>24 (16%)</td>
<td>11 (9%)</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Yes</td>
<td>194 (71%)</td>
<td>110 (74%)</td>
<td>84 (67%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81 (29%)</td>
<td>39 (26%)</td>
<td>42 (33%)</td>
<td></td>
</tr>
<tr>
<td>Type of breast surgery</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lumpectomy</td>
<td>69 (25%)</td>
<td>39 (26%)</td>
<td>30 (24%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>208 (75%)</td>
<td>110 (74%)</td>
<td>96 (78%)</td>
<td></td>
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<tr>
<td>Breast pCR</td>
<td>22 (11%)</td>
<td>11 (10%)</td>
<td>11 (13%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total No. LNs removed</td>
<td>18 (13, 23)</td>
<td>18 (14, 23)</td>
<td>18 (13, 22)</td>
<td>0.2</td>
</tr>
<tr>
<td>Total No. positive LNs</td>
<td>2 (1, 5)</td>
<td>2 (1, 5)</td>
<td>2 (1, 6)</td>
<td>0.8</td>
</tr>
<tr>
<td>RT done</td>
<td>256 (94%)</td>
<td>143 (99%)</td>
<td>116 (92%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Nodal RT</td>
<td>254 (92%)</td>
<td>139 (93%)</td>
<td>115 (91%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Frequency (column percent) reported for categorical variables and median (IQR) reported for continuous variables

*CLS-B unknown in 6 cases
#CTx, n = 5
Denominator includes only women treated with NAC (n = 194)
Abbreviations: CLS-B crown-like structures of the breast; BMI body mass index; HR hormone receptor; HER2 human epidermal growth factor receptor 2; pCR pathologic complete response; LN lymph nodes; RT radiotherapy

Disclosure(s):
Andrea Barrio, MD: No financial relationships to disclose
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Varadan Sevilmudu, MBBS, DrPH: No financial relationships to disclose
Ethan Gomez, BS: No financial relationships to disclose
Dilip Giri, MD: No financial relationships to disclose
Babak Mehrara, MD: Pfizer: Consultant (Ongoing); PureTech: Royalty (Ongoing); Regeneron and PureTech: Investigator-initiated grant (Ongoing)
Monica Morrow, MD: Exact Sciences: Consulting Fees (e.g., advisory boards) (Ongoing); Roche: Consulting Fees (e.g., advisory boards) (Ongoing)
Safety and Tolerability of Paxman Scalp Cooling at Lower Temperatures to Improve Efficacy with Anthracycline Chemotherapy

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  Country: United States

Background: Chemotherapy induced alopecia is one of the most distressing side effects of cancer therapy since it is a constant reminder of the underlying malignancy. Anthracycline chemotherapy induces total alopecia. Although scalp cooling devices have been used to prevent this alopecia, there is still a need to improve efficacy with anthracycline therapy. This study was performed to evaluate if the Paxman Scalp Cooling System is safe, tolerable, and more efficacious at lower temperatures.

Objectives: The primary end point is to assess the safety and tolerability of the Paxman Scalp Cooling System at lower temperatures (-7.5 Celsius and -10 Celsius), defined as the ability of patients to undergo scalp cooling without any DLTs during the treatment period. The secondary end point is successful hair preservation assessed using the Common Terminology Criteria for Adverse Events version 4.0 scale (grade 0 [no hair loss] or grade 1 [< 50% hair loss not requiring a wig] were considered to have hair preservation) after anthracycline chemotherapy.

Methods: 34 women with stage I-III breast cancer who were receiving anthracycline-based neoadjuvant or adjuvant therapy were enrolled on study. The first 7 patients received scalp cooling at -7.5 Celsius and the subsequent 27 patients received scalp cooling at -10 Celsius. Patients completed safety and tolerability assessments at each visit. In addition, participants
had standardized scalp photography to assess the superior, vertex and frontal scalp views, trichoscopic assessments, alopecia grading and completed PROs (CADS, Tolerability, Change in scalp coverage).

Results: Thirty-four women (56% White, 18% Black, 8% Asian, 18% other) with a mean age of 44 (range 20-68) were enrolled on this IRB-approved pilot study. Seventy-four percent received ddAC-T, 18% received ddAC-THP and 8% received ddAC/Pembro-T/Carbo/Pembro. Twenty-six patients were evaluable for the DLT end point. Three patients are still on study and five patients left the study before completion (2 due to lack of efficacy, 1 shaved her head, 1 was removed from study due to hospitalization for sepsis and 1 patient changed her mind and never started scalp cooling). There were no DLTs in any patient throughout the study. Both the -7.5 and -10 Celsius temperatures were found to be tolerable with no difference in tolerability. The most common reported AEs were headaches 48%, discomfort 13%, scalp pain 9.7%, dizziness 9.6%, scalp coldness 6%, feeling cold 3% and lightheadedness 3%. Twenty-nine percent of patients reported that scalp cooling triggered a headache and the average level of pain was mild. Only 16% of patients reported pain killer use due to scalp cooling, which effectively resolved headaches or discomfort. Sixty-one percent of patients reported hair preservation at the primary end point. Hair regrowth was reported in patients after they experienced grade 2 alopecia and while still on study. More detailed data on hair preservation will be forthcoming once all of the photos and trichoscopic measures are assessed.

Conclusions: Paxman Scalp Cooling System is safe, tolerable and even more efficacious at lower temperatures. The -10 Celsius is more efficacious and as tolerable as -7.5 in patients being treated with anthracycline therapy. When using the Paxman Scalp Cooling System in patients being treated with anthracycline therapy, you should consider performing scalp cooling at lower temperatures.

<table>
<thead>
<tr>
<th>Table 1: Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Disclosure(s):
**Shari B. Goldfarb, MD**: Ms. Medicine LLC: Consulting Fees (e.g., advisory boards) (Ongoing); NanOlogy: Consulting Fees (e.g., advisory boards) (Ongoing); Paxman Cooling LTD: grant recipient (Ongoing); Revision Skincare: Consulting Fees (e.g., advisory boards) (Ongoing); Sermonix Pharmaceuticals LLC: Consulting Fees (e.g., advisory boards) (Ongoing); Spectrum Pharmaceuticals: Consulting Fees (e.g., advisory boards) (Ongoing); Sprout Pharmaceuticals: Grant Recipient (Ongoing)
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Introduction Axillary de-escalation is driven by both a desire to minimize injury and a growing awareness of the oncological safety of axillary conservation. However, the evidence of the impact of axillary procedures is largely subjective and based on patient questionnaires. Sensing technologies such as Wearable Activity Monitors (WAM) can acquire functional postoperative data, enabling objective analysis of patients' physical activity (PA) levels. This technology implementation would help surgeons better comprehend the post-operative recovery phase and provide individualized interventions for patients. We aimed to use WAMs in order to investigate differences in physical recovery between axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) – with a hypothesis that the ALND group has slower recovery compared to SLNB. Methods A single centre, prospective non-randomized observational study was conducted from September 2019 to May 2022. Consecutive patients undergoing breast and axillary surgery were identified from theatre lists. Patients with movement disorders or upper limb impairment and those using mobility devices or aids were excluded. Eligible consented patients wore WAMs (AX3, Axivity, UK – triaxial accelerometer) on both wrists at least one day pre- and up to two weeks post-operatively. The Mann-Whitney U test and the Wilcoxon Signed Rank Test were performed to analyze the PA levels between arms and surgeries. Patient demographics and potential confounders such as concomitant breast/reconstruction surgery were recorded. Results A total of 53 patients were recruited. Greater PA level was observed in the control arm compared to the surgically treated side in both SLNB and ALND groups in week 1 (SLNB: 69.6% vs 61.1%, p=0.006; ALND: 75.3% vs 60.4%, p< 0.001) and 2 (SLNB: 77.6% vs 71.1%, p=0.113; ALND: 81.9% vs 70.2%, p< 0.001) respectively. When comparing activities of the surgically treated side only, the ALND patients
had significantly lower PA level compared to SLNB group in post-operative day 7-9 (65.4% vs 72.5%, p=0.035). Subgroup analysis was performed to compare surgically treated side of ‘Mastectomy Only and SLNB’ versus ‘Mastectomy Only and ALND‘. PA level was significantly lower in the latter than the former in week 2 (78.5% vs 83.5%, p=0.027). There were no significant differences in demographics between the 2 groups. Conclusion ALND consistently results in decreased PA level compared to SLNB. The findings also demonstrate the longitudinal impact of SLNB, which impacts PA levels, even up to 2 weeks after surgery. Monitoring recovery objectively after breast cancer surgery provides patients and surgeons with more information about the likely outcomes of their treatment and may help them choose the best option, particularly where oncological outcomes are equivocal. This information could also be used to improve outcomes by identifying vulnerable patients who would benefit from early exercise intervention, encouraging physical activity, and keeping track of individualised PA that could be added to the feedback rehabilitation care plan.

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Lifestyle factors and patient-reported outcome measures using the European Organisation for Research and Treatment of Cancer survivorship questionnaire in early breast cancer patients attending for surveillance imaging.

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Background: An increasing number of patients survive their early breast cancer (EBC) but may treatment. Survivors are also at risk of other possibly life-shortening chronic diseases due to concomitant risk factors (smoking, drinking >14 units of alcohol/week, and low exercise levels). Little is known about the lifestyle factors and long-term challenges facing EBC survivors. We report the initial results of a questionnaire (containing patient-reported outcomes measures (PROMS), and lifestyle factor questions) completed by EBC survivors at the Royal Marsden hospital (RMH), UK. Methods: We prospectively identified a patient cohort of patients (October 2021 to June 2022) with stage I-III EBC who had completed their curative treatment (endocrine treatment (ET) may be ongoing) and who were attending for their annual surveillance breast imaging at years 1, 2, 4, and >5 years. Patients completed PROMS (using EORTC (European Or -SURV100 and -BR23) and questionnaires regarding smoking, alcohol, and exercise levels (via the International Physical
analysis (it is anticipated data will be available for 350 at the time of SABCS 2022). Patients were attending for their year 1 (N=66, 35.3%), 2 (N=43, 23%), 4 (N=43), or >5 years (N=35, 18.7%) imaging post-surgery. 62 (86.6%) patients were Eastern Cooperative Oncology Group Performance Status 0-1, and 31 (16.6%) had >2 of other comorbidities. 123 patients (65.8%) were post-, 16 (8.6%) peri-, and 48 (25.7%) premenopausal. 178 (95.2%) underwent primary surgery. Of those patients undergoing surgery, 19 (10.2%) had a mastectomy, and 168 (89.8%) breast conserving surgery. All patients had axillary surgery: 26 (13.9%) axillary dissection, and 158 (84.5%) sentinel lymph node biopsy. 166 patients (88.8%) received adjuvant ET and for most patients (N= 149, 79.7%) this was ongoing at time of analysis. 31.6% (N= 59) had prior exposure to cardiotoxic treatment. Risk groups for other chronic health conditions could be identified: 92 (49.2%) patients had a BMI of >25, 5 (4.2%) were current smokers, and 16 (13.6%) were classified as at-risk drinking. Patients reported that their physical function was affected following their diagnosis and treatment, with 51 (27.3%) having trouble running short distances and 52 (27.8%) taking a long walk carrying a heavy backpack. Nonetheless all patients (N=118 available for IPAQ analysis) had moderate (N=61, 51.7%), or high-level (N=58, 49.2%) levels of exercise. 85 patients (45.5%) had pain in the past week, and 101 patients (54%) were dissatisfied with the appearance of their body. Most patients (N=152, 81.3%) of the QoL symptom scales were compared between patient groups. Patients who had chemotherapy suffered ongoing from hair loss (52.6% vs 45.2%) than chemo-naïve patients. There were no major differences between groups who received ET and those ET naïve. Conclusions We were able to identify groups of patients at risk for other comorbidities and concerns. PROMS should be routinely assessed in EBC survivors to better address subgroups at higher risk, inform consultations, and treatment decisions.

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Frequency of low bone mineral density in young women with breast cancer and associated factors

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Background: Young women with breast cancer (YWBC) may experience bone mineral density (BMD) loss due to the effects of cancer treatment on estrogen levels. Studies assessing BMD
in breast cancer (BC) patients have had a limited representation of young women. This study aimed to analyze the frequency of low BMD and its associated factors in this specific age group.

0-III BC, treated with chemotherapy (CT) and/or endocrine therapy (ET) between 2010-2020, and with no documented bone metastases during follow-up. The protocol was conducted in 5 BC referral centers in Mexico. Demographic, clinical and treatment data were collected, as well as bone dual-energy X-ray absorptiometry (DEXA) results. Low BMD was defined as T-score ≤ -1.0 or Z-score ≤ -2.0 at the lumbar spine (L1-L4) or femoral neck.

The frequency of low BMD was analyzed with descriptive statistics. Binary logistic regression using complete case analysis was conducted to calculate odds ratios (OR) and 95% confidence intervals (95%CI) of experiencing low BMD according to demographic, clinical and therapeutic factors.

Results: In total, 716 YWBC met inclusion criteria. Median age at BC diagnosis was 36 years (21-40); 708 (99%) women were premenopausal at diagnosis. Most were married (355; 50%), had higher education (381; 53%), were unemployed (433; 61%), and were non-smokers (552; overweight/obese) in 14 (2%) and 392 (58%) cases, respectively. The most common BC subtype was hormone receptor (HR) positive/HER2 negative (371; 52%), followed by triple negative (168; 24%), HR positive/HER2 positive (122; 17%) and HR negative/HER2 positive (55; 8%). Patients were mostly diagnosed with stage II (346; 48%) or III (276; 39%) disease. As for treatment, CT in 667 (93%), ET in 468 (65%), anti-HER2 therapy in 168 (24%), and radiotherapy was administered in 562 (79%) cases.

DEXA scans were documented in 213/716 (30%) patients. In total, 286 DEXA results were available. The time elapsed from the start of the first systemic treatment to the DEXA result was 0-12 months in 42 cases (15%); 13-36 months in 103 (36%); 37-60 months in 72 (25%); and >60 months in 69 (24%). Overall, 133/213 patients (62%; 95%CI 56-69%) had at least one low BMD report after the start of CT or ET. T-scores and Z-scores in each period are detailed in the Table. No fractures were recorded in any case after BC diagnosis. The only variable associated with low BMD was BMI ≥25.0 kg/m² (OR, 1.88; 95%CI, 1.04-3.40). The described demographic, clinical and treatment factors were not significantly associated with low BMD.

Conclusion: This study showed a suboptimal frequency of bone DEXA monitoring in YWBC. A considerable proportion of YWBC experienced low BMD after initiation of CT and/or ET; and a significant association was found between obesity/overweight at BC diagnosis and subsequent low BMD. These data reflect the importance of requesting DEXA scans in young patients on a regular basis and promoting the maintenance of an adequate body weight, in line with international recommendations. Further studies evaluating the degree of BMD loss and its determinants would contribute to establish the optimal periodicity to monitor BMD in relation to BC therapy, allow timely offering of interventions to reduce bone morbidity, as well as improve the quality and life and survivorship of this young group of patients.

Table. DEXA T-scores and Z-scores.
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Blockade of CD47/Thrombospondin-1 signaling increases glycolytic metabolism as a protective mechanism against chemotherapy-associated cardiac injury in a model of Triple-Negative Breast Cancer.

Due to advances in diagnosis and treatment, cancer–related mortality has decreased, and by the year 2030, there will be 22 million cancer survivors in the United States. This success comes with an increased incidence of serious adverse effects, mainly in the cardiovascular system. While new treatment modalities are emerging for Triple-negative breast cancer (TNBC), most current strategies include anthracycline-based regimens to manage disease. Therefore, novel strategies are needed to overcome anthracycline-induced cardiotoxicities in this patient population. Activation of the TSP1/CD47 signaling axis is implicated in the progression of heart failure, with reported increases in TSP1 levels following myocardial infarction. Therefore, we examined the potential of CD47 blockade as a strategy to prevent cardiac injury as a consequence of cancer chemotherapy. Our data in a syngeneic orthotopic breast cancer model shows that blockade of CD47 using an in vivo anti-sense phosphodiesterase morpholino (PMO) preserved ejection fraction, fractional shortening, and cardiac output when compared to DOX treatment while preserving oncologic efficacy of chemotherapy. To determine a potential mechanism of cardioprotection, hearts of control and CD47 PMO-treated mice were subjected to RNA sequencing. Gene set enrichment analysis (GSEA) showed significant positive enrichment for metabolic pathways including pyruvate metabolism (NES= 2.3 , p< 0.002), and oxidative phosphorylation (NES=2.0, p< 0.01). During cardiac insult, metabolic flexibility of cardiomyocytes results in metabolic reprogramming from fatty acid oxidation to a glycolytic mechanism to overcome injury. Thus, DOX-associated
cardiotoxicity may be mediated by an increase in TSP1 and a decrease in glycolysis, leading to the inability to overcome acute cellular stress. In vitro cellular bioenergetics, analysis revealed that TSP1 caused a dose-dependent reduction in glycolytic flux and glycolytic capacity in cardiac myoblast. This, coupled with preserved cardiac viability of cardiac cells treated with CD47 PMO in the presence of DOX, suggests that TSP1 may act through CD47 to prevent cardiac cell metabolic reprogramming needed to overcome injury. Furthermore, anti-sense experiments with siRNAs to Glut-4 and Hexokinase-II showed that the protection conferred by CD47 is mediated by activating these proteins. Therefore our studies suggest that the TSP1/CD47 axis may be central to the interplay of metabolism to preserve cardiac tissue integrity; thus, targeting this pathway may prevent the onset of chronic cardiac disease due to chemotherapy in cancer patients.

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Reducing Rates of Chronic Breast Cancer Related Lymphedema with Screening & Early Intervention: An Update of Recent Data

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Background: Breast cancer related lymphedema (BCRL) represents a dreaded complication of breast cancer treatment that can lead to morbidity, diminished quality of life, and psychosocial harm and is associated with increased costs. Increasingly, data has supported the concept of prospective BCRL surveillance coupled with early intervention to mitigate these effects.

Methods: We performed a systematic review of the literature searching for published randomized and prospective data evaluating prospective BCRL surveillance with early intervention. Results: We identified 12 studies (2,907 patients) including 4 randomized trials (1,203 patients) and 8 prospective studies (1,704 patients). Randomized data consistently demonstrate that early intervention reduces rates of progression to chronic BCRL with multiple paradigms and diagnostic modalities utilized; the strongest data in the review comes from the randomized PREVENT trial which demonstrated early detection with bioimpedance spectroscopy (BIS), coupled with a compression garment applied for 12 hours a day over 4 weeks, significantly reduced the rate of chronic BCRL compared to tape measurement.

Conclusions: Current data support the role of prospective BCRL surveillance with early detection and intervention to reduce rates of chronic BCRL. Breast cancer patients at risk for BCRL should undergo prospective surveillance as part of survivorship. Given the level 1 data demonstrating that BIS is superior to conventional tape measure, it should be included as the standard BCRL diagnostic modality unless an equally effective modality is employed.

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"It's like Coming Home": A Qualitative Evaluation of Project Life a Virtual Wellness Community for People Living with Metastatic Breast Cancer

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Background: Project Life is a virtual wellness house led by people living with metastatic breast cancer (MBC) for people with MBC. Through the organization’s targeted programming and curated content, Project Life promotes key dimensions of wellness: physical, emotional, social, spiritual, and financial. Project Life was created to fill the gaps in survivorship care for people with MBC specifically. The objective of this study was to qualitatively evaluate members’ experiences with Project Life, understanding the impact of the organization and potential areas for future growth. Methods: From March 2022 to May 2022, we conducted semi-structured qualitative interviews virtually with members of the Project Life wellness community. The study design and primary objectives were designed in direct collaboration with Project Life leadership. A study flyer was distributed by e-mail and social media to the Project Life community. Participants were eligible if they self-identified as having MBC, were a member of the Project Life community and could complete the interview in English. Participants were asked a series of questions about how they heard about the organization, the types of programming they have participated in, the greatest benefits of Project Life, and areas for future growth and improvement. Interview transcripts were transcribed verbatim and analyzed. We then analyzed transcripts with phronetic iterative analysis, to uncover contextually grounded, emergent themes through synthetic coding. Results: We interviewed 36 women with MBC who were members of the Project Life Wellness Community in Spring 2022. Overall, 22% of participants identified as people of color, including Black, Latina and Asian women. In terms of age, 8 participants were 30-45, 15 were 46-59, and 13 were 60+. The overwhelming majority heard about Project Life through social media, with only one participant indicating they learned about the organization from their cancer center. Many participants stated that they wished cancer centers connected patients to external MBC support organizations like Project Life. The most commonly utilized Project Life programs included healing circles, legal clinics, cooking classes, and therapeutic art. Many participants endorsed having improvements in quality of life from being engaged with Project Life through MBC-specific curated content and the strong sense of community. Several participants indicated the appeal of participating in an organization that was developed by people with MBC for people with MBC. Additional suggestions for content
included finding information about clinical trials and increasing caregiver programming. Suggested opportunities for growth included programming across time zones, facilitating geographic connections, and partnering with other MBC advocacy organizations. Conclusions: Patient-led and curated virtual communities are filling substantial gaps in survivorship care for individuals with metastatic breast cancer. Through its virtual format, the Project Life wellness community has a widespread reach and offers a promising model for intentionally curated metastatic survivorship care. The unique virtual format of Project Life should spark creativity in how quality survivorship care for people with MBC can be delivered. Healthcare settings including cancer centers can play a larger role in connecting people with MBC to external support organizations to better ensure survivorship needs are being holistically met.

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Monitoring for cardiotoxicity in early breast cancer: an Australian experience

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Background Breast cancer is the most commonly diagnosed cancer in Australia. Patient outcomes continue to improve with current 10 year survival of 86%. Given this, greater focus is needed to minimise potential long term toxicities of prescribed therapies. Anthracyclines and HER2 targeted therapies are commonly prescribed agents for high risk early breast cancers and are associated with acute and long term cardiotoxicity. Despite this, screening of cardiotoxicity in Australian patients receiving these therapies remains variable due to a lack of endorsed national screening guidelines. We conducted a retrospective review of screening procedures for cardiotoxicity in 2 major oncology centres in metropolitan Sydney and compared the findings to current international recommendations from ASCO/ESMO guidelines. Methods Patients were included if they received doxorubicin, epirubicin or trastuzumab with neoadjuvant or adjuvant intent during 2021. Baseline patient and tumour characteristics including cardiovascular risk factors were reviewed. Baseline ECG, transthoracic echocardiogram (TTE) or cardiac biomarkers (cardiac troponin or brain natriuretic peptide) were recorded, as well as frequency of serial monitoring and incidence of cardiotoxicity and cardiology referrals. Results 111 patients receiving initial curative therapy were included of which 45 received anthracycline therapy without trastuzumab. 66 received trastuzumab of which 34 also received anthracycline. 38 patients were aged greater than 60 and 31 had 2 or more cardiovascular risk factors. Of the patients receiving anthracycline only, 96% had a baseline TTE. All patients receiving trastuzumab only had a baseline TTE and of the 34 patients who received anthracycline and trastuzumab 3 did not undergo baseline TTE but underwent one prior to commencing trastuzumab. 3 patients total had a baseline ECG. No patients had baseline biomarkers measured. Only 5 patients had biomarkers measured at 1 year and all 5 had developed grade 1 heart failure on treatment. These 5 patients were referred for cardiology review and 2 required an interruption of trastuzumab. All patients receiving trastuzumab underwent 3 monthly TTEs on treatment. Of the 35 patients now more than 1 year post treatment completion, only 3 patients had a TTE at 12 months. No patients referred to cardiology have reached 12 months post treatment. Discussion International guidelines recommend screening to identify and treat early cardiotoxicity and prevent long term morbidity. ASCO and ESMO guidelines both recommend patients receiving anthracycline undertake a TTE at baseline and at 6-12 months after completing therapy. Both recommend 3 monthly TTEs for patients receiving trastuzumab. The ESMO guidelines recommend a baseline ECG and consideration of further TTE at 2 years post therapy. For high risk patients the ASCO guidelines discuss offering routine TTEs during treatment. The ESMO guidelines recommend measurement of cardiac biomarkers for patients receiving anthracycline prior to each cycle and routine monitoring can be considered for patients receiving anti HER2 therapy. The ASCO guidelines reserve use of cardiac biomarkers...
for patients who develop signs or symptoms of cardiac dysfunction. Our study demonstrates that while baseline cardiac assessment is well performed a personalised approach to cardiac monitoring during curative therapy is not. These were unexpected findings given both treatment units are located in well resourced areas of Sydney. An outcome of this study has been the development of a cardio-oncology group within our oncology and cardiology departments. This has led to the development of new clinical guidelines to screen and manage high risk breast cancer patients receiving cardiotoxic therapies. This has empowered patients, care coordinators and physicians to proactively manage cardiac risks from therapy and we hope these institutional guidelines will be adopted nationally.

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A novel free-to-use software for upper limb volume quantification in breast cancer related lymphedema: implementing cutting-edge technology in the individualized therapeutic approaches of breast cancer survivors

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BACKGROUND: Breast cancer related lymphedema (BCRL) is a detrimental condition affecting a growing number of breast cancer (BC) survivors worldwide [1]. Effective screening programs and early diagnosis are mandatory in the clinical management of this disabling condition and limb volume assessment plays a crucial role [1]. However, a reproducible volumetric assessment is still challenging in clinical practice. In this scenario, augmented reality tools have been recently proposed for volumetric quantification of BCRL [2]. Despite the advantages in safety and time effectiveness, the integration of these devices in clinical practice is affected by several barriers, and free-to-use software for volume quantification are still lacking [3]. Therefore, the aim of this study was to develop and validate a free-to-use software for volume quantification of BCRL in order to overcome barriers to technology implementation in the complex management of BC patients.

METHODS: A cohort of mixed-gender young adults was assessed by tridimensional laser scanning, centimetric method, and water displacement method. The upper limb volume measures were saved and processed using a software package composed of three programs (Edit 3D, Slice 3D, Cut 3D). The novel software package was specifically developed and freely released on the online site https://mn-visions.gitbook.455io/software-kit-for-3dls-limb-volume-quantification/. In addition, hand volume has been assessed two groups (experimental group and optimization group). Digital volume quantification algorithms have been specifically designed using the gift wrapping (GW) or cubic
tessellation (TE) method. The novel software package was subsequently used to assess a small pilot sample of BCRL patients. The upper limb volumes were analyzed to assess linear regression and correlation, level of agreement, and consistency between the different methods.

RESULTS: Forty upper limb volumes of 20 participants were assessed in the present study. The linear regression analysis showed a statistically significant correlation between laser scanning method and centimetric method (R² = 0.99, p< 0.0001). A high level of agreement was reported (R² interval from 0.93 to 0.97, r ranged from 0.965 to 0.984) between the centimetric method and the novel software package. Hand volume has been assessed in 5 subjects (experimental group). The optimization group (n: 4) demonstrated that the hand volumes calculated from digital method (tessellation method) show a high correlation with the values obtained with water displacement.

were recently assessed (n:3) and suggested a high correlation between LS3D and centimetric method (R²= 0.96). CONCLUSION: Our data underlined promising results for the implementation in clinical setting of the three programs Edit 3D, Slice 3D, Cut 3D for the upper limb volume quantification. In addition, significant correlations between water displacement method (gold standard) and hand digital volume method were highlighted, suggesting intriguing implications in a precise quantification of hand volume in clinical setting. These findings might provide advantages in reproducibility between different operators enhancing data sharing between different centers. Future data on BCRL patients are needed to confirm the role of this novel free-to-use software in the rehabilitation management of breast cancer survivors.


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Neoadjuvant hormonal therapy plus palbociclib versus hormonal therapy plus placebo in women with operable, hormone sensitive and HER2-negative primary breast cancer

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Background: Early biologic response to endocrine therapy, such as changes in Ki67 labeling index (LI), has been suggested to predict long-term outcomes in hormone sensitive breast cancer. The addition of a CDK4/6 inhibitor to endocrine therapy has been shown to augment biological response in breast cancer. Pre-operative Endocrine Prognostic Index (PEPI) scores, generated based on post-treatment Ki67 LI, have been shown to predict patient outcomes.
EndoPredict® is a multigene assay that predicts the risk of distant recurrence in patients with operable estrogen receptor (ER)-positive HER2-negative breast cancer. This study was conducted to evaluate the efficacy of the neoadjuvant endocrine therapy plus palbociclib versus neoadjuvant endocrine therapy plus placebo. Patients and Methods: This is a phase III randomized, double-blind study of neoadjuvant hormonal therapy plus palbociclib versus neoadjuvant hormonal therapy plus placebo in untreated pre/peri- and post-menopausal women with operable, hormone receptor-positive (ER and/or progesterone receptor), HER2-negative breast cancer. Patients were randomly assigned 1:1 to receive 16 weeks of hormonal therapy plus palbociclib or hormonal therapy plus placebo. Hormonal therapy consisted of letrozole for post-menopausal patients and tamoxifen plus LH-RH agonist for pre/peri-menopausal patients. The co-primary endpoints included PEPI score and EPclin Risk Score, a score combining EndoPredict® molecular score with clinical factors. These scores were sequentially analyzed on a modified intent-to-treat basis according to the gatekeeping procedure: if statistical significance was detected on the PEPI score, the statistical significance of EPclin Risk Score would be assessed. The sample size was 100 patients in each arm, which was calculated with < 5% type I error rate (two sided) and 80% power. Results: Between 16 July 2019 – 7 July 2021, 141 eligible patients were randomized from 25 participating institutes in Japan, Korea, Taiwan, Hong Kong and Australia. One hundred twenty-six patients completed the treatment duration and surgical samples were collected to evaluate endpoints. All randomized patients were evaluable for safety assessment. Randomization was well-balanced in terms of age, menopausal status and cancer stage. The proportion of patients who had a low, moderate, or high PEPI score was 15.2%, 50.0% and 34.8% in the hormonal therapy plus palbociclib arm and 13.3%, 55.0% and 31.7% in the hormonal therapy plus placebo arm, respectively. There was no statistically significant difference in PEPI score between two arms (one-sided p-value=0.563). The proportion of patients who had a high risk EPclin Risk Score seemed lower in the palbociclib arm than in the placebo arm (62.1% vs 68.3%) although hypothesis testing was not performed on EPclin Risk Score because statistical significance was not detected on the PEPI score. No new safety signals were found in the study. Permanent discontinuation from the study in association with adverse events was reported for 7 (9.7%) patients in the hormonal therapy plus palbociclib arm and for 0 patients in the hormonal therapy plus placebo arm. Conclusions: The addition of palbociclib to neoadjuvant hormonal therapy did not improve efficacy measured by PEPI score. In palbociclib arm, the rate of patients who had a high risk EPclin Risk Score after treatment was lower than in placebo arm. Translational researches are ongoing to analyze molecular changes by treatments. The role of chemotherapy after neoadjuvant therapy is under investigation. Clinical trial identification: NCT03969121 Funding: Pfizer Inc.

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BACKGROUND: Neoadjuvant Endocrine Therapy (NET) is seldom used in breast cancer management except in patients with several comorbidities or in elderly patients in which chemotherapy is not an option. Clinical response with NET is not typically achieved until after several months of treatment. In the NET setting, reduction of Ki67 (< 10%) after 2-4 weeks has
been used as a predictor of positive response, but studies such as ALTERNATE have questioned this association. It remains uncertain whether a single gene or protein can adequately predict outcomes or inform how NET alters a variety of cancer genes and global tumor biology. This study evaluated the effect of short-term NET on the tumor genomics of patients with early-stage breast cancer (EBC) by comparing whole transcriptome gene expression changes in matched pre- and post-NET tumor samples. METHODS: In this single-institution FLEX substudy performed at Johns Hopkins, patients (n=30) with matched pre- and post-treatment specimens who received at least two weeks of NET between 2019 – 2021 were included. Premenopausal and male patients with breast cancer received Tamoxifen (n=10) and postmenopausal women received either Letrozole (n=10) or Exemestane (n=10). Limma R package was used for quantile normalization and differential gene expression analysis. Significant differentially expressed genes (DEGs) had a false discovery rate of < 0.05 and >2-fold change. Pathway enrichment analysis was performed using Reactome. For patients with available clinical information, changes in immunohistochemistry (IHC) between pre- and post-NET were quantified using absolute values, and the median percent change was reported, with significance assessed using the Wilcoxon test. The observational FLEX trial (NCT03053193) enrolls patients with EBC who have MammaPrint (MP) with or without BluePrint testing and consent to clinically annotated full transcriptome data collection. MammaPrint classifies tumors as having a Low Risk (LR) or High Risk (HR) of distant recurrence. BluePrint is a molecular subtyping assay, and together with MammaPrint, tumors are classified as Luminal A-Type (MP LR), Luminal B-Type (MP HR), HER2-Type, or Basal-Type. RESULTS: Transcriptional profiles between pre- and post-NET samples were distinct with short-term NET inducing 774 DEGs. The majority of significant DEGs (n=748) such as MGAT1, IQGAP3, and PRC1, which are associated with tumor aggressiveness and metastasis, were downregulated in post-NET samples. Upregulated genes in post-NET tumors, such as FOS, JUN, and EGR1, are involved in estrogen signaling and NF-κB pathways, which may be more informative when combined with a single IHC biomarker (ER/PR/Ki67). CONCLUSIONS: In this study, significant gene expression changes were discovered within a shorter timeframe than when clinical responses are usually observed in the NET setting. This could indicate biological complexity and diverse response pathways, which may be more informative when combined with a single IHC biomarker (ER/PR/Ki67). Results from this study should be confirmed using a larger cohort. Future studies will determine the significance of these DEGs and their impact on outcomes, and will further define gene expression changes by endocrine therapy type (tamoxifen versus aromatase inhibitors). ACKNOWLEDGMENTS: We would like to thank Lynn and Robert Downing for their generous support of our study.

Disclosure(s):
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Purpose: Neoadjuvant endocrine treatment (NET) has become a useful tool for the downstaging of luminal-like breast cancers in postmenopausal patients. It enables us to increase breast conserving surgery (BCS) rates and provides an opportunity for assessing in vivo NET effectiveness and studying any biological changes that may act as valid biomarkers. The purpose of this study was to evaluate the effectiveness of NET as well as to assess the role of Ki67 proliferation rate changes as an indicator of endocrine responsiveness.

Methods: From June 2016 to January 2022, a single-institution cohort of patients treated with NET was performed after four weeks. Information regarding histopathological and clinical changes, as well as surgical management, was gathered.

Results: A total of 168 estrogen receptor positive (ER+)/HER2 negative patients were included. The median age at than pretreatment size measured by ultrasound (p<.0001), showing an inverse linear relationship surgical sample (p< 0.0001). Other significant downgrading changes were observed with respect to tumor grade (p< 0.0001) and progesterone receptor (PR) expression (p< 0.0001). BCS was performed on 145 patients (86.3%). One case of pathological complete response was recorded. A larger Ki67 fold-change after four weeks was significantly related to a PEPI score
of 0 (p< 0.002). No differences were observed between luminal A- and B-like tumors with regard to fold-change and PEPI score. No treatment abandonment was produced during the study.

Conclusions: In our cohort, NET has proven effective for tumor size and Ki67 downstaging. This results in a higher rate of conservative surgery, aids in therapeutic decision-making, provides prognostic information, and constitutes a safe and well-tolerated approach.

Biological changes after NET

<table>
<thead>
<tr>
<th>Differences</th>
<th>Pre-NET / Pathological</th>
<th>Pre-NET / Intermediate</th>
<th>Intermedial / Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (g)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Estrogen Receptor Expression (g)</td>
<td>&lt;0.02</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Progestin Receptor Expression (g)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Ki67 (g)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>nd</td>
</tr>
<tr>
<td>Histological Grade</td>
<td>&lt;0.0002</td>
<td>&lt;0.0001</td>
<td>&lt;0.0002</td>
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Patient and tumor characteristics
<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>(n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>66 (39.3)</td>
</tr>
<tr>
<td>IIA</td>
<td>70 (41.7)</td>
</tr>
<tr>
<td>IIB</td>
<td>24 (14.3)</td>
</tr>
<tr>
<td>IIIA</td>
<td>8 (4.8)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clinical N stage</th>
<th>(n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>94 (81.7)</td>
</tr>
<tr>
<td>cN1</td>
<td>21 (18.3)</td>
</tr>
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<table>
<thead>
<tr>
<th>Histological type</th>
<th>(n/%)</th>
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<tbody>
<tr>
<td>Ductal</td>
<td>125 (74.4)</td>
</tr>
<tr>
<td>Lobular</td>
<td>31 (18.5)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (7.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological grade</th>
<th>(n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>31 (18.5)</td>
</tr>
<tr>
<td>G2</td>
<td>112 (66.7)</td>
</tr>
<tr>
<td>G3</td>
<td>25 (14.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>(n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 (18)</td>
</tr>
</tbody>
</table>

| Pre-NET ER expression (%) | 100 (0) |
| Pre-NET PR expression (%) | 70.0 (80) |
| Pre-NET Ki67 (%)         | 20.0 (18) |

Disclosure(s):

Covadonga Marti, MD PhD: No financial relationships to disclose
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Marcos Meléndez, n/a: No financial relationships to disclose
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Efficacy of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy in pre-menopausal patients with hormone-responsive and HER2-negative, lymph node-negative breast cancer.

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Background: Neoadjuvant endocrine therapy (NET) has demonstrated efficacy in post-menopausal patients with hormone-responsive and her2-negative breast cancer. This trial was designed to compare the efficacy of neoadjuvant chemotherapy (NCT) with NET in pre-menopausal patients with hormone-responsive, her2-negative and lymph node-negative breast cancer.

Materials and Methods: In this prospective, randomised study, pre-menopausal patients with hormone-responsive, her2-negative and lymph node-negative breast cancer were recruited. Enrolled patients were randomly assigned (1:1) to receive either NCT or NET with goserelin and tamoxifen, followed by goserelin and anastrozole. The primary purpose was to evaluate the non-inferiority of NET compared to NCT using clinical response, assessed by ultrasound.

Results: A total of 68 patients were assigned to receive NCT (n = 31) or NET (n = 37). The clinical response rate was 16.1% for NCT and 35.1% for NET (estimated difference 19%, 95%CI: -1.1% - 39.1%, non-inferior p = 0.002). Rates of breast-conserving surgery were similar between NCT and NET (90.3% vs 83.8%, p=0.494).

Conclusions: The clinical response rate of NET is non-inferior to NCT in pre-menopausal patients with hormone-responsive, HER2-negative, lymph node-negative breast cancer.

Summary of ultrasound clinical response
The breast surgery and MP grading system

<table>
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<tr>
<th></th>
<th>Chemotherapy</th>
<th>Endocrine therapy</th>
<th>p</th>
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<tbody>
<tr>
<td>N=31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast surgery</td>
<td></td>
<td></td>
<td>0.494</td>
</tr>
<tr>
<td>BCS</td>
<td>28(90.3%)</td>
<td>31(83.8%)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>3(9.7%)</td>
<td>6(16.2%)</td>
<td></td>
</tr>
<tr>
<td>MP grading system</td>
<td></td>
<td></td>
<td>0.445</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>9(29.0%)</td>
<td>14(37.8%)</td>
<td></td>
</tr>
<tr>
<td>Grade 3-5*</td>
<td>22(71.0%)</td>
<td>23(62.2%)</td>
<td></td>
</tr>
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Disclosure(s):
chongshan gu, n/a: No financial relationships to disclose
yingjian he, n/a: No financial relationships to disclose
jinfeng li, n/a: No financial relationships to disclose
tianfeng wang, n/a: No financial relationships to disclose
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A phase II, single-arm study of histone deacetylases inhibitor Tucidinostat and Exemestane as neoadjuvant therapy in patients with hormone receptor positive HER2 negative breast cancer (NeoTEE trial)

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Background: Tucidinostat (formerly known as chidamide) plus exemestane is approved for postmenopausal patients with advanced, hormone receptor-positive breast cancer. We evaluated the efficacy and safety of tucidinostat plus exemestane as the neoadjuvant strategy in hormone receptor-positive early breast cancer patients. Methods: NeoTEE is an open-label, single-center, phase II study. Patients with HR-positive, HER2-negative and stage II/III breast cancer were enrolled at the First Affiliated Hospital of Sun Yat-sen University. Eligible patients received 25 mg oral exemestane once daily for 2 weeks followed by 30 mg oral tucidinostat twice weekly in combination with 25 mg oral exemestane once daily for 24 weeks. GnRHa was used for premenopausal patients. Endpoints assessed here included objective response rate (ORR), complete cell cycle arrest (CCCA, Ki-67 ≤ 2.7%) at surgery, disease control rate (DCR), pathological complete remission (pCR) and safety. Results: Between July 2020 and July 2022, 26 patients were enrolled, of whom 24 were evaluable for response per RECIST 1.1 criteria. Partial response (PR) was observed in 18 patients, with an ORR of 75% (18/24). The DCR was 100%. Of the 14 patients with surgery, one patient achieved pCR and 8 patients were exempt from postoperative adjuvant chemotherapy. CCCA at surgery was 64.3% (9/14). The follow-up remains ongoing and updated results will be presented thereafter. Most adverse events (AEs) were grade 1 or 2. Grade 3 AEs occurred in 8 of 26 patients, the most common were neutropenia 19.2%, leukopenia 7.7%, anemia 3.8%, ALT increased 3.8%, pneumonitis 3.8%. Only 1 patient experienced grade 4 neutropenia. Grade 3/4 neutropenia recovered after dose
reduction or discontinuation of tucidinostat. No patient received G-CSF. Conclusions: Tucidinostat combined with exemestane was well tolerated and demonstrated meaningful responses in neoadjuvant setting for women with early HR+/HER2- breast cancer. Further investigation is warranted. Clinical trial information: NCT04465097.

Disclosure(s):
- zhen shan, MD • PhD: No financial relationships to disclose
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- xiaoling zhang, MD • PhD: No financial relationships to disclose
- huijuan shi, MD • PhD: No financial relationships to disclose
- yanling zheng, MD • PhD: No financial relationships to disclose
- jia luo, MD • PhD: No financial relationships to disclose
- tiantian zhen, MD • PhD: No financial relationships to disclose
- ruping chen, assistant: No financial relationships to disclose
- Ying Lin, n/a: No financial relationships to disclose
Phase 2 study of anlotinib combined with taxanes and lobaplatin in the neoadjuvant treatment of triple-negative breast cancer: efficacy, safety and biomarker analysis from the SWH-B006 (neoALTALL) trial

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Yi Zhang, n/a, Professor - Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University
Background: Anlotinib, a novel multi-target tyrosine kinase inhibitor that effectively inhibits VEGFR, PDGFR, FGFR, c-KIT, c-MET, and RET, monotherapy has been proven effective in HER-2 negative metastatic breast cancer, but its efficacy in early-stage triple-negative breast cancer (TNBC) is unknown. This phase 2 study aims to evaluate the efficacy and safety of adding anlotinib to neoadjuvant chemotherapy in patients (pts) with primary TNBC.

Methods: Pts with clinical stage II/III TNBC were to be treated with 5 cycles of anlotinib (12mg, d1-14, q3w) plus 6 cycles of taxanes (docetaxel 75 mg/m2 or nab-paclitaxel 125 mg/m2, d1 and d8, q3w) and lobaplatin (30 mg/m2, d1, q3w), followed by surgery. The primary endpoint was pathological complete response (pCR) in the breast and axilla (tpCR; ypT0/is ypN0) and the secondary endpoints include pCR in the breast (bpCR; ypT0/is), event-free survival (EFS), invasive disease-free survival (iDFS), overall survival (OS), and safety. Exploratory study included biomarker analysis and efficacy comparation based on FUSCC classification (IHC-based).

Results: From Jan 2021 to Feb 2022, a total of 24 pts were enrolled. The median age was 50 years (range, 26-64), 54% were postmenopausal, 75% were nodal involved, 29% had stage III, and 79% were Ki-67 high (≥30%). At the data cut off time of 30th Jun 2022, all 24 pts received at least one dose of study treatment and underwent surgery. Overall, 21 pts received five courses of anlotinib. Two pts discontinued anlotinib for safety reason, and one pt discontinued anlotinib due to missed dose in cycle 4. After surgery, 14 out of 24 pts achieved a tpCR (58.3%; 95% CI, 36.6%–77.9%), and the bpCR rate was also 58.3% (14/24). Of the 18 pts with the node-positive disease at diagnosis, 15/18 (83.3%) became ypN0. Based on the FUSCC IHC-based subtypes, the tpCR rates were 66.7% (6/9) for BLIS subtype, 80% (4/5) for IM subtype and 0% (0/4) for LAR subtype, respectively. Next-generation sequencing revealed that the most commonly mutated genes in these pts were TP53 (19/21, 90.5%), MYC (7/21, 33.3%), BRCA1 (5/21, 23.8%), PIK3CA (4/21, 19.0%), BCL2L11 (4/21, 19.0%), and RB1 (3/21, 14.3%). Subgroup analysis showed that the tpCR were 71.4% (5/7) and 42.9% (6/14) in MYC-amplified and wild-type pts, respectively, and 80% (4/5) and 43.8% (7/16) in BRCA1-mutated and wild-type pts, respectively. All of 24 pts in the safety population showed at least one treatment emergent adverse events (TEAEs). Grade 3 or 4 TEAEs occurred in 14 pts (58.3%), and the most common events were leucopenia (29.2%; n=7), neutropenia (29.2%; n=7), thrombocytopenia (20.8%; n=5), anemia (16.7%; n=4), hypertension (12.5%; n=3), and oral mucositis (8.3%; n=2), respectively. No treatment-related deaths occurred.

Conclusions: The addition of anlotinib to neoadjuvant chemotherapy showed manageable toxicity and promising antitumor activity for pts with early-stage TNBC. The study is still ongoing, and the enrollment has been completed. Clinical trial information: ChiCTR2100043027. Funding: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. L.
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<td>All patients (N=24)</td>
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</tr>
<tr>
<td>tpCR (ypT0/is, ypN0)</td>
<td>14/24</td>
<td>(58.3%)</td>
<td>36.6%–77.9%</td>
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<td>bpCR (ypT0/is)</td>
<td>14/24</td>
<td>(58.3%)</td>
<td>36.6%–77.9%</td>
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<tr>
<td>Lymph node positive (N=18)</td>
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<tr>
<td>apCR (ypN0)</td>
<td>15/18</td>
<td>(83.3%)</td>
<td>58.6%–96.4%</td>
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<tr>
<td>FUSCC IHC-based subtypes (N=18)</td>
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<td>BLIS subtype</td>
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Epithelial-Mesenchymal Plasticity is Regulated by Inflammatory Signaling Networks Coupled to Cell Morphology

Presenting Author(s) and Co-Author(s):
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Purpose: During development and homeostatic processes such as wound repair, certain cells undergo a remarkable process where they radically transform in cell shape and state, from epithelial to mesenchymal cells. This ability is referred to as 'Epithelial-Mesenchymal Plasticity' (EMP), triggered by both mechanical (i.e. loss of cell-cell contact) and soluble cues (i.e. TGFβ), and is absolutely essential in both embryonic and adult organisms. Dysregulation of EMP also occurs in cancer; where tumor cells undergo EMP to become metastatic, stem-like, and drug resistant. Critically, increased EMP correlates with increased cancer severity. However, it is largely a black box as to how EMP is regulated and how epithelial cells sense physical, geometrical, and soluble cues in their environment to assume a mesenchymal fate. This work inferred that cell shape is a determinant of not only fates – but of long-term outcomes. That is, we provide mechanistic explanations between cell context, environment, and cancer severity. In this work, we investigated how mechanical and soluble cues are coupled to the dynamics of signaling pathways that regulate transcriptional and post-transcriptional events that underpin EMP. Especially with regards to mechanical cues, we attempt to unlock the 'black box' as to how changes in adhesion, ECM (Extracellular Matrix) stiffness, and environment geometry are coupled to the transcriptional events that drive EMP. Results: We show that changes in cell and nuclear shape result from the actions of the cytoskeleton and important drivers of EMP in upregulating ‘interlocking’ networks that promote EMP-driving inflammation and suppressing insulin signaling. Using a combination of cell biology, proteomics, and new statistical methods, we provide a systems biology model demonstrating: Cell shape → MT bound Kinesin-1 activity and nuclear shape → inflammation (IKK, JNK), insulin signaling (IRS), and YAP/TAZ → EMP. Our work connects observable changes in phenotype to causal changes in signaling network architecture and cell fates. We used an integrative -omic approach to analyze tumors from breast cancer patients. We identified a novel tumor suppressor – JAM3 – whose loss is associated with altered nuclear shape in vivo, inhibiting JAM3 in cells, or stimulation with canonic microtubules and alters nuclear shape. During EMP we observe there is upregulation of a pro-inflammatory, insulin resistant, signaling network that is predictive of mesenchymal states of Kinesin-1 motors. This rescue is explained by changes in inflammatory and insulin signaling. We show that while Kinesin-1 activity is responsible for upregulation in canonical signalling and network ‘hubs’, changes in nuclear shape upregulate ‘effectors’ of these hubs. Thus, microtubules and nuclei differentially regulate different parts of ‘interlocking’ networks. Conclusions: This work has integrated image-omics, comprehensive global proteomics, and quantitative cell biology to provide a mechanistic –and systems-level understanding of how epithelial cells differentiate into mesenchymal forms during disease development and progression. This work is of major significance for three reasons. First, it shows how cell shape can mechanistically regulate cell fates on an unprecedented systems-level. Second, we identify an EMP network that is conserved across cancers and may indeed be conserved across both normal and diseased mesenchymal cells. Indeed, we speculate that different types of diseased
cells may all share the same network. Finally, we introduce the concept of interlocking networks – where hubs and effectors are regulated by different cellular components. Our work has been extensively validated, using chemical and genetic approaches and in vivo model of in human breast cancer.

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Zheng Yin, PhD: No financial relationships to disclose
WITHDRAWN
Knockdown of TMEM45A regulates malignant progression of triple-negative breast cancer by inhibiting TGF-β/Smad signaling pathway-mediated EMT

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  Country: United States
- Shengchun Liu, n/a, Prof. - Chongqing Medical University
  Country: United States

Objectives: The incidence of breast cancer has jumped to first place in the global malignant tumor. As an essential component of the TMEM family, TMEM45A is abnormally highly expressed in some malignant tumors, and plays a role in promoting and regulating the occurrence and development of tumors. This study analyzed the expression of TMEM45A in breast cancer tissues and breast cancer cell lines, and explored the relationship with clinical subtypes. To examine the effects of TMEM45A on TNBC cell proliferation, migration, invasion and other biological functions, and to preliminarily clarify the molecular mechanism of TMEM45A regulating the epithelial-mesenchymal transition of TNBC cell lines. Methods: 1. Download and analyze the TCGA database, analyze the difference in the expression of TMEM45A in normal breast tissue and different subtypes of breast cancer tissue, and detect the protein expression level of TMEM45A in 8 pairs of cancer tissues and adjacent tissues by western blot experiment. 2. Detection of TMEM45A protein expression in normal breast epithelial cell line MCF 10A and five breast cancer cell lines (MCF-7, MDA-MB-231, BT-549, MDA-MB-468, SK-BR-3) by western blot experiment. 3. Using small interfering RNA technology to down-regulate the protein expression levels of MDA-MB-231 and BT-549 TNBC cell lines with relatively high TMEM45A expression. The changes in cell proliferation ability were detected by CCK8 assay and clone formation assay, and the changes in cell migration ability and invasion ability were detected by wound healing assay and transwell assay, respectively. 4. After down-regulating TMEM45A in two TNBC cell lines, the expression changes of epithelial cell phenotype marker E-cadherin, mesenchymal phenotype marker N-cadherin, Vimentin, and critical molecules in TGF-β/Smad signal transduction pathway (TGFβ1, Smad2, Smad3, p-Smad2, p-Smad3) were detected by western blot experiment. Results: 1. Based on the TCGA database, the results showed that the expression level of TMEM45A mRNA in breast cancer was significantly higher than in normal breast tissue. The expression level of TMEM45A mRNA in any breast cancer subtype was higher than that in normal breast tissue, and it was the highest in the TNBC subtype. In the results of western blot experiments of clinical breast cancer specimens, the expression of TMEM45A in breast cancer tissues was significantly higher than that in the corresponding adjacent tissues, which further confirmed the reliability of the results of the TCGA database. 2. In normal breast epithelial cell line MCF10A and five breast cancer cell lines, MCF10A has the lowest expression level of TMEM45A protein. Among the five breast cancer cell lines, MDA-MB-231 had the highest expression of TMEM45A, followed by BT-549. 3. CCK8 assay, clone formation assay, wound healing assay and transwell assay showed that down-regulating TMEM45A protein levels in the two TNBC cell lines could significantly reduce cell proliferation, migration and invasion abilities. 4. After down-regulating TMEM45A protein levels in two TNBC cell lines, EMT-related indicators E-cadherin protein expression levels increased, N-cadherin and Vimentin protein expressions decreased, and the expression levels of essential protein molecules Smad2 and Smad3 in the TGF-β/Smad pathway did not change significantly, while p-Smad2, p-Smad3 and TGF-
expressions decreased. Conclusions: TMEM45A is relatively highly expressed in breast cancer tissues and cell lines, especially in the subtype of TNBC. Down-regulation of TMEM45A expression can inhibit the proliferation, migration and invasion of TNBC cell lines. Mechanistically, TMEM45A may reverse EMT by inhibiting the activity of the TGF-
pathway.

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Differentially expressed genes and their pathways in breast cancer patients with mesenchymal CTC.

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Background: Circulating tumor cells (CTC) with phenotype of epithelial-mesenchymal transition (CTC_EMT) represent novel subpopulation of CTC associated with inferior outcome in primary breast cancer (PBC). However, molecular characterization of primary tumors associated with this CTC subpopulation is lacking. The aim of this study was to identify signaling pathways associated with presence of CTC_EMT in PBC patients using a comprehensive genomics approach. Methods: This translational study included 17 patients with PBC and 5 donors of normal breast tissue. CTC_EMT were detected before surgery by quantitative RT-PCR assay for expression of epithelial-mesenchymal transition (EMT) genes (TWIST1, SNAIL1, SLUG, ZEB1). Total RNA was extracted, in parallel, from fresh frozen primary tumor and whole-trancriptome profiles were obtained using RNA sequencing and additionally mRNAs profiles by microarray. Genes expressions were further validated by qRT-PCR. Results: Analyzing RNA sequencing and microarray data, we found set of genes differentially expressed in absence or presence of CTC_EMT in PBC. We identified 157 genes differentially expressed in CTC_EMT phenotype compared to patients with non-detectable CTC. Namely, keratin family is represented by genes KRT5, KRT14, KRT17. Gene ontologies related to membrane structure...
or communication and immunology appears to be involved in CTC-related processes, pathways related to cell junction and various signaling pathways including PI3K and Ras-signaling appear to be significant in processes leading to CTC EMT presence. Conclusions: We suspect multiple genes of having a role in primary tumour processes leading to CTC EMT production in breast cancer patients. Data suggest, that PI3K & Ras-signalling and pathways related to cell junction are the key pathways for changes inside of primary tumour tissue between CTC EMT and CTC-phenotype of breast cancer patients. We propose, additional study with single-cell resolution is needed for better understanding of the processes.

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Draft Proposal
Title: MUTYH In A Cancer Population
Author: Linda Ann Smith

Background:
Germline genetic testing has become a critical quality point in caring for breast cancer patients and high risk patients. Originally testing panels were extremely limited, but now expanded hereditary cancer testing panels are more common and have raised the question of other genes being linked to cancer risk. In this cohort, we examine the prevalence of the gene mutation MUTYH in a high risk population tested with expanded panels.

Method:
Patient data was obtained from an IRB-approved multi-center longitudinal, observational study, in which 2276 patients underwent expanded (>9 gene) germline genetic testing and also contributed personal and family history of cancer information. The average age in this cohort was 58.58 years old, with 2197 (96.53%) Female and 1762 (77.43%) with a personal cancer diagnosis and 1625 (71.40%) with a family history of cancer. Germline genetic tests were lab agnostic and tested an average of 73.2 genes (1214 or 53% tested with 85 gene panel) and a range of 9-85 genes tested.

Results:
Overall, the patients had a 16.70% positivity rate for pathogenic germline result of genetic test, with 42 (1.85%) reporting a Monoallelic MUTYH pathogenic variant (PV) result. Of those reporting a MUTYH PV, the average age was 58.48, with 40 (95.24%) females and 35 (83.33%) with a personal cancer diagnosis and 32 (76.19%) with a family history of cancer. Those patients with and without a personal and family history of cancer were compared, and found that a personal history of cancer has a very significant difference in MUTYH PV rate (9.56e-6) while family history of cancer does not have a significant difference (0.496). In the patients with a MUTYH PV and a diagnosis of cancer, 31 (88.57%) had a breast cancer diagnosis and only 1 (2.86%) had a colorectal cancer diagnosis - 73.81% and 2.38% of all MUTYH carriers. Of the 32 patients who had information about their family cancer diagnoses, there were 27 patients with multiple diagnoses and only 5 with a single family diagnosis, with 116 total family members with reported diagnosis. There were 44 breast cancer diagnoses in 23 of the MUTYH PV carriers' families, which is 71.88% of all patients with family cancer information and 54.76% of all MUTYH PV carriers. There were 6 colorectal cancer diagnoses in 6 of the MUTYH PV carriers’ families, which is 18.75% of all patients with family cancer information and 14.29% of all MUTYH PV carriers.

Conclusions:
Our findings match with other reported cancer cohorts (on the order of 1-2%, Thompson et al). Monoallelic MUTYH has a significant association with both personal history of cancer. These findings suggest that patients with a personal and or family history of cancer should consider expanded gene panel testing which includes MUTYH.

Disclosure(s):
Linda Ann Smith, MD: No financial relationships to disclose
Germline variants detected by next-generation sequencing-based multigene panel testing in patients with suspected hereditary breast cancer at a University Hospital in Japan

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Background: The usefulness of prophylactic surgery and surveillance for hereditary breast cancer has been demonstrated, and germline testing for BRCA1 and BRCA2 had been covered by insurance since 2020 in Japan. In addition to BRCA1 and BRCA2, several other genes are also associated with an increased risk of developing breast cancer, such as PALB2, ATM, BARD1, CHEK2, PTEN, and TP53. Next-generation sequencing-enabled multigene panel testing provides information about these gene variants at the same time, and at a low cost. Although germline testing of BRCA1 and BRCA2 has become widespread in Japan, multi-panel gene testing for germline variants has been conducted only in a limited number of facilities, partly due to the difficulty associated with dealing with the gene variant information obtained from the test. The aim of this study was to clarify the current status of multigene panel testing in our institute, and reveal the characteristics of the variants detected in patients with, or predisposed to, hereditary breast cancer. Methods: This retrospective study included 37 individuals who underwent next-generation sequencing-based multigene panel testing in order to investigate any inherited genetic variants due to a suspicion of hereditary breast cancer. Eighteen patients had a diagnosis of breast cancer with a family history of breast and/or ovarian cancer, nine patients had a diagnosis of breast cancer without family history of breast or ovarian cancer, and 10 patients had a family history of breast cancer but had not developed breast cancer themselves. Results: Utilizing mutigene panel testing, at least one alteration was found in 24 genes, and a total of 39 variants were found in the 37 patients. Of these 37 patients, nine (24.3%) had a pathogenic/likely pathogenic variant with or without other variants of uncertain significance (VUS), 15 (40.5%) had VUS, and 13 (35.1%) had negative genetic test results. Among the nine patients with pathogenic/likely pathogenic variants, seven had variants in either BRCA1 or BRCA2 (one BRCA1 pathogenic variant, five BRCA2 pathogenic variants, and one BRCA2 likely pathogenic variant), while the remaining positive results were attributed to other genes (one MLH1 pathogenic variant, and one SDHB pathogenic variant). VUS included BRCA1 and BRCA2, as well as other breast cancer-associated genes, such as ATM (n=2), CDH1 (n=2), NF1 (n=2), PALB2 (n=1), CHEK2 (n=1), NBN (n=1), and RAD51D (n=1). VUS also included other cancer syndrome-related genes, such as MLH1 (n=2), MUTYH (n=2), APC (n=1), and RET (n=1). Conclusion: Multigene panel tests in our institute revealed pathogenic/likely pathogenic variants in 24.3% of individuals who suspected hereditary breast cancer.
cancer. As expected, multigene panel tests also revealed more VUS than pathogenic variants and 40.5% individuals were detected with VUS, which included many genes associated with hereditary breast cancer and other cancer syndromes, in addition to BRCA1 and BRCA2. Individuals with VUS will need to cope with new information if the interpretation of the variant changes in the future. We need to be aware of the characteristics and limitations of this type of panel testing, and to properly utilize the test results and information obtained for good quality patient care.

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Intratumor heterogeneity and intrinsic immune activation are associated with response to chemotherapy in BRCA-related breast cancers

Background Breast cancers in women with a germline BRCA1/2 mutation (gBRCAm) have homologous recombination deficiency (HRD) and are sensitive to therapies causing double-
strand DNA breaks. In TBCRC 031 (INFORM), both neoadjuvant cisplatin and
doxorubicin/cyclophosphamide ("AC") in gBRCAm carriers resulted in a complete pathologic
response in 18% and 26% respectively in patients with newly diagnosed HER2–negative breast
cancer. Herein, we describe molecular features from tumor whole exome (WES) and
transcriptome sequencing (RNAseq) associated with response. Methods TBCRC 031 (the
INFORM Trial - NCT01670500) was a randomized phase II neoadjuvant trial comparing the
efficacy of cisplatin versus AC in gBRCAm carriers with stage I-III HER2–negative breast
cancer. Of 118 patients enrolled, 92 patients provided fresh frozen research biopsies, collected
prior to chemotherapy initiation, which were subjected to WES and RNAseq. Variants were
called using GATK best practices and intratumoral heterogeneity was inferred from mutations
and variant allele frequencies using Mutant Allele Tumor Heterogeneity (MATH) scores.
Mutational Signature 3 (Sig3) and Genomic Instability Score (GIS) were calculated with SigMA
and scarHRD, respectively. RNAseq data were utilized to perform differential gene expression
and functional analyses, while cellular deconvolution was performed with CIBERSORTx trained
against breast cancer single cell data. Patients were grouped according to their residual cancer
burden (RCB) as responders (RCB-0 or 1), or non-responders (RCB-2 or 3). P-
values ≤ 0.05
were considered statistically significant and when appropriate, adjustment for multiple testing

(64%) had triple-negative and 33 (36%) were hormone-receptor positive HER2-negative breast
cancer, 40 (43%) were classified as responders and 52 (57%) as non-responders. WES
across most samples irrespective of receptor status and not significantly different among
responders and non-responders. In contrast, responders exhibited lower levels of intratumor
heterogeneity than non-responders (median MATH 42.9 vs. 33.5, p = 0.01). 223 genes were
differentially expressed between responders and non-responders following control for tumor
hormone receptor status, BRCA1/2 mutation, and menopausal status. Pathways identified as
significantly enriched in upregulated genes were indicative of intrinsic immune activation in
responders (e.g., T-cell activation, immune response-signaling, and regulation of leukocyte
activation). Cellular deconvolution of the tumor microenvironment confirmed that responders
presented a higher proportion of T-cells (p = 0.025) and myeloid cells (p = 0.003) in the tumor
samples, while perivascular-like cells were enriched in non-responders (p = 0.034). Conclusion
In this analysis of the largest cohort of treatment-naive gBRCAm breast cancer to date, we
found that response to cytotoxic chemotherapy is associated with a transcriptional program of
intrinsic immune activation and an increased population of intratumoral T-cells and myeloid
cells. Lower levels of intratumor heterogeneity and higher immune activation were associated
with response to chemotherapy gBRCAm carriers while HRD scores were not.

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12/8/2022
5:00 PM - 6:15 PM
P5-12-04
WITHDRAWN
Introduction: Women carrying mutations in reparative genes frequently ask about the safety of pregnancy or the use of fertility-promoting techniques. The evidence on gestation and breast cancer (BC), specifically in mutated BRCA, provides contradictory results1,3. On the one hand, there are studies that support the protective nature of pregnancy, while others show that gestation is a factor that promotes it1. Likewise, some point to differences in the association according to the type of mutation, BRCA1 or BRCA22.

Objectives: To prove whether there is a relationship between pregnancy and BC in patients with mutations in DNA repair genes and to establish a solid knowledge base for counseling these patients in clinical practice.

Patients and methods: We conducted an analytical, observational and retrospective study of 259 women with mutations in DNA repair genes, whether they had developed cancer or not, with different gestational histories in the Medical Oncology Service. The genes studied were: BRCA1and2, MUTYH, hMSH2,
hMSH6, RAD51C, APC, CHECK2, ATM, PALB2, PTEN, BRIP1, ATM+RAD51D, BRCA1+NTHL1, CDKN2A, TP53, NF1, RAD51D.

Results: The proportion of patients who develop cancer in the pregnant group is 46.9%.

We observed that the diagnosis of BC occurred before the age of 40 years in 40% of pregnant women, compared to 30% in nulliparous women. Likewise, we observed that from the third pregnancy onwards, the percentage of women suffering from BC is higher, with a peak in the fourth pregnancy (68.8% vs. 31.3%) (p=0.135) and that 51.3% of women whose first pregnancy was before the age of 30 years developed BC, compared to 38.6% in those whose first pregnancy was at a later age (X2=4.16, p=0.041). Finally, we observed that 80% of breast cancers developed after 10 years from the first birth.

Conclusions: Considering our results, we cannot affirm that at present there is an association between gestation and BC in women with mutation in genes involved in DNA repair.

Table: Cross table between cancer (Yes/No) and pregnancy (Yes/No)

<table>
<thead>
<tr>
<th>Breast cancer</th>
<th>Pregnancy</th>
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<th>No</th>
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<tbody>
<tr>
<td></td>
<td>Count</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>46.9%</td>
<td>37.3%</td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>102</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>53.1%</td>
<td>62.7%</td>
</tr>
<tr>
<td><strong>Totally</strong></td>
<td>Count</td>
<td>192</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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Comprehensive analysis of DNA damage repair gene germline mutations in Chinese breast cancer patients

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Background: Germline DNA damage repair (DDR) mutations has been associated with increased cancer risk, PARP inhibitor therapeutic opportunity for breast cancer (BC) patients. However, the profile of germline mutations in BC covering comprehensive DDR genes remains unclear.

Methods: A total of 341 women with breast cancer who tested 102 germline related genes (including 50 DDR genes) between April 2021 to May 2022 in Guangdong Provincial People's Hospital were identified. Variants were classified into pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign and benign groups according to the ACMG/AMP Standards and Guidelines. We defined pathogenic and likely pathogenic variants as deleterious mutations.

Results: The median age of 341 breast cancer patients was 48 (range, 20-89) at the first diagnosis of BC. A total of 47 patients (13.78%) carried 53 deleterious germline variants in 21 cancer predisposition genes, 16 of which were DDR genes. DDR deleterious mutations were detected in genes including BRCA2 (n=18), BRCA1(n=7), FANCA (n=4), PMS2 (n=4), PALB2 (n=2), RECQL4 (n=2), PALB2 (n=2), etc. The younger age at diagnosis (less than 40 year-old) were significantly associated with deleterious mutations in DDR pathway(P=0.02). At least one VUS was identified in 238 (69.79%) patients. The top 5 DDR VUS genes were FANCM (n=21), ATM (n=20), RAD54L (n=17), FANCD2 (n=15) and ATR (n=14). Breast or ovarian cancer family history were significantly correlated with VUS germline mutations in DDR pathway(P=0.039). Interesting, we found that patients with pCR efficacy of neoadjuvant therapy were more likely to have VUS mutations in DDR pathway (table 1).

Conclusion: We provided a comprehensive view of germline DDR gene mutations in BC patients and also analyzed the association between clinical characteristics and germline DDR mutation status. DDR mutations are prevalent in Chinese BC patients. Patients with younger and breast or ovarian cancer family history were more likely to carry DDR alterations. Moreover, patients with higher frequency of DDR VUS mutations may benefit from neoadjuvant therapy.

Table 1
Clinicopathological characteristics between germline mutation carriers and non-carriers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ORR pathway genes</th>
<th>P-value</th>
<th>ORR pathway genes</th>
<th>ORR pathway genes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (yr)</td>
<td>1.50 (0.30-2.70)</td>
<td>1.20</td>
<td>1.50 (0.30-2.70)</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>Family history of breast or ovarian cancer</td>
<td>1</td>
<td>0.02</td>
<td>1</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Efficacy of Neoadjuvant</td>
<td>1</td>
<td>0.00</td>
<td>1</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>pCR</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>non-pCR</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00</td>
<td>0.00 (0.00-0.00)</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

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Polygenic Risk Score in a cohort of 105 Breast Cancer patients previously tested with a multi gene panel for hereditary cancer.

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AIM: Most patients tested by a 44-gene panel for hereditary cancer (HerediGene), even though they had a strong family history, have a negative result or a finding in a low-risk gene. This creates a question about the risk for these individuals to develop breast cancer. The Polygenic Risk Score is a tool used to identify and calculate the lifetime risk of developing breast cancer and thus we are investigating whether it can be used in our cohort of patients to identify this risk. PATIENTS AND METHODS: Among 111 patients analyzed with a 44-gene hereditary cancer panel, we were able to produce the Polygenic Risk Score for 105 of them. All the patients were diagnosed with breast cancer, and they all had a strong family history. We analyzed the ability of the PRS to identify the risk of the patients in combination with the findings of the 44-gene panel. RESULTS: Overall, 74% of patients with a family history had a negative PRS (with a cut-off of 20%). Among the BRCA positive patients all of them had a positive PRS and among all the high-risk gene positive cases, 70% had a positive PRS. On the other hand, among the low-risk genes and the negative cases 18.5% had a positive PRS. There is a positive correlation between the findings from the NGS panel analysis and the PRS. CONCLUSION: Our analysis shows that PRS is correlated to the findings of the 44-gene NGS panel having the majority of the PRS positive patients carry high risk mutations. In addition to this, in 18.5% of the patients with low-risk findings or negative result from the 44-gene panel, the PRS was positive which can explain the outcome of the patient since breast cancer had developed. This is an indication that the combination of PRS with the findings from the 44-gene panel can identify individuals with a higher risk of developing breast cancer.

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Christos Markopoulos, n/a: No financial relationships to disclose
INTRODUCTION: Breast cancer are the main cause of related deaths cancer among women, corresponding to 25% of new cases each year. When diagnosed at early stages, it has an overall five-year survival rate of up to 90%. However, in more advanced stages, survival is reduced to about 24%, with 90% of women in stage IV dying as a result of complications related to metastases. Considering that brain metastasis is an unfavorable prognostic site, and the identification of genetic-molecular profiles in primary tumors and in metastatic sites are a subject poorly described in the literature, we understand that the identification of mutational profiles may contribute to elucidate the genetic-molecular mechanisms associated with tumor progression. AIM: The aim of this study was to identify clonal and subclonal driver mutations that lead to evolution of metastatic clones from a breast cancer progression model. MATERIAL AND METHODS: For tumor progression model, automated extraction of DNA from buffy coat and paraffin samples of breast tumors and paired brain metastases (n=9) was performed. In the present work, we used a subclonal reconstruction model based on the combination of machine learning and population genetics concepts. This proposal is based on the frequency spectrum of each somatic mutation (SNVs or indels), considering VAF (Variant Allele Frequency - ratio of mapped reads of the mutant allele) in relation to the coverage of variant locus, as known as CCF (Cancer Cell Fraction). CCF is defined as the proportion of neoplastic cells that have a certain set of mutations and then is normalized considering the sample purity and the segments with changes in number of DNA copies (Copy Number Alterations). Then, a statistical model based on finite Dirichlet mixtures with mixed distributions is applied. In this model, Beta components capture clonal expansions and population genetics concepts were applied to mutant alleles in each population considering principles of cancer evolution. Finally, confidence was computed using both parametric and non-parametric bootstraps. The functions for building the model are implemented at https://caravagnalab.github.io/mobster/, and for visualization and construction of graphs, packages in R statistical-mathematical environment were used, such as ggplot2, sads, cli, clisymbols, cowplot, crayon, ctree, dndscv, dplyr, magrittr, reshape2, and tidyr. RESULTS: With this model was possible to identify the distribution of clones according to somatic alterations in patients with breast cancer and brain metastasis. It was possible to observe common patterns, such as alterations of the SF3B1 gene as a common ancestral clone in both conditions and the frequency of the AKT1 gene in a subclonal condition. Other genes relevant to breast cancer carcinogenesis, such as PIK3CA and TP53, are found in a
different clonal hierarchical pattern between the two conditions. CONCLUSION: This data suggests a model of clonal evolution capable to identify which drivers clones and subclones are involved in the metastatic process.

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Real-world clinico-genomic data reveal differences in genomic landscape associated with CDK4/6 inhibitors in HR+/HER2- breast cancer

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Purpose: Studies based on data from routine clinical practice (real-world data, RWD) benefit from larger patient numbers and are more representative of patient diversity than clinical trial studies. When combined with comprehensive genomic profiling (CGP), RWD may uncover the impact of therapies and patient characteristics on tumor genomic landscape. Here we aimed at assessing the feasibility of using RWD to identify changes in the prevalence of genomic alterations upon treatment and proposed a methodology to address RWD inherent caveats.

Experimental Design: To explore associations between tumor genomics and treatment chosen by physicians, we evaluated data from 5323 patients with metastatic hormone receptor-positive HER2-negative (HR+/HER2-) breast cancers from a nationwide real-world clinico-genomic database, originating from approximately 280 US cancer clinics (~800 sites of care). To perform our comparisons, we defined groups based on the therapy administered in the metastatic setting and the timing of the CGP relative to treatment. We used bootstrapping to estimate the significance of the effect and stratified analyses to assess the impact of potential confounders such as the site of the collected samples or disease history.

Results: ESR1 alteration prevalence increased from 5.6% (CI: 2.8-8.9) pre-treatment to 21.4% (CI: 13.3-29.6) following aromatase inhibitor. Yet, it was significantly less than the prevalence following treatments including CDK4/6 inhibitors (CDK4/6i; 37.1% [CI: 27.8-46.4]; P=0.006). Further, exposure to CDK4/6i led to an increase in FGFR1 and TP53 alterations as well as genes of the cell cycle (FDR< 0.2). Overall, we found that more pathways were likely to be altered in a given tumor following AI+CDK4/6i than after AI alone (P=0.02). In particular, alterations of the MAPK pathway were not exclusive to ESR1 alterations in the post-AI+CDK4/6i group compared to AI only, suggesting that MAPK pathway alterations alone may not overcome CDK4/6i-based treatments. Differences following exposure to CDK4/6i were retained in samples taken after the second-line treatment. Stratified analyses confirmed that these results are independent of exposure to adjuvant therapy or treatment duration and showed that ESR1 mutations occurred in both primary and metastatic samples.

Conclusions: Analysis of EHR-derived clinical data linked to CGP results from routine care can replicate associations previously observed in clinical trials and uncover unknown changes in tumor genomic landscape. Bootstrapping and stratified analysis reinforced our confidence in the results and thus allowed us to identify that CDK4/6i exposure led to a different – more altered – genomic landscape in HR+/HER2- breast cancer patients. This finding can inform design of clinical trials post-CDK4/6i and may help guide treatment choice for late stage patients. Thus, our work demonstrates the feasibility of leveraging real-world clinico-genomic data for translational research in oncology and leads the way for analyses including a more diverse patient population.

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Clonal evolution of mammary epithelial cells into breast cancers

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[Introduction] Proliferative lesions in the breast have been implicated in the development of breast cancer. Previous studies showed that some proliferative lesions and adjacent breast cancers shared common genetic alterations, suggesting that these originated from the same ancestral cell. However, the clonal structure of normal epithelia and their clonal history during evolution to cancer are poorly understood. In this study, we analyzed genetic profiles of normal epithelia and proliferative lesions in the cancer-borne breast to illustrate the clonal evolution of cancer from a normal epithelial cell. [Methods] Single cell-derived organoids (n=47) were established from breast milk of 4 healthy women aged 22–36 and normal breast tissue of 15 breast cancer patients aged 29–83 to evaluate somatic mutation rate in normal epithelial cells. Multiple normal lobules and proliferative lesions together with cancer lesions were collected using laser-capture micro-dissection (LCM) from fresh frozen (n=3) or formalin-fixed paraffin-embedded (n=5) surgical specimens in 9 premenopausal breast cancer patients. Somatic mutations and copy number alterations were evaluated using whole-genome sequencing. [Results] The mutation profile of single cell-derived organoids suggests that somatic mutations accumulate in normal mammary epithelial cells at a constant rate of 19.4/genome/year before menopause, and the mutation rate decreases to 6.9/genome/year after menopause. Parity was negatively associated with mutation number (-49.3 per life birth). In total, we analyzed 143 LCM samples, including those from 72 normal lobules, 43 proliferative lesions, and 19 non-invasive and 9 invasive cancer samples. Five cases showed a large expansion of proliferative lesions sharing a substantial number of somatic mutations with cancer. These lesions expanded over a distance of 35-90 mm, sharing tens to hundreds of mutations including those in breast cancer-related driver genes, such as PIK3CA, AKT1, GATA3, CBF and PTEN, while harboring private mutations or copy number alterations of their own. Of interest, the cancers in 4 out of these 5 cases was luminal-A type invasive ductal carcinoma in situ, and characterized in common by the presence of der(1;16), concurrent whole-arm 1q gain and 16q loss, in both cancer and proliferative lesions. Phylogenetic analysis adapted with the mutation rate in normal cells predicted that der(1;16) had been acquired between puberty and early 20’s, and the common ancestors of non-cancerous and cancerous lesions emerged by early 30’s, >10 years earlier than at the time of cancer diagnosis. By contrast, analysis of non-cancerous lobules unrelated to cancer showed that der(1;16)-negative non-cancer clones that had emerged after puberty stayed within a single lobule or spatially confined to adjacent lobules and rarely expanded to a large area as observed for those carrying der(1;16), even if the clones had acquired mutations in driver genes such as PIK3CA and PIK3R1, which highlighted the role of der(1;16) in wide clonal expansion. [Conclusions] Our results suggest that in some breast cancer cases, particularly in those with der(1;16), a highly recurrent translocation accounting for the major subset of Luminal A breast cancer, the clones with the funder driver alterations expanded macroscopically long before the onset of cancer, in which further clonal evolutions recursively occur multi-focally, giving rise to multiple proliferative lesions and ultimately, invasive cancers. Our findings provide new insight into the early development of breast cancer.

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DNA of many breast tumors is barraged by C-to-T/G mutations within TCW (W:T,A). These mutations are attributed to the aberrant expression and activity of APOBEC3 enzymes. They have been shown to account for many driver mutations in genes such as PIK3CA, ERBB2, and PPP2R1A, however their precise source and also their roles in tumor development, evolution, and patient survival are debated. Currently, quantification of APOBEC3 expression changes in tumor cells is confounded by the ubiquitous expression of these enzymes in immune infiltrating cells. In this study, we used a novel quantitative biology approach to determine the expression profiles of APOBEC3 enzymes in breast tumor and tumor microenvironment cells from >1,000 patients. We combined diverse datasets including tumor/matched normal RNAseqs, tumor somatic mutations, cell line RNAseqs and mutations, estimates of tumor purities and immune cell compositions, and expression of purified cell populations to show that in breast cancer there is only a single APOBEC3 dysregulation process. This process is subtype-independent and is represented by APOBEC3B upregulation and extreme APOBEC3C downregulation. Compared to all other tumor types, breast tumors are affected the most by this process.
Overexpression of somatic mutation in NSDHL promotes breast cancer cell migration and tumor growth

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Background: We had identified somatic mutations of the NAD(P) Dependent Steroid Dehydrogenase-Like (NSDHL) gene from breast tumors of patients with distant metastasis using whole-exome sequencing. This study aimed to investigate the function of NSDHL mutants in breast cancer. Methods: ER-positive and tamoxifen-resistant human breast cancer cell line (ZR75-1) and mouse macrophage cell line (RAW264.7) were used. GFP-tagged NSDHL mutants were generated by subcloning the mutant NDHL into a lentiviral vector yielding an in-frame fusion of 3′ to GFP. ZR75-1 cells expressing the GFP-tagged NSDHL mutants were selected by puromycin with subsequent FACS analysis. The following experiments were performed: western blot, immunofluorescence staining, qRT-PCR, CellTiter-Glo assay, cell cycle assay, transwell migration assay, wound healing assay, tumor spheroid formation assay, and total cellular cholesterol measurement. An orthotopic breast tumor mouse model by injection of ZR75.1 cells into mammary gland fat pad was used in vivo. Results: Four novel NSDHL somatic mutations were discovered in the breast tumor tissues of patients. While total cholesterol levels in NSDHL mutant-transduced cells did not significantly increase, they were notably higher in wild-type NSDHL-transduced cells than in parent ZR75-1 cells. When compared to the parent and wild-type NSDHL-transduced cells, there was a minor increase in growth rate and a large increase in migratory capacities in NSDHL mutant-transduced cells (P<0.05). The size of tumor spheroids is significantly larger in NSDHL mutant-transduced cells than in wild-type NSDHL-transduced cells. Both EGFR expression and epithelial to mesenchymal transition (EMT) markers were higher in NSDHL mutant-transduced cells than in parent and wild-type NSDHL-transduced cells. The NSDHL mutant-transduced cells' conditioned media...
promoted the migratory ability and M2 polarization of RAW264.7 cells. In an orthotopic xenograft mouse model, NSDHL mutant-transduced cells were shown to promote tumor growth better than parent and wild-type NSDHL-transduced cells, suggesting that somatic mutation of the NSDHL contributes to the malignant progression of breast cancer cells. Conclusion: The present data indicate that breast cancer cells harboring somatic mutants of the NSDHL gene seem to display more aggressive behavior by gaining biological worse phenotype both in vitro and in vivo. More investigation is required into the mechanisms behind the function and accumulation of mutant NSDHL proteins to speed the development of therapies for patients with breast cancer harboring mutant NSDHL.

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Transcriptomic insights into lobular breast cancer biology: a retrospective analysis of the MINDACT clinical trial

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Background: Invasive lobular carcinoma (ILC) represents the second most common subtype of breast cancer after invasive breast cancer of no special type (NST). In this retrospective analysis of the MINDACT trial, we aimed at identifying/refining the transcriptomic differences between: 1) estrogen receptor positive/HER2-negative (ER+/HER2-) ILC versus ER+/HER2-NST, 2) classic and non-classic ER+/HER2- ILC, and, 3) recurring and non-recurring ER+/HER2- ILC in the subgroup of patients with a low clinical and low genomic (cL/gL) risk (as defined by a modified version of Adjuvant Online! and the 70-gene signature). Patients and methods: Central pathology review was performed for histological subtype, grade and Ki67 (G.V.) for 5929/6693 (88.6%) of the patients included in the MINDACT trial (NCT00433589). Analysis of transcriptomic data adjusted for age and grade was performed using the R/Bioconductor package 'limma' to identify differentially expressed genes (DEGs). DEGs having absolute log-

-adjusted p-value (q-value) < 0.05 were
considered. Gene set enrichment analyses (GSEA) of MSigDB hallmark gene sets were performed. Adjusted Cox regression models were used to evaluate the association of these hallmarks with disease free survival (DFS) and distant recurrence free survival (DRFS).

Results: After central pathological review, 464 patients with ER+/HER2- ILC and 3798 patients with ER+/HER2- NST were identified. Patients with ILC were significantly older at diagnosis, had larger tumors, less axillary nodal involvement, more grade 2 tumors than patients with NST. At the transcriptomic level, we observed a high number of DEGs between these 2 subgroups, confirming their distinct phenotype. CDH1, the gene coding for E-cadherin, was as expected the most highly overexpressed gene in NST versus ILC. We further observed an increased expression of leptin (LEP), leptin receptor (LEPR), lipoprotein lipase (LPL), and the fatty acid transporter CD36 in ILC. This could suggest that ILC relied on increased lipid uptake thanks to the increased contact of ILC tumor cells with the adipocytes. IGF1 was also overexpressed in ILC versus NST, as a potential consequence of high LEP and high LEPR expression. Differences were also evident with regard to the extracellular matrix (ECM), with many collagens, matrix metalloproteinases (MMPs) and other key enzymes (e.g. LOXL1) being differentially expressed. We confirmed a decreased ER-signaling and increased PI3K/Akt signaling in ILC versus NST. Out of the 464 ER+/HER2- ILC tumors, 253 (55%) were classic ILC and 211 (45%) non-classic ILC. There were more grade 3 tumors, more highly proliferative tumors and more nodal involvement in patients with non-classic versus classic ILC. At the transcriptomic level, differences were subtler than the differences seen above. Still, a significant enrichment of the hallmarks related to cell cycle in the non-classic ILC, and of the hallmarks related to epithelial-to-mesenchymal transition, hypoxia, adipogenesis and IL6/JAK/STAT3 signaling in classic ILC was observed. Finally, 216/464 patients with ER+/HER2- ILC (47%) were assigned to the cL/gL risk group and did not receive chemotherapy. 28/216 of these patients (13%) relapsed (DFS, median FU: 8.7 years). Enrichment of hallmarks related to apoptosis, inflammatory response, hypoxia and oncogenic signaling (PI3K/Akt, Ras, c-Myc) was associated with worse survival. Conclusion: This represents, to the best of our knowledge, the largest set of gene expression data for patients with ILC, issued from a clinical trial where histology was reviewed centrally. These results could be used to personalize treatment for patients with ILC. This project is funded by the Breast Cancer Research Foundation.

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Identifying oncogenic enhancer elements in TNBC of the Basal-like subtype using single-cell ATAC-seq and RNA-seq

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Identification of the cis-regulatory elements controlling oncogenic transcriptional programs is critical to understanding tumor biology. To find cis-regulatory elements (i.e. gene enhancers) of oncogenic dependencies in Triple-Negative Breast Cancers (TNBC) of the Basal-like gene expression subtype, we generated matched single-cell transcriptome (scRNA-seq) and chromatin accessibility (scATAC-seq) profiles for two human Basal-like tumors and four normal mammary reduction samples. This unique dataset enabled us to correlate variations in chromatin structure with variations in gene expression revealing putative enhancers that are specifically active within cancer cells, but not within normal mammary ductal epithelial cells. We then leveraged the Cancer Dependency Map (DepMap) portal at the BROAD Institute to infer gene expression dependencies in breast cancer cell lines of the Basal-like molecular subtype. Putative cancer-specific enhancers were prioritized based on the transcriptional dependency of their target gene(s) in Basal-like cell lines as reported by the DepMap portal. Based on our
preliminary analyses, we report several cancer-specific enhancers that drive the expression of important transcription factors such as EN1 and SOX4. These transcription factors are known to have profound effects on tumor biology, especially considering that high expression of EN1 is associated with brain metastasis and SOX4 is known to regulate immune evasion and PI3K/Akt signaling. Moreover, both of these transcription factors portend a worse outcome in TNBC patients. Thus, our analysis suggests that high levels of expression of these transcription factors is sustained specifically within the malignant cell types of these tumors, by the activity of these cancer-specific enhancers that are not typically active in normal epithelial cells. We are now performing CRISPR dCas9-KRAB experiments to epigenetically silence these cancer-specific enhancers and measure the consequences on expression of their predicted target genes. Additionally, we are investigating the trans-acting transcription factors that may physically bind to these enhancers to further regulate oncogenic transcription. By defining the regulatory logic of cancer cells at single-cell resolution, our work highlights the importance of cancer-specific and clinically relevant oncogenic regulatory elements in TNBC of the Basal-like subtype.

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Clonal hematopoiesis of indeterminate potential after (neo)adjuvant chemotherapy versus endocrine therapy for early breast cancer: the CIRCE-eBC prospective cohort study

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Title: Clonal hematopoiesis of indeterminate potential after (neo)adjuvant chemotherapy versus endocrine therapy for early breast cancer: the CIRCE-eBC prospective cohort study

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition associated with higher risk of hematologic malignancies, cardiovascular disease, and all-cause mortality. Patients (pts) with early breast cancer (eBC) receiving chemotherapy (CT) have increased risk of treatment-related myeloid neoplasms (tMN); the benefit of CT in eBC pts is often limited. Little is known about the prevalence and dynamics of CHIP in eBC pts. Methods: We prospectively identified two cohorts of pts with eBC: cohort A – pts receiving (neo)adjuvant CT with or without adjuvant endocrine therapy (ET); cohort B – pts receiving ET only. Blood was collected prior to initiation of treatment (T1) and after either (neo)adjuvant CT or 6-18 months of adjuvant ET (T2). We performed targeted sequencing of cryopreserved peripheral blood mononuclear cell (PBMC)-derived geno

cohort A were younger (median age 51 vs 57, p< 0.001), less frequently Caucasian (83.9 vs 96.6%; p=0.005) and former/current smokers (28.0 vs 43.1%, p=0.038). All pts in cohort B had hormone receptor-positive (HR+) eBC; in cohort A 50% of pts had HR+/HER2-, 16% had HR+/HER2+, 8.5% had HR-/HER2+ and 25.4% had HR-/HER2- eBC (p< 0.001). Pts in cohort A had higher stage (stage II-III 68.7 vs 27.6%; p< 0.001) and grade (grade 3 65.3 vs 15.5%; p< 0.001) tumors. Genetic testing was more frequently performed in pts receiving CT (88.1 vs 68.1%, p< 0.001), though the rate of germline pathogenic variants was similar (13.5 vs 17.7%, p=0.079). In cohort A, 38% received anthracyclines, 7% platinum and 57% anthracycline/platinum-sparing CT. Median time between T1 and T2 was 189.5 (150,406) and 280 (147, 425) days in cohort A and B (p< 0.001). The prevalence of CHIP, defined by
of pts with new CHIP variants at T2 was also similar (A 3.4% vs B 6.0%) (p=0.373). After adjusting for age and stage, odds ratio (OR) of developing new CHIP variants in cohort B vs A was 1.28 (95% CI 0.32 – 5.68, p=0.733). Age correlated with baseline prevalence of CHIP (p<0.001). Most frequent new CHIP variants at T2 in cohort A were DNMT3A (3), PPM1D (1), NF1 (1). To investigate whether pts receiving CT were more likely to have emergence of small detected at T1 in 55 (46.6%) and 61 (52.6%) pts in cohort A and B, respectively. Few pts without pathogenic variants at T1 developed them at T2 (3 pts in cohort A and 4 in cohort B). 21 pts (27 variants) in cohort A and 11 pts (12 variants) in cohort B had new variants at T2. Pts with new variants vs not (32 vs 202 pts) had similar characteristics, excepting age (median 60.5 vs 54.0, p=0.011). After correcting for age and stage, OR of developing new pathogenic variants given ET vs CT was 0.25 (95% CI 0.10-0.62, p=0.003). Most frequent newly detected variants were in DNMT3A (14), PPM1D (5), TET2 (4) and TP53 (2) in cohort A; DNMT3A (3), TET2 (3) and ZNF318 (2) in cohort B. Conclusions: In the CIRCE-eBC study, CT administration did not lead to emergence of CHIP over a 6-9 month period vs ET alone. This finding is reassuring in the setting of long life-expectancy for eBC pts and the association of CHIP with significant morbidity and mortality. However, consistent with known risk of development of MN, CT was associated with emergence of low frequency pathogenic variants in PPM1D and TP53, which have been associated with elevated risk of tMN. The evolution and prognostic role of these small clones is unclear and warrants additional investigation.

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Background The hormone receptor (HR)-positive metastatic breast cancer (MBC) patients show a diverse range of tumor mutational burden (TMB), but its biological and clinical implication has been largely unrevealed. Here we report genomic landscape of 117 HR+ MBC patients who were included in the pre-screening tissue genomic analysis of MUTATION-1 study (SABCS 2021; Abs P1-19-03) according to TMB of tumors. Patients and method The MUTATION-1 study (NCT03608865) enrolled HR-positive MBC patients who received prior ≥ 1 line of systemic therapy, and performed prescreening with whole exome sequencing (WES) and RNA-seq of fresh-frozen tissue of metastatic or recurred tumors. Patients who met upper 30% of TMB were eligible for treatment phase and received durvalumab plus tremelimumab. This study analyzed 117 prescreening tissues of MUTATION-1 study patients for mutation and transcriptomic landscape analysis. (WES, n=117; RNA-seq, n=107) Results The 117 patients showed diverse TMB (range 0~21.7 mut/Mb, median 2.0 mut/Mb) and genomic alterations. The most frequently mutated gene included PIK3CA (29.1%), TP53 (27.4%), ESR1 (23.9%), GATA3 (19.7%), and MAP3K1 (12.0%). There was no association between patient survival and TMB. We estimated single base substitution (SBS) mutational signature of patients with SigMA algorithm. The patients were classified according to their dominant mutational signatures: APOBEC (25.6%), HRD (41.0%), clockwise (28.2%), SBS8, and SBS17. The APOBEC patients showed higher TMB (median 3.47 mut/Mb) and higher mutation prevalence in PIK3CA (63.3% vs. 29.1%), ARID1A (16.7% vs. 6.0%), and NF1 (16.7% vs. 6.8%) compared with other patients. The high TMB positively correlated with time from MBC diagnosis to biopsy. Tumors the timing of biopsy. In the matched RNA-seq analysis, TMB was higher in luminal B and HER2-enriched intrinsic subtype pati 3.16 mut/Mb, cutoff used for treatment phase patient selection) patients showed upregulation of G2/M checkpoint, MYC, E2F1, and MTORC1 signature compared to low TMB patients. In the tumor microenvironment analysis by CIBERSORT, PIK3CA mutant patients showed lower score of cytotoxic T cell than others. Conclusions The high TMB in HR+ breast cancer was associated with longer time duration from MBC diagnosis to biopsy, high APOBEC signature, and cell cycle/MYC signature gene upregulation. Further therapeutic targeting of high TMB patients is warranted based on their genomic and immunologic characteristics.

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Tumor Genomic Landscape in Older Women with Metastatic Breast Cancer (MBC)

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Background. Patients (pts) who develop MBC at older ages are underrepresented in clinical trials, are less likely to be included in comprehensive biomarker characterization studies, and experience worse breast cancer-specific survival than their younger counterparts. Elucidating genomic underpinnings of MBC and possible therapeutic targets for older breast cancer patients are critical priorities. Methods. We identified pts age >70 years at MBC diagnosis and a younger cohort (ages 50-69; age < 50), who were treated for MBC at a single center and who had their metastatic (or if not available, the primary) tumor, assessed by a targeted, tumor-only next generation sequencing (NGS) platform (OncoPanel) between 2013-2020. The NGS panel included mutations, copy number variation, tumor mutational burden (TMB), and hypermutation (HM) status, with mutations classified as oncogenic using the OncoKB tool and additional annotation. Copy number events were selected as being "oncogenic" if a high amplification was called for an oncogene or a deep deletion for a tumor suppressor. We compared findings for older (age >70) vs. younger (age < 50 and ages 50-69) MBC pts using Chi-Square and Kruskal-Wallis tests. To determine genomic event enrichment, logistic regression (LR) models were used, controlling for age (continuous), background rate, and tumor subtype (those with unknown subtype [n=27] were excluded from models). False discovery rate (FDR) was used to correct for multiple hypothesis testing. Results. The final analytic cohort included 2,380 pts. The median age at MBC diagnosis was 54.1 years overall (range 18.5- 91.9) and 73.6 years for
those age >70. A total of 137 metastatic and 76 primary tumors were sequenced in pts age >70; in those age < 70, 1383 metastatic and 784 primary tumors were sequenced (for age < 50 [n=857] and 50-69 [n=1310]). Older pts were more likely to present with HR+/HER2- tumors (70.9% v. 62.4% v. 52.4%), and less likely to present with HER2+ (9.4% v. 14.4% v. 22.8%) or triple-negative breast cancer (TNBC) (18.8% v. 21.9% vs. 24.0%) at MBC diagnosis (listed >70, 50-69, < 50; P=1e-7). Older pts had higher average TMB vs. younger pts (9.57 in pts > 70, 8.56 in ages 50-69, 7.34 in ages < 50; P=3.5e-5). This was due to older pts having a higher incidence of hypermutation status as defined as TMB >10: 26.3% in age >70, 23.2% in ages 50-69, 16.8% in age < 50. Using q=0.1 as the threshold of significance, the presence of CDH1, PIK3CA, MAP3K1, TET2, and AKT oncogenic mutations were also enriched in older pts, while the presence of oncogenic GATA3, BRCA2, and TP53 mutations, as well as any mutation in BRCA1 were enriched in younger pts (too few oncogenic BRCA1 mutations were present for accurate modeling). The frequency of oncogenic PIK3CA mutations in HR+/HER2- tumors was highest in the oldest pts (44.4% in pts age >70 v. 31.6% in age 50-69 v. 26.7% in age < 50). Of pts who had oncogenic BRCA1/2 mutations identified on tumor-only NGS testing and underwent clinical germline testing (n=7 v. 60 v. 67, oldest to youngest), older pts had the lowest incidence of germline BRCA pathogenic variants (14.3% vs. 47.2% vs. 67.2%; p=0.01); most BRCA mutations identified on NGS testing in older patients were considered likely somatic. When assessing enrichment in copy number events, ERBB2, RAD21, and BRIP1 amplifications were all significantly less frequent in older pts (q< 0.1), even when accounting for tumor subtype. Conclusions. In a large cohort of pts with MBC, the mutational and copy number landscape for older pts differs from that in younger pts, even after controlling for tumor subtype. Key actionable findings include a higher proportion of high TMB and PIK3CA-mutated tumors, emphasizing the importance of genomic profile testing in this pt population and further exploration of efficacy and tolerability of relevant therapies in those age >70 years.

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Somatic mutations of ER and HER2 subtypes exhibit divergent evolutionary trajectories determined by selective epistasis revealed in phylogenetic reconstruction and stage-specific analyses

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Estrogen-receptor positive (ER+) and human epidermal growth factor receptor positive (HER2+) subtypes of breast cancers feature distinct histopathologies and prognoses. Their molecular profiles inform subtype-specific treatment combinations and possible therapeutic targets. However, the evolutionary trajectory of somatic mutations within each subtype has not been characterized, despite its utility in prioritizing drug development and therapeutic efficacies. Quantifying the selective effects of somatic mutations on cancer conveys the likely efficacy of extant targeted therapies between subtypes. Furthermore, knowledge of epistatic interactions involving targetable mutations enables precision therapy at any stage of tumorigenesis. The strength of these interactions differ between receptor subtypes, mediated by differences in the adaptive landscape of each subtype. To investigate differences in subtype etiologies, we quantified selection on single-nucleotide mutations within ER and HER2 receptor subtypes using an aggregated multi-institutional cohort of tumor samples. We observed differential selection acting on mutations: PIK3CA H1047R is a strongly selected variant for which selection varied significantly based on the receptor subtype, experiencing maximal selection in ER+ HER2− breast cancer. On a stage-specific basis, we show that adaptive landscapes change, altering optimal timings for treatment. We then infer epistasis by 1) stage-specific analysis that suggests likely orderings of mutations, 2) calculation of pairwise selective epistasis amongst mutations, which lends mechanistic explanations to these orderings, and 3) phylogenetic reconstruction of the evolution of ten breast cancers, revealing common orderings that further support inferred selective epistatic interactions. Our estimates of differential and stage-specific selection and epistasis between subtypes suggest distinct adaptive landscapes for breast cancer subtypes. These estimates should inform the development of targeted therapeutics and guide treatment schedules based on molecular profiling of the cancer.

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Machine learning based histopathology images analysis reveals cancer stemness in TNBC patient with 17p loss

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Background: The area of computational pathology has made huge progresses due to advances in artificial intelligence (AI) and machine learning technologies. It has been applied to many research and translational tasks which provide great improvement on medical diagnosis and treatment. Cancer stem-like cells (CSC) have been consistently reported for its key role in Triple negative breast cancer (TNBC). Given the large amount of existing H&E stained histological slides of TNBC, digital identification of CSC could benefit the evaluation of tumor status and prediction of patients’ response to chemotherapy. Here we proposed an AI framework based on Convolutional Neural Network (CNN) to predict CSC from the histological images of TNBC patient. And our preliminary work suggested that chromosome 17p loss, a common genetic variations in breast cancer, is linked to cancer stemness.

Methods: A modified GoogleNet model was adopted as our CNN classifier. Consecutive breast cancer tissue microarrays (TMA), which stained with H&E, SOX2, OCT4 and NANOG antibodies respectively by IHC, were used as training dataset for the CNN model. Gene expression data from the TCGA and METABRIC datasets were used to identify gene signatures associated with CSC. The connectivity map (CMAP) and Cancer Cell Line Encyclopedia (CCLE) were used for screening compounds that target stemness in cancer cell lines with chromosomal 17p loss. HS578T and EO771 cells with or without heterozygous 17p loss (11b in EO771) were used for in vitro experiments. Female immunodeficient nude (Nu/J) mice were used for animal studies.

Results: The well trained GoogleNet model was applied to TNBC patient diagnosis images in TCGA BRCA dataset. By analyzing patient genomic alteration on chromosomal level, we found that loss of chromosome 17p associate with high cancer stemness in TNBC. Flow cytometry assays also demonstrated higher ALDH1 activity and higher CD44+/CD24−/low cell population in HS578T cells with 17p loss. RNA-seq of HS578T cells revealed that most CSC marker genes were located in the unregulated differentially expressed genes (DEGs) of 17p loss cells. We next compared the cytotoxicity of chemotherapy drugs including doxorubicin, paclitaxel, docetaxel and cisplatin on 17p loss and 17p intact HS578T cells, 11b loss and 11b intact...
EO771 cells, in terms of IC50 value. The IC50 value of indicated drug on 17p loss HS578T cells were 3-6 fold higher than their IC50 on 17p intact HS578T cells. Similar result was observed in EO771 cells. Next, 17p loss and 17p intact HS578T cells were orthotopically implanted into the Nu/J mice. Under the doxorubicin treatment, mice bearing 17p loss HS578T derived tumors had larger and heavier tumors in compare to mice bearing 17p intact tumors. Next, we did a computational drug screening to identify compounds that can target the cancer stemness in 17p loss cells. Screened out compounds were tested for their cytotoxicity on 17p loss and 17p intact HS578T cells and FK866 showed the most pronounced efficacy on inhibiting the viability of 17p loss cells, compared to 17p intact cells. Followup experiments demonstrated that FK866 can decrease the CSC features induced by doxorubicin, both in vitro and in vivo. FK866 also potentiates the effect of doxorubicin on treating TNBC cells with 17p loss, which provide a drug combination potential for TNBC patient with 17p loss. Conclusions: A CNN based model was developed to identify CSC from TNBC histopathology images. The images analysis combined with patient genomic data revealed that chromosome 17p loss associated with cancer stemness in TNBC. This result was confirmed using assays on TNBC cells with or without 17p loss. A computational drug screening was performed to identify candidates that targeting stemness in 17p loss cells. FK866 was identified and it potentiates the anti-tumor effect of doxorubicin on treating TNBC cells with 17p loss. Our study provides a novel strategy on applying AI to precision treatment for cancers.

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Comparison of cell-free DNA genomics of breast cancer associated-chest wall disease vs. age & subtype matched controls with metastatic breast cancer not involving the chest wall

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Background: Breast cancer associated-chest wall disease (CWD) clinically behaves in an aggressive manner. However, little is known about the genomics of CWD. Cell-free DNA (cfDNA) can identify oncogenic mutations in metastatic breast cancer (MBC). We hypothesized
that the cfDNA genomics of CWD may vary from MBC cases without CWD. We compared the 
cfDNA genomics of patients with CWD to that of age and subtype matched MBC controls 
without CWD.

Methods: Patients with MBC at an academic institution who underwent cfDNA testing 
(Guardant360, next generation sequencing (NGS), 74 gene assay) from 2/2016-2/2021 were 
identified. Patients with documented CWD (chest wall recurrence with nodules, ulceration, 
and/or skin metastases on imaging and/or examination) at the time of cfDNA testing (coinciding 
with MBC diagnosis) were included in the CWD cohort. Age and subtype matched MBC 
controls without CWD (CON) during the same time period with cfDNA results at MBC diagnosis 
were identified. A retrospective review was conducted to determine clinical features and cfDNA 
genomics of CWD and CON. A two-sample test of proportions was used to compare CWD to 
CON, with p< 0.05 for statistical significance.

Results:
Thirty-one patients with CWD and 63 CON were identified. Both groups were well-matched in 
median age at MBC diagnosis (CWD 57 vs. CON 59 years, p=0.93) and subtype distribution 
(CWD: TNBC 35%, HR+/HER2- 58%, HER2+ 6%; CON: TNBC 29%, HR+/HER2- 65%, HER2+ 
6%, p=0.78). Patients also had similar racial distribution in both cohorts (p=0.57).

(p=0.62). Median number of cfDNA mutations for CWD was 4.5 (range 0-16) vs. 4 (range 0-21) 
in CON (p=0.32). The most common cfDNA mutations in CWD were TP53 (58%), NOTCH1 
(19%), PIK3CA (16%), BRCA1 (13%), NF1 (13%), FGFR2 (13%), ESR1 (13%), STK11 (10%), 
NTRK1 (10%), APC (10%), and KIT (10%). In comparison, the most common cfDNA mutations 
in CON were TP53 (54%), PIK3CA (35%), ESR1 (14%), GATA3 (13%), and ATM (11%). Table 
cohort analyzed. In HR+/HER2- MBC, NOTCH1, STK11, NTRK1, DDR2, and NF1 were 
significantly more common in CWD than CON. For TNBC, NOTCH1 was numerically more 
common in CWD vs. CON (p=0.06).

Conclusions: The cfDNA genomic spectrum of CWD varies from MBC that does not infiltrate 
the chest wall. Mutations that are associated with metastasis (NOTCH1), inhibition of tumor 
suppression (STK11), tumor migration (DDR2), proliferation (NTRK1), and endocrine resistance 
(NF1) were significantly more common in HR+/HER2- CWD than matched controls. Further 
research is needed to validate these findings and determine the impact of matched targeted 
therapies for CWD.

Table 1
<table>
<thead>
<tr>
<th>Mutation</th>
<th>Entire cohort CWD (n=31) vs CON (n=63)</th>
<th>TNBC: CWD (n=11) vs CON (n=18)</th>
<th>HR+/HER2- CWD (n=18) vs CON (n=41)</th>
<th>HER2+ CWD (n=2) vs CON (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOTCH1</td>
<td>19% vs 3%, p=0.0056</td>
<td>18% vs 0%, p=0.06</td>
<td>22% vs 4.8%, p=0.03</td>
<td>N/A</td>
</tr>
<tr>
<td>STK11</td>
<td>9.6% vs 0%, p=0.009</td>
<td>N/A</td>
<td>17% vs 0%, p=0.004</td>
<td>N/A</td>
</tr>
<tr>
<td>CCNE1</td>
<td>6.4% vs 0%, p=0.055</td>
<td>9% vs 0%, p=0.19</td>
<td>0.06% vs 0%, p=0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>NTRK1</td>
<td>9.6% vs 1.5%, p=0.056</td>
<td>0% vs 0.06%, p=0.43</td>
<td>17% vs 0%, p=0.004</td>
<td>N/A</td>
</tr>
<tr>
<td>DDR2</td>
<td>6% vs 1.6%, p=0.18</td>
<td>0% vs 0.06%, p=0.43</td>
<td>11% vs 0%, p=0.02</td>
<td>N/A</td>
</tr>
<tr>
<td>NF1</td>
<td>13% vs 4.7%, p=0.13</td>
<td>0% vs 0.06%, p=0.43</td>
<td>22% vs 2%, p=0.0068</td>
<td>0% vs 25%, p=0.44</td>
</tr>
</tbody>
</table>

N/A: mutation not observed

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Targetable alterations and genomic signatures within breast cancer brain metastases: Data from comprehensive genomic profiling of 761 breast cancer brain metastases

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Background: Breast cancer brain metastasis (BCBM) represents an area of unmet clinical need. We previously demonstrated the genomic differences between primary BC and BCBM. In this study we examined the genomic differences between BCBM by BC subtypes and the potential actionable targets that might be taken forward for each subtype in clinical trials.

Material and Methods: A total of 761 BCBMs were analyzed by comprehensive genomic profiling (CGP) for alterations in up to 395 genes (Foundation Medicine, USA). The samples were classified by immunohistochemistry (IHC) of the BCBM to ER+ (ER+/HER2-, ER+/HER2+), ER-/HER2+ and ER-/HER2-. Homologous recombination deficiency (HRD-gLOH; cutoff 16%), tumour mutational burden (TMB; cutoff 10 mutations/Mb), microsatellite instability (MSI) and PD-L1 prevalence and expression by IHC using the VENTANA SP142 assay (Immune Cell Score [IC] cutoff 1%) were also investigated.

Results: For all BC subtypes the most enriched gene alterations in BCBM (>20% prevalence)
were: TP53, MYC and PIK3CA. ESR1 and ERBB2 were more prevalent in ER+ and HER2+ tumours respectively, with ESR1 alterations significantly enriched in ER+/HER2- BCBM (p < 0.0001). Frequently altered genes by BCBM subtype were: ER+/HER2-: CDH1 (8%) and BRCA2 (7%); ER+/HER2+: PIK3CB (11%), MDM4 (11%), TBX3 (9%) and AKT2 (8%); ER-/HER2+: LYN (9%). Significantly enriched genes (p < 0.01) by BCBM subtype were: HER2+: CDK12 (15%); ER-/HER2-: BRCA1 (14%), CCND3 (9%), VEGFA, JAK2 (8% each) and the immune checkpoint inhibition (ICPI) biomarkers PDCD1LG2 (PD-L2), CD274 (PD-L1) (7% each). HRD-gLOH was high in ER+/HER2-: (43%) and ER-/HER2-: (70%). TMB and MSI were present in 10%-21% and 1-3% of BCBM respectively, whereas PDL1 protein expression by subtypes was: ER+/HER2- 23%, ER+/HER2+ 27%, ER-/HER2+ 57% , ER-/HER2- 48%. Table 1 summarizes the proportion of BCBMs with actionable alterations and selected clinical trials in BCBM.

Conclusion:
Clinically-relevant genomic alterations were identified across all BCBM subtypes. High HRD-gLOH, TMB and MSI were observed across all the BCBMs subtypes whereas PDL1/PDL2 alterations were a distinctive feature of ER-/HER2- BCBM. These data highlight the need to assess the genomic landscape of BCBM to enable rational treatment decisions with targeted agents, as well as to enable enrichment of relevant populations within clinical trials.

Table 1. Selected studies with targeted therapy and/or immunotherapy in breast cancer brain metastases.

<table>
<thead>
<tr>
<th>Gene alteration</th>
<th>Targeted Therapy</th>
<th>Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>ER+/HER2-</th>
<th>ER+/HER2+</th>
<th>ER-/HER2-</th>
<th>ER-/HER2+</th>
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<td>ERBB2/HER2 alterations</td>
<td>Trastuzumab, T-DM1</td>
<td>Phase 3</td>
<td>NCT02575647</td>
<td>2.6%</td>
<td>3.0%</td>
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<td></td>
<td>Kenetumab, Trastuzumab</td>
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<td>NCT02856339</td>
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<td></td>
<td>Atezolizumab, T-DM1</td>
<td>Phase 2</td>
<td>NCT04106897</td>
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<tr>
<td></td>
<td>GSK2636509, Trastuzumab</td>
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<td>NCT02806288</td>
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<td></td>
<td>Pertuzumab, Vencezumab, Trastuzumab</td>
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<td>NCT03223632</td>
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<td></td>
<td>APX006, Trastuzumab</td>
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<td></td>
<td>Necitumumab, Capricorn</td>
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<td>Abemaciclib, Vencezumab</td>
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<td>Atezolizumab, Targeted radiotherapy</td>
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<td>NCT02740055</td>
<td>26.27%</td>
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<td>28.47%</td>
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<td>PIK3CA mutations</td>
<td>GSK2636509</td>
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<td>26.24%</td>
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<tr>
<td></td>
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<td>Phase 2</td>
<td>NCT03447094</td>
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<tr>
<td>BRCA2/2 mutations</td>
<td>Veliparib, Olaparib</td>
<td>Phase 2</td>
<td>NCT03000068</td>
<td>5.33%/1.53%</td>
<td>3.15%/2.31%</td>
<td>4.49%/1.09%</td>
<td>3.17%/1.09%</td>
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<tr>
<td>PD1</td>
<td>Pembrolizumab, Anti-PD1/2, Anti-CTLA4</td>
<td>Phase 2</td>
<td>NCT04006647</td>
<td>11.40%</td>
<td>9.00%</td>
<td>21.50%</td>
<td>17.40%</td>
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<td></td>
<td>Pembrolizumab, Stereotactic radiotherapy</td>
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<td>NCT03006201</td>
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<td>PKD1</td>
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<td>11.40%</td>
<td>9.00%</td>
<td>21.50%</td>
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<td>3.00%</td>
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</tbody>
</table>

The percentage (%) of actionable alterations by ER and HER2 status is summarized. ND: Not Detectable.

Disclosure(s):
Athina Giannoudis, Dr: No financial relationships to disclose
Ethan Sokol, PhD: Foundation Medicine: Salary (Ongoing); Roche: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing)

Shakti Ramkissoon, MD, PhD: Foundation Medicine: Salary (Terminated, January 2, 2022)

Talvinder Bhogal, Mr: No financial relationships to disclose

Jeff Ross, n/a: Foundation Medicine: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing)

Kimberly McGregor, MD: Foundation Medicine: Salary (Ongoing)

Evangelia Razis, Prof: AstraZeneca: Consulting Fees (e.g., advisory boards) (Ongoing), Contracted Research (Ongoing); Bristol-Myers Squibb: Travel, Accommodations, Expenses (Ongoing); Bristol-Myers Squibb: Consulting Fees (e.g., advisory boards) (Ongoing), HONORARIA (Ongoing); Exelixis: Contracted Research (Ongoing); Faran: Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus) (Ongoing); Genekor: Travel, Accommodations, Expenses (Ongoing); Genesis Pharmaceuticals: Travel, Accommodations, Expenses (Ongoing); Ipsen: Travel, Accommodations, Expenses (Ongoing); LEO Pharma: Travel, Accommodations, Expenses (Ongoing); Merck: Travel, Accommodations, Expenses (Ongoing); Novartis: Contracted Research (Ongoing), Travel, Accommodations, Expenses (Ongoing); Parexel: Contracted Research (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing), Travel, Accommodations, Expenses (Ongoing); Roche: Travel, Accommodations, Expenses (Ongoing); Sanofi: Travel, Accommodations, Expenses (Ongoing); Tesaro: Contracted Research (Ongoing)

Rupert Bartsch, Assoc. Prof. Dr.: AstraZeneca: Consulting Fees (e.g., advisory boards) (Ongoing); Daiichi: Consulting Fees (e.g., advisory boards) (Ongoing); Eisai: Consulting Fees (e.g., advisory boards) (Ongoing); Eli Lilly: Consulting Fees (e.g., advisory boards) (Ongoing); Gilead: Consulting Fees (e.g., advisory boards) (Ongoing); Gruenenthal: Consulting Fees (e.g., advisory boards) (Ongoing); MSD: Consulting Fees (e.g., advisory boards) (Ongoing); Novartis: Consulting Fees (e.g., advisory boards) (Ongoing); Pfizer: Consulting Fees (e.g., advisory boards) (Ongoing); Pierre Fabre: Consulting Fees (e.g., advisory boards) (Ongoing); Puma: Consulting Fees (e.g., advisory boards) (Ongoing); Roche: Consulting Fees (e.g., advisory boards) (Ongoing); SeaGen: Consulting Fees (e.g., advisory boards) (Ongoing)

Richard S. Huang, MD: Foundation Medicine, subsidiary of Roche: 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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Rearrangements in CDH1, ESR1, and ERBB2 are commonly observed in breast cancer and may influence diagnosis and treatment

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Background The status of CDH1, ERBB2, and ESR1 is important for the diagnostic and treatment workup for patients with breast cancer. Most alterations in these genes occur in the form of short variants (eg missense and indel alterations) or copy number alterations (eg amplifications of ERBB2 or deletions in CDH1). The prevalence and characteristics of rearrangement events have been understudied.

Materials and Methods: Comprehensive genomic profiling using a hybrid-capture based approach was performed on 44,842 breast carcinomas during the course of routine clinical care (FoundationOne® or FoundationOne®CDx) examining all classes of alterations in up to 395 genes, including CDH1, ESR1, and ERBB2. All rearrangements were included in the analysis (known/likely pathogenic and variants of uncertain significance). Estrogen receptor status was extracted from pathology reports for a subset of samples. Results: Rearrangements in CDH1, ESR1, and ERBB2 were observed in 0.26% (115/44842), 0.34% (153/44842), and 1.33% (598/44842) of breast cancer samples, respectively. As expected, CDH1 rearrangements were most common in invasive lobular carcinoma (ILC) (0.64%; 16/2516) though events were observed in samples originally submitted as invasive ductal carcinoma (IDC) (0.16%; 26/15,836), suggesting possible misdiagnosis. CDH1 rearrangements were predominantly loss of function consisting of large deletions, inversions, and truncation events. ESR1 rearrangements were observed at the highest frequency in ER+/HER2- tumors (0.58%) and were never seen in ER-/HER2- and ER-/HER2+ tumors. ESR1 rearrangements were observed with a variety of partners, with recurrent events with CCDC170, SYNE1, RMND1, PLEKHG1, ARMT1, MTHFD1L, and ZBTB2. Consistent with a possible role in therapy resistance, ESR1 rearrangements were enriched in metastatic samples relative to those biopsied from the breast (OR = 2.25; p = 8E-05). ERBB2 rearrangement events were commonly observed in HER2 amplified tumors (13.4%) and rarely in other subtypes (0.12% in ER+/HER2- and 0.28% in ER-/HER2-). Most of the events were intra-chromosomal and typically represented non-fusion duplication fragments that may have generated the ERBB2 amplification. Fusions were much rarer. Out of the 598 rearrangement events, only 18 were predicted to create in-frame and in-strand fusion products retaining the HER2 kinase domain following manual review of the events. Most fusion events were unique,
though a fusion with IKZF3 was seen recurrently (n=2). Conclusions Rearrangement events in
diagnostically important breast cancer genes (CDH1, ESR1, and ERBB2) were commonly
observed in breast cancer with subtype-specific enrichment. Since these alterations have
implications in disease diagnosis and therapy response (eg endocrine therapy resistance),
comprehensive genomic profiling can provide value in breast cancer care.

Disclosure(s):
**Ethan Sokol, PhD**: Foundation Medicine: Salary (Ongoing); Roche: Ownership Interest
(stocks, stock options, patent or other intellectual property or other ownership interest excluding
diversified mutual funds) (Ongoing)
**Dexter Jin, PhD**: Foundation Medicine: Salary (Ongoing); Roche: Ownership Interest (stocks,
stock options, patent or other intellectual property or other ownership interest excluding
diversified mutual funds) (Ongoing)
**Jeffrey S. Ross, MD, DSc**: Foundation Medicine: Ownership Interest (stocks, stock options,
pattern or other intellectual property or other ownership interest excluding diversified mutual
funds) (Ongoing), Salary (Ongoing)
**ADRIAN V. LEE, PhD**: Astrazeneca: Contracted Research (Ongoing); Ocean Genomics:
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pattern or other intellectual property or other ownership interest excluding diversified mutual
funds) (Ongoing); PUMA Biotechnology inc: Contracted Research (Ongoing); UPMC
Enterprises: Salary (Ongoing)
**Steffi Oesterreich, PhD**: Astrazeneca: Contracted Research (Ongoing); Ocean Genomics:
Ownership Interest (stocks, stock options, pattern or other intellectual property or other
ownership interest excluding diversified mutual funds) (Ongoing); puma: Contracted Research
(Ongoing); UPMC Enterprise: Employee (Ongoing)
ESR1-alterations in HR+HER2- breast cancer patients

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Introduction/Background
Endocrine therapy remains the fundamental treatment for advanced HR+ breast cancer (BC). For those patients who become refractory to endocrine therapy, resistance may be associated with mutations, amplifications, and fusions in the ESR1-encoded estrogen receptor. Here we examine the frequency of ESR1 alterations and the associated genomic landscape.

Methods
HR+/HER2- BC samples were sequenced with the Oncomap™ ExTra assay, which uses whole-exome DNA sequencing with germline subtraction to detect somatic single nucleotide substitutions, indels, and copy number alterations (CNAs), and uses RNA sequencing to detect gene fusions. Tumor mutational burden (TMB) and microsatellite instability (MSI) are also reported. For analysis, BC samples were grouped by site: local (primary breast or regional lymph node) versus metastatic. Prior treatment history was unknown. Testing for a possible association between ESR1 and other biomarkers (genes, MSI, and TMB) was done using Fisher's Exact Test (p≤0.05).

Results
A total of 988 HR+HER2- breast cancer patient samples were included in the analysis. Of these, 821 (83.1%) were local samples and the remaining 167 were metastatic samples, with liver (63, 37.7%), bone (20, 12.0%), skin (16, 9.6%) and chest wall (15, 9.0%) being the most common locations. ESR1 alterations were present in 84 tumor samples, 37 local and 47 metastatic, representing 4.5% and 28.1% of samples, respectively. ESR1 alterations included missense mutations (54 samples), fusions (29 samples), and amplifications (8 samples). The most common missense mutations were Y537S (20 samples, 37.0%), D538Q (20 samples, 37.0%), and E380Q (6 samples, 11.1%), which were located in the ligand binding domain and included both clonal and subclonal events. There were 30 ESR1 fusions identified, 17 (2.1%) in local and 13 in metastatic (7.7%) samples. Most fusions (24 samples, 82.8%) involved the same partner, CCDC170, while the other 6 fusions had unique partners. Examination of the 143 other biomarkers altered among ESR1-altered samples revealed 15 genes and MSI-high status that appeared to be over-represented (Table 1). However, none of the associations were statistically significant after correcting for multiple comparisons. Further, there was no evidence that the prevalence of ERBB2, TP53, AKT1 and PIK3CA alterations differed by ESR1 status (Table 1).

Conclusions
ESR1 alterations were significantly more common in HR+/HER2- metastatic breast cancer samples compared to local samples. Comprehensive genomic profiling with RNA sequencing identified both common and rare ESR1 fusions, which were most frequent in the metastatic samples. No significant difference in the molecular profile of ESR1 altered vs ESR1 wildtype samples was found in this cohort. Clinical trials with novel selective ER degraders (SERDs) to target these ESR1 alterations are ongoing.

Table 1. Biomarkers that showed the highest association with ESR1 and other notable breast cancer biomarkers.
<table>
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<th>Co-mutated biomarker</th>
<th>$ESR_1$ alteration (N=84)</th>
<th>No $ESR_1$ mutation (N=904)</th>
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<td>$FGF19$</td>
<td>18 (21.4%)</td>
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<td>$FGF3$</td>
<td>16 (19.0%)</td>
<td>82 (9.1%)</td>
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<tr>
<td>$FGF4$</td>
<td>16 (19.0%)</td>
<td>79 (8.7%)</td>
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<td>$CTTN$</td>
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<td>$FADD$</td>
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<td>13 (1.4%)</td>
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<tr>
<td>$CDKN2A$</td>
<td>4 (4.8%)</td>
<td>12 (1.3%)</td>
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<tr>
<td>$TUBB3$</td>
<td>4 (4.8%)</td>
<td>12 (1.3%)</td>
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<td>$AR$</td>
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<td>7 (0.8%)</td>
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<td>$MLH1$</td>
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<td>2 (0.2%)</td>
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<td>$AURKA$</td>
<td>2 (2.4%)</td>
<td>1 (0.1%)</td>
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<tr>
<td>$KDM5A$</td>
<td>2 (2.4%)</td>
<td>1 (0.1%)</td>
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<td>$MSH6$</td>
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</tr>
<tr>
<td>MSI-high</td>
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<td>$AKAP9$</td>
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<tr>
<td>$TP53$</td>
<td>26 (31.0%)</td>
<td>217 (24.0%)</td>
</tr>
<tr>
<td>$PIK3CA$</td>
<td>35 (41.7%)</td>
<td>416 (46.0%)</td>
</tr>
<tr>
<td>$AKT1$</td>
<td>4 (4.8%)</td>
<td>48 (5.3%)</td>
</tr>
<tr>
<td>$ERBB2$</td>
<td>1 (1.2%)</td>
<td>32 (3.5%)</td>
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</table>

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Benefits of Oncotype DX genomic screening in a geriatric vs. non-geriatric cohort. Analyzing key factors in therapy decision making process

Introduction
In early luminal HER2 negative breast cancer Oncotype DX® Recurrence-Score (RS) has been broadly validated in pre- and postmenopausal patients and can predict prognosis and benefit of chemotherapy. Its value in elderly breast cancer populations has not been deeply addressed. This study analyses clinical and pathologic factors, RS distribution and outcomes in an elderly vs. non-elderly breast cancer population with the purpose of establishing RS added value to the therapy decision-making process in a geriatric cohort.

Methods
This is a retrospective analysis of available data from patients with early luminal HER2 negative breast cancer treated at the University Hospital Basel and the Cantonal Hospital Baselland between 2010 and 2022. Cohort A (A) consists of patients < 70 years old and cohort B (B) of ion for adjuvant treatment all patients had known RS result.

Results
A and B included 266 (81%) and 60 (19%) patients, respectively. The median age in A was 55.2 and in B, 74 years. The following clinical and pathologic factors were different in B vs. A: co- size (31.3 mm vs 23.6 mm p=0.021). Geriatric patients also tended to have a clinically higher risk status (83% vs. 70%; p=0.05). There was a trend for a higher mastectomy rate in B vs. A (41.7% vs. 29%, p=0.065), significantly less radiotherapy use (65% vs. 81%, p=0.009) and more osteo-oncologic treatment (61% vs 43%, p=0.013). RS distribution was not significantly
different between cohorts (A vs. B was: RS 1-15: 44.3% vs 41.7%, RS 16-25 41.2% vs 35% and 22.9% of A (p=0.116) and adjuvant endocrine therapy in 98.3% of B vs. 93.5% of A (p=p=0.214). Tumor board suggested systemic treatment was not implemented in 22% vs 15%, (B vs. A; p =0.087). With a median follow-up of 36.6 months, recurrence rate was higher, but not statistically significant in B vs. A (10% vs 6%, p=0.259). Relapse rate was higher with -25 (13.5% in B vs. 5.7% in A; p=0.043).

Conclusions

Older breast cancer patients tend to have higher clinical risk status, more co-morbidities and higher BMI. RS distribution was not significantly different between the two cohorts, however higher RS did pose a higher relapse rate for older patients in our cohort. Although RS based guidelines, still apply in therapy decision making in the case of geriatric breast cancer patients, clinical practice points to a rather individualized treatment in which all clinical and pathological factors are weighted.

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The genomic landscape of radiotherapy-induced breast angiosarcoma: an ACC initiative for an unmet need in cancer

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Introduction Radiotherapy-induced breast angiosarcoma (RIBAS) is a late, uncommon complication of radiotherapy (RT) in breast cancer. The incidence of RIBAS (0.3 – 1% of post-RT cases) is expected to increase in the next few years, following the widespread adoption of breast-sparing surgery in combination with RT[1–4]. RIBAS is poorly responsive to chemotherapy, and life expectancy is as low as 25% at five years. No actionable gene mutations are described for this disease. Aims The aims of the present study are: 1) to understand the genomic aberrations of RIBAS and identify actionable mutations for novel targeted therapies; 2) to compare the genomics of RIBAS with those sporadic breast angiosarcoma (sBAS); 3) to understand the association of genomic aberrations with clinical features of RIBAS and its outcomes in clinical practice. Patients and methods We have retrospectively collected FFPE tumor and germline samples, obtained by surgery or biopsy, from 2 European centers (INT - Milan and IRCCS San Martino - Genoa). Specimens from a third center, Katholieke Universiteit of Leuven, are being selected for analysis. Samples were subjected to whole exome sequencing (WES, NovaSeq 6000 Illumina). Raw data were analyzed using the opensource nf-Sarek pipeline[5]. Results We identified samples with matched normal tissue from 43 cases (30 RIBAS, 8 sBAS, 5 with no clinical info). All the patients were female, the overall median age at diagnosis was 68.8 years (IQR: 52.1 – 75.1), 69.8 (IQR: 61.4 – 76) for RIBAS and 41.2 (IQR: 28.6 – 53.7) for sBAS patients. WES was performed on 20 cases (14 RIBAS, 6 sBAS). The main mutations in RIBAS involve coding regions related to transcription factors and cytoskeletal, microtubule, and musculoskeletal-associated proteins. Among actionable mutated genes, MTOR and MAP3K21 were identified. Deletions and were shared between RIBAS and sBAS. FLT4 for a recurrent, potentially actionable amplification[7]. To our knowledge, our study is the first to address the genomic landscape of RIBAS in the effort of linking its physiopathology with clinical management. Our results may shed light on novel prognostic and predictive biomarkers in this neglected but increasingly frequent tumor. Associations with treatment, RNAseq and methylation arrays results, as well as data from the extended data cohort, will be presented at the meeting. Acknowledgements The study is sponsored by a Ricerca Corrente Reti ACC grant: Unmet Needs in Cancer genomics. References 1. Monroe, A. T. et al Cancer, 2003. 2. Sheth, G. R. et al. Oncologist, 2012. 3. Torres, K. E. et al. Ann. Surg. Oncol., 2013. 4. West, J. G. et al. Breast J., 2005. 5. Garcia, M. et al. F1000Res, 2020. 6. Fraga-Guedes, C. et al. Breast Cancer Res. Treat., 2015. 7. Gordon, K. et al. Hum. Mutat., 2013.
Rediscovering IRF5: A prognostic indicator with novel roles in mammary gland development, ribosome biogenesis, tumor initiation, and metastasis

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Breast cancer is the second leading cause of death for women in the United States. However, only 10% of breast cancers have been linked to inherited genomic mutations. Thus, identifying biomarkers to predict cancer progression and metastasis remains a clear need in the research and medical world. Here, we report a novel role for Interferon Regulatory Factor 5 (IRF5) in mammary gland development, tumorigenesis, and metastasis. Historically, IRF5 has been studied as a transcription factor in the context of genetic risk for autoimmune diseases. However, mining of The Cancer Genome Atlas revealed that loss of IRF5 expression in human breast cancer is significantly linked with progression to high grade carcinoma, increased metastasis, and decreased overall and recurrence-free survival. Supporting these analyses, we demonstrated that female Irf5-/- BALB/c mice have higher incidence of spontaneous atypical ductal hyperplasia (ADH), increased progression to DCIS, and ultimately, increased incidence of IDC. Using qPCR, FISH and IHC, we confirmed that IRF5 is expressed in both luminal and basal myoepithelial cells, but expression is higher in basal cells. Histologic analysis of whole mount preparations of Irf5-/- mammary glands revealed aberrant ductal morphogenesis, characterized by expansion of luminal and basal myoepithelial cells with a loss of organized glandular structure. RNAseq of primary mammary epithelial cells from wild type and Irf5-/- littermate mice showed Irf5-/- mammary epithelial cells to be enriched in ribosome biogenesis pathways, the physiologic consequences of which were demonstrated through increased rates of protein synthesis. Transferring our studies in vivo, we demonstrated that loss of tumor IRF5 expression resulted in decreased tumor-infiltrating lymphocytes and increased pulmonary metastasis in the murine orthotopic 4T1 implantation model. Mechanistically, we found that—as in our studies utilizing primary mammary epithelial cells—IRF5 expression in tumors regulated protein translation and ribosome biogenesis. In light of these findings, we propose IRF5 as a novel prognostic biomarker, loss of which alters mammary gland development, drives tumor initiation and metastasis, and dysregulates mammary epithelial cell protein synthesis.

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Matthew Rice, n/a: No financial relationships to disclose
Carter Somerville, PhD: No financial relationships to disclose
Discussion 1 + Q&A: PD13-01, PD13-02, PD13-03 & PD13-04

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12/8/2022
5:00 PM - 6:15 PM
Discussion 2 + Q&A: PD13-05, PD13-06, PD13-07 & PD13-08
Presenting Author(s) and Co-Author(s):
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12/8/2022
5:00 PM - 6:15 PM

**Discussion 3 + Q&A: PD13-09, PD13-10, PD13-11 & PD13-12**

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Poster Spotlight Discussion 13: Therapeutic Approaches for HR+/Her2- Breast Cancer

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PD13-01 Elacestrant in postmenopausal women with estrogen receptor positive and HER2-negative early breast cancer: primary efficacy and safety analysis of the preoperative, window of opportunity SOLT1-1905-ELIPSE trial

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Introduction Elacestrant is the first oral, non-steroidal, selective estrogen receptor degrader (SERD) to demonstrate improved efficacy compared to standard of care endocrine treatment, with greater relative benefit in ESR1-mutated tumors, and manageable safety profile in pretreated patients with metastatic breast cancer (BC) (Bidard F.C., JCO 2022). SOLTI ELIPSE trial (NCT04797728) is a prospective, multicenter, window of opportunity trial designed to assess whether a short-course of preoperative elacestrant may suppress tumor proliferation in postmenopausal women with estrogen receptor positive (ER+)/HER2-negative early BC (Vidal M., SABCS 2021). Here, we present the results of the primary efficacy and safety study.
Eligible patients with operable, untreated ER+/HER2-negative BC that were T1c (≥1.5 cm) - T3 by ultrasound, clinically or radiologically N0 and had a locally assessed Ki67 ≥10%, received elacestrant 400 mg once a day continuously for a total of 4 weeks. At the study treatment completion, patients were treated according to local practice. Centralized assessment of post-treatment (D28) Ki67 from surgical specimen or tumor biopsy was required for the primary endpoint evaluation. Primary efficacy endpoint was complete cell cycle arrest (CCCA), defined as Ki67 lymphocytes (TILs), switch in PAM50 subtypes and differential expression of 192 genes from baseline (D1) to D28 was also explored. Adverse events (AEs) were graded according to CTCAE v5.0. Results Between April 2021 and February 2022, 24 patients were enrolled and 22 were evaluable for the primary endpoint. Baseline characteristics were: mean age 69 years (range 50-81); ductal histology 74%; T1c 61%; T2 39%; grade 1-2 83%; median local Ki67 20% (10-70). Baseline PAM50 subtypes distribution was: Luminal A (n=12), Luminal B (n=8), Basal-like (n=1), Normal-like (n=1). At D28, CCCA was achieved in the 27% (n=6) of the patients. Ki67 varied consistently in both Ki67 < 20% (rr=-38%; 95% CI, -16 to -46%; 95% CI, -20 to -72%) groups. Overall, elacestrant was associated with a shift towards a more endocrine sensitive and less proliferative phenotype based on PAM50 gene signatures. CCCA occurred in 45% of Luminal A tumors, whereas no CCCA was observed among Luminal B tumors. Levels of TILs were significantly higher at D28 (mean difference, +3.73; p=0.004). Elacestrant induced high expression of immune-response genes including IGJ, GZMB, CD4, CD8a and suppressed proliferation (e.g., UBE2T, MYBL2, BIRC5, MK67) and estrogen-signaling (e.g., ESR1, PGR, CCND1, BRCA2) genes (false discovery rate 5%). These changes in gene expression were observed both in tumors with D28 Ki67 ≤2.7% and in those with D28 Ki67 >10%. Overall, elacestrant was associated with relevant biological and molecular response and with manageable safety profile. Globally, these findings support further exploration of this highly potent, novel oral SERD in early BC.

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PD13-02

PD13-02 Exploratory gene expression analysis of coopERA Breast Cancer (BC): a study evaluating neoadjuvant giredestrant versus anastrozole alone and in combination with palbociclib in ER-positive, HER2-negative untreated early BC

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Background: Endocrine therapy remains the mainstay treatment for ER+ BC. CDK4/6 inhibitors induce cell cycle arrest and decrease tumor cell proliferation, as measured by the biomarker Ki67, when used in combination with aromatase inhibitors (AI) such as anastrozole (A). Giredestrant is an oral, well-tolerated, and highly potent selective ER degrader (SERD) that achieves robust ER suppression and has demonstrated antitumor activity in the metastatic setting either as monotherapy or in combination with the CDK4/6 inhibitor palbociclib. The randomized, phase 2 coopERA Breast Cancer study (NCT04436744) evaluated giredestrant in postmenopausal women with untreated ER+/HER2- early BC and met its primary endpoint, demonstrating superior Ki67 suppression with giredestrant vs A after two weeks of single agent treatment. This suppression was maintained at surgery where giredestrant vs A was evaluated in combination with palbociclib. Here, we present gene expression analysis and associations with Ki67 response. Methods: 221 eligible patients with measurable ER+/HER2– untreated early BC and baseline Ki67 ≥ 5% were randomized 1:1 to receive 30 mg oral daily (PO QD) giredestrant or 1 mg PO QD A on Days 1–14 of a neoadjuvant window-of-opportunity phase, followed by four 28-day cycles of Days 1–21 before surgery. FFPE specimens were collected at baseline, week 2 and surgery; and RNA-sequencing (seq) was performed. Gene expression analysis included ER pathway activity, PAM50 intrinsic subtypes, and other pathway analyses, assessed by Ki67 response. Results: 112 and 92 patients had paired tumor samples at baseline/week 2 and baseline/surgery, respectively, that were evaluable for RNA-seq and Ki67. The trend for greater Ki67 protein suppression by giredestrant vs A from baseline to week 2 was maintained in the RNA-seq evaluable subset. Interestingly, the same subset revealed similar suppression of both proliferation gene signatures and ER pathway activity between A and giredestrant. PAM50 subtyping showed that 69% of tumors were luminal (Lum) A and 29% were LumB at baseline. Less than 1% were classified as basal or HER2. Interestingly, giredestrant (G) showed greater suppression of both Ki67 and ER pathway activity vs A in LumB tumors (Ki67: -82% [G] vs -62% [A]; ER activity: -0.83 [G] vs -0.66 [A]) compared to LumA at week 2 (Ki67: -74% [G] vs -71% [A]; ER activity: -0.60 [G] vs -0.70 [A]). Moreover, at week 2, 83% (13/18) of LumB tumors at baseline transitioned into a LumA subtype after giredestrant treatment compared to 46% (5/11) of A-treated tumors. Giredestrant-treated tumors also achieved lower mean ER pathway activity compared to those treated with A at surgery (p=0.023). Gene set enrichment analysis showed downregulation of cell-cycle and ER-related pathways at week 2 and surgery in both treatment arms. A subset of cytokine signaling and immune response pathways were increased at week 2 compared to baseline after treatment with A but not with giredestrant. These pathways were also associated with Ki67 resistance (Ki67 ≥ 7.4%) in A-treated tumors. Notably, IL12 signaling was enriched in tumors resistant to A but not giredestrant. Conclusions: Giredestrant has a greater effect on Ki67 protein suppression in ER+/HER2- early BC compared to A, which is more pronounced in LumB tumors. This benefit may involve differential regulation of cytokine and immune responses. These exploratory findings reveal novel mechanisms that may differentiate the activity of SERDs vs AIs, which warrant further validation.

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12/8/2022
5:00 PM - 6:15 PM
PD13-03 WITHDRAWN
BACKGROUND

Endocrine therapy (ET) is the mainstay for management of estrogen receptor (ER)+ advanced breast cancer (aBC). Giredestrant is a highly potent, nonsteroidal, oral selective ER antagonist and degrader (SERD) that achieves robust ER occupancy. The Phase II randomized, open-label acelERA BC study (NCT04576455) evaluated giredestrant vs physician’s choice of ET (PCET) in the second- or third-line ER+, HER2– aBC setting. While the study did not reach statistical significance for its primary endpoint of investigator-assessed progression-free survival (INV-PFS), the giredestrant arm demonstrated a numerical improvement vs the PCET arm, with a hazard ratio of 0.81 (95% confidence interval: 0.60, 1.10), and encouraging results
for key secondary efficacy endpoints (clinical benefit rate [CBR]: 32% vs 21%, respectively; objective response rate [ORR]: 13% vs 7%, respectively). We report exploratory subgroup analyses of these efficacy endpoints by prior treatments and by baseline circulating tumor (ct)DNA biomarkers.

METHODS
Patients were post- and pre- or peri-menopausal women, or men, with ER+, HER2– aBC who had progressed after 1–

(30 mg oral daily) or PCET between fulvestrant or an aromatase inhibitor (AI), stratified by disease site (visceral vs non-visceral), prior CDK4/6 inhibitor, and prior fulvestrant. Biomarkers were assessed in baseline ctDNA isolated from plasma using the FoundationOne Liquid CDx or PredicineCARE assays. ESR1 mutations were defined as short variants with known or likely impact on ER protein function.

RESULTS
Among the 303 patients enrolled, prior aBC therapies included CDK4/6 inhibitors (42%), fulvestrant (19%), and chemotherapy (32%). Overall, most baseline characteristics were balanced across arms in subgroups. Efficacy in key subgroups by prior treatment and in ESR1-mutated tumors is shown in the table. Efficacy by PCET (75% received fulvestrant; 25%, an AI) and by type of ESR1 mutation will be presented. Clinical benefit (INV-PFS, CBR, ORR) was most prominently observed with giredestrant in patients with ESR1-mutated tumors. In the baseline ctDNA-evaluable population (232/303 patients; 77%), ESR1 and PIK3CA were the most prevalent mutations overall (39% and 36%, respectively). The most common ESR1

as ESR1-mutated had multiple ESR1 mutations detected (range of 2–7 mutations), demonstrating clonal heterogeneity. Clinical benefit was also observed with giredestrant in patients expressing different ESR1 mutations. Updated data will be presented.

CONCLUSIONS
Exploratory subgroup analyses showed favorable outcomes with giredestrant in terms of INV-PFS, CBR, and ORR across most key subgroups. The benefit was more pronounced in a) patients with ESR1-mutated tumors and b) patients who received prior fulvestrant (the majority of AI-treated patients in the PCET arm). Overall, these data support continued investigation of giredestrant to advance and improve treatment outcomes in hormone receptor+ BC.

Exploratory subgroup analyses
<table>
<thead>
<tr>
<th>Exploratory subgroup analyses</th>
<th>INV-PFS (95% CI)</th>
<th>Median INV-PFS, months</th>
<th>CBR, %</th>
<th>ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CDK4/6i</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gideorexirat (n = 63)</td>
<td>0.80 (0.92, 1.23)</td>
<td>3.7</td>
<td>27.0</td>
<td>14.3</td>
</tr>
<tr>
<td>PCET (n = 62)</td>
<td>3.5</td>
<td>11.3</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>No prior CDK4/6i</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gideorexirat (n = 88)</td>
<td>0.92 (0.61, 1.38)</td>
<td>7.2</td>
<td>35.2</td>
<td>11.4</td>
</tr>
<tr>
<td>PCET (n = 90)</td>
<td>5.6</td>
<td>27.8</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy for abBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gideorexirat (n = 47)</td>
<td>0.92 (0.53, 1.58)</td>
<td>5.6</td>
<td>39.2</td>
<td>14.9</td>
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<tr>
<td>PCET (n = 49)</td>
<td>5.5</td>
<td>24.5</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>No prior chemotherapy for abBC</td>
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<td></td>
<td></td>
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<tr>
<td>gideorexirat (n = 104)</td>
<td>0.87 (0.61, 1.24)</td>
<td>5.5</td>
<td>29.8</td>
<td>11.5</td>
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<tr>
<td>PCET (n = 103)</td>
<td>5.4</td>
<td>19.4</td>
<td>5.8</td>
<td></td>
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<tr>
<td>Prior fulvestrant</td>
<td></td>
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<tr>
<td>gideorexirat (n = 29)</td>
<td>0.65 (0.35, 1.23)</td>
<td>3.6</td>
<td>6.9</td>
<td>0</td>
</tr>
<tr>
<td>PCET (n = 29)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*ESRT mutation</td>
<td></td>
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</tr>
<tr>
<td>gideorexirat (n = 51)</td>
<td>0.55 (0.33, 0.93)</td>
<td>3.5</td>
<td>25.5</td>
<td>13.7</td>
</tr>
</tbody>
</table>

* Almost all received an AI.

aBC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate (complete or partial response, or stable disease for ≥6 months, calculated in the full analysis set); CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CI, confidence interval; HRunstr, unstratified hazard ratio; INV-PFS, investigator-assessed progression-free survival; ORR, objective response rate (confirmed complete or partial response, calculated in the full analysis set); PCET, physician’s choice of endocrine therapy.

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PD13-05

PD13-05 Updated results of a Phase 1b study of gedatolisib plus palbociclib and endocrine therapy in women with hormone receptor positive advanced breast cancer: Subgroup analysis by PIK3CA mutation status

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Background: Addition of PI3K/mTOR inhibitor after progression on CDK4/6 inhibitor (CDK4/6i) and endocrine therapy (ET) can potentially restore sensitivity to CDK4/6i and prevent adaptive activation of the PI3K/mTOR pathway. To evaluate this hypothesis, we conducted a Phase Ib study of gedatolisib (G), a dual inhibitor of PI3K/mTOR, palbociclib (P) a CDK4/6i, and ET (with letrozole [LET] or fulvestrant [FUL]) in women with hormone receptor positive (HR+)/HER2-advanced breast cancer (ABC). Manageable toxicity and preliminary antitumor activity were observed in 35 patients (pts) enrolled in the dose escalation portion of the study (Forero-Torres, ASCO 2018) and 103 pts enrolled in the expansion portion of the study (Layman, SABCS 2021). Here, we report updated efficacy and safety data and sub-group analysis by PIK3CA mutation status in the four expansion study arms with a March 3, 2022, data cut-off.

Methods: Pts with HR+/HER2- ABC were treated in four expansion arms: A) G+P+LET as first-line treatment, B) G+P+FUL as 2nd line treatment in pts without prior CDK4/6i; C & D) G+P+FUL as 2nd or 3rd line therapy in pts with prior CDK4/6i. P, LET, and FUL were administered at standard doses. G 180 mg was intravenously administered weekly in Arms A, B, and C and three weeks on/one week off in Arm D. The primary endpoint was investigator assessed objective response rate (ORR). Secondary endpoints included safety, duration of response and progression free survival (PFS).

Results: Of the 103 pts treated with G+P+ ET in the expansion arms (A-D), 100% had measurable disease at baseline, 71% (73/103) lacked PIK3CA mutations (wild type; WT), 27% (28/103) had PIK3CA-mutations (MT), 70% (72/103) had evidence of bone metastases, and 59% (61/103) had liver metastases. The most frequent grade 3 and 4 treatment related AEs (TRAE) with G+P+ET included neutropenia (63%), stomatitis (27%), rash (20%), fatigue (11%) and hyperglycemia (7%). Treatment discontinuation due to TRAEs was 6.5% in Arm A, 15.4% in Arm B, 9.4% in Arm C and 3.7% in Arm D. Efficacy data for each arm is presented in Table 1. Promising ORR and PFS were seen in all arms regardless of PIK3CA mutation status. In Arm D, ORR was 63% overall, 73% in PIK3CA-MT pts, and 60% in PIK3CA-WT pts. Median PFS in Arm D was 12.9 months with a median follow up of 29 months. 60% and 48% of pts in the PIK3CA-MT and PIK3CA-WT Arm D sub-groups, respectively, were progression free at 12 months.
Conclusions: These preliminary data demonstrate promising activity of G+P+ET combination in pts who were CDK4/6i-naïve and in those whose disease progressed on or after CDK4/6i therapy regardless of PIK3CA mutation status. Encouraging results in CDK4/6i treatment naïve patients warrant further evaluation of gedatolisib in combination with CDK4/6i treatment in the front-line setting. Arm D results provide a strong basis for the initiated Phase 3 study (VIKTORIA-1) in pts whose disease progressed on or after CDK4/6i therapy.

Table 1. Efficacy Data by Expansion Arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (full, resp. evaluable)</td>
<td>31, 27</td>
<td>13, 13</td>
<td>32, 28</td>
<td>27, 27</td>
</tr>
<tr>
<td>Patients</td>
<td>1L: CDK4/6i-Naive</td>
<td>2L+ CDK4/6i-naive</td>
<td>2L/3L: CDK4/6i-pretreated</td>
<td>2L/3L: CDK4/6i-pretreated</td>
</tr>
<tr>
<td>PIK3CA Status</td>
<td>WT / MT (78% / 22%)</td>
<td>WT / MT (69% / 31%)</td>
<td>WT / MT (71% / 29%)</td>
<td>WT / MT (56% / 41%)</td>
</tr>
<tr>
<td>ORR (evaluable)</td>
<td>85%</td>
<td>77%</td>
<td>36%</td>
<td>63%</td>
</tr>
<tr>
<td>mPFS (mos)</td>
<td>Not Reached</td>
<td>12.9</td>
<td>5.1</td>
<td>12.9</td>
</tr>
<tr>
<td>Median follow-up (mos)</td>
<td>33.1</td>
<td>Not Reached</td>
<td>27.6</td>
<td>29.0</td>
</tr>
<tr>
<td>PFS % at 12 mos</td>
<td>72.1%</td>
<td>54.5%</td>
<td>24.9%</td>
<td>53.3%</td>
</tr>
</tbody>
</table>

*Response evaluable analysis set per RECIST v1.1 including uPR; **full analysis set; † Baseline PIK3CA mutation status missing for one pt; 1L = first line; 2L = second line; 3L = third line; mos = months; WT = wild type; MT = PIK3CA Mutation

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PD13-06

PD13-06 Long-Term and Very-Long-Term Disease Control in Patients From BYLieve Study Cohort A With PIK3CA-Mutant, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, Advanced Breast Cancer

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Introduction: PIK3CA mutations, seen in ~40% of patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC), are associated with treatment (Tx) resistance and shorter survival. Alpelisib (ALP) is an α-selective PI3K inhibitor and degrader indicated for treating this population in combination with fulvestrant (FUL) after endocrine therapy (ET). Previous results from the SOLAR-1 study showed that progression-free survival (PFS) ≥18 mo is achievable for pts treated with ALP on/after prior Tx with aromatase inhibitor (AI). Here, we analyze pts from BYLieve study Cohort A who achieved long-term (LT) and very-long-term (VLT) disease control with ALP + FUL after prior Tx with cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and AI.

Methods: BYLieve was a Phase II, nonrandomized, open-label, 3-cohort study of ALP + ET in pts with PIK3CA-mutated, HR+, HER2– ABC whose disease progressed on/after prior CDK4/6i. In Cohort A, median (m) PFS was 7.26 mo. LT disease control was defined as ≥12 mo PFS and VLT disease control as ≥18 mo PFS. Pts with < 12 mo PFS were defined as non-LT. Baseline characteristics are summarized by duration of disease control. Incidence rate (IR) per 100 patient-treatment years (PTY) was calculated to assess exposure-adjusted adverse events (AE). To assess tumor complexity in LT/VLT pts, median circulating tumor DNA (ctDNA) fraction, chromosome (chr) 8/11 amplification, and ESR1 mutations were determined by next-generation sequencing.

Results: In BYLieve Cohort A, 31 of 121 pts (25.6%) achieved LT disease control with an mPFS of 24.8 mo (95% CI 18.2 mo to not estimable [NE]) and 20 of 121 pts (16.5%) achieved VLT disease control (mPFS NE; 95% CI 22.1 mo to NE). Pts with LT/VLT disease control had lower BMI and ECOG score, longer time from initial diagnosis to first recurrence/relapse, more frequent bone-only lesions, and fewer liver metastases than non-LT pts (Table). Median ALP relative dose intensity was 86.7%, 91.7%, 85.0%, and 85.1% for all Cohort A pts (n=127), non-LT (n=96), LT (n=31), and VLT disease control (n=20), respectively, whereas median ALP exposure was 5.13 mo, 3.61 mo, 21.29 mo, and 25.25 mo respectively. The IRs per 100 PTY of diarrhea, hyperglycemia, and rash were lower in LT (IR 128.4, n=24; IR 78.0, n=20; IR 21.6, n=10 respectively) and VLT (IR 93.5, n=15; IR 51.2, n=11; IR 24.9, n=8 respectively) pts than non-LT pts (IR 250.5, n=57; IR 251.5, n=56; IR 85.4, n=30 respectively). In LT and VLT pts ctDNA fraction was 2% and 5% respectively, whereas ctDNA fraction in non-LT pts was 14%. Incidence of chr 8/11 amplification was 10% in both LT and VLT pts and 20% in non-LT pts; incidence of ESR1 mutations was 26%, 25%, and 27% in LT, VLT, and non-LT pts respectively.

Conclusions: In pts with PIK3CA-mutated, HR+, HER2– ABC treated with ALP + FUL after CDK4/6i, LT and VLT disease control was observed in 25.6% and 16.5% of patients, respectively. Visceral disease, development of AEs, and ESR1 mutations did not preclude LT/VLT disease control. These data confirm that targeting the PIK3CA driver mutation with ALP + FUL post-CDK4/6i Tx may lead to LT disease control.
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### Table - Baseline characteristics in BYL 001 Cohort A overall and by duration of disease control

<table>
<thead>
<tr>
<th></th>
<th>Overall population (n=127)</th>
<th>Non-LT disease control (&lt;12 mo PFS) (n=58)</th>
<th>LT disease control (12 mo PFS) (n=31)</th>
<th>VL-T disease control (18 mo PFS) (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), y</strong></td>
<td>56.7 (48.0-65.0)</td>
<td>58.8 (47.5-64.5)</td>
<td>57.9 (48.0-67.0)</td>
<td>66.0 (50.0-68.0)</td>
</tr>
<tr>
<td><strong>Body mass index, median (range), kg/m²</strong></td>
<td>25.3 (16.1-46.6)</td>
<td>26.1 (16.1-46.6)</td>
<td>24.7 (16.5-35.3)</td>
<td>24.3 (16.5-33.5)</td>
</tr>
<tr>
<td><strong>Eastern Cooperative Oncology Group performance status, n (%)</strong></td>
<td>81 (63.8)</td>
<td>59 (61.5)</td>
<td>22 (71.0)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>0</td>
<td>41 (32.3)</td>
<td>33 (34.4)</td>
<td>8 (25.8)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>1</td>
<td>2 (1.6)</td>
<td>2 (2.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (2.4)</td>
<td>2 (2.1)</td>
<td>1 (3.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Time from initial diagnosis to first recurrence/relapse, median (range), mo</strong></td>
<td>33.1 (8.4-239.7)</td>
<td>29.2 (7.7-239.7)</td>
<td>70.4 (0.4-201.4)</td>
<td>83.6 (0.5-201.4)</td>
</tr>
<tr>
<td><strong>Extent of metastatic disease, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>2 (1.6)</td>
<td>2 (2.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone</td>
<td>108 (85.0)</td>
<td>73 (82.3)</td>
<td>29 (93.5)</td>
<td>18 (90.0)</td>
</tr>
<tr>
<td>Bone only</td>
<td>24 (18.9)</td>
<td>12 (12.6)</td>
<td>12 (38.7)</td>
<td>6 (30.6)</td>
</tr>
<tr>
<td>Brain</td>
<td>6 (4.7)</td>
<td>4 (4.2)</td>
<td>2 (6.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Visceral</td>
<td>85 (66.9)</td>
<td>69 (75.9)</td>
<td>16 (51.6)</td>
<td>12 (60.0)</td>
</tr>
<tr>
<td>Lung</td>
<td>43 (33.9)</td>
<td>33 (34.4)</td>
<td>10 (32.3)</td>
<td>8 (40.0)</td>
</tr>
<tr>
<td>Liver</td>
<td>59 (46.5)</td>
<td>55 (55.2)</td>
<td>6 (19.4)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Other visceral</td>
<td>8 (6.3)</td>
<td>5 (5.3)</td>
<td>2 (6.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (3.1)</td>
<td>2 (2.1)</td>
<td>2 (6.5)</td>
<td>1 (5.0)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>36 (28.3)</td>
<td>32 (33.3)</td>
<td>4 (12.9)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9.4)</td>
<td>9 (9.4)</td>
<td>3 (9.7)</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>1 (0.8)</td>
<td>1 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Number of prior lines of medical therapy in metastatic setting, n (%)</strong></td>
<td>0</td>
<td>2 (1.6)</td>
<td>2 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>101 (79.5)</td>
<td>74 (77.1)</td>
<td>27 (87.1)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>2</td>
<td>38 (30.1)</td>
<td>18 (15.8)</td>
<td>4 (12.9)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.8)</td>
<td>1 (1.0)</td>
<td>0</td>
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PD13-07

PD13-07 Combination therapy with the AKT inhibitor, ipatasertib, endocrine therapy, and a CDK4/6 inhibitor for hormone receptor positive (HR+)/HER2 negative metastatic breast cancer (MBC): results from the phase I TAKTIC trial.

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) provide significant clinical benefit in patients with HR+/HER2- metastatic breast cancer (MBC) and have become a standard of care treatment. Prior insights from tumor profiling and preclinical analyses suggest that AKT1 activation can induce CDK4/6i resistance. We hypothesized that targeting AKT1 following CDK4/6i progression may be an effective therapeutic strategy and conducted a clinical trial to evaluate both doublet (ET+AKTi) and triplet (ET+AKTi+CDK 4/6i) therapy.

Methods: TAKTIC is an open-label phase Ib clinical trial (clinicaltrials.gov NCT03959891) evaluating the combination of the AKT inhibitor ipatasertib (ipat) with fulvestrant (Arm A), an aromatase inhibitor (Arm B), or the triplet combination (Arm C) with fulvestrant + palbociclib (palbo). The primary objective is to evaluate the safety (NCI CTCAE 5.0) and tolerability of ipat in combination with endocrine therapy +/- CDK4/6i. Secondary objectives include clinical efficacy, as determined by objective response rate (RECIST v1.1), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS). Key inclusion criteria include unresectable HR+/HER2- MBC; at least 1 prior therapy for MBC including any CDK4/6i; up to 2 prior lines of chemotherapy for MBC (no limit on prior endocrine therapy). Here, we present an updated interim analysis from all study arms.

Results: The trial completed accrual with 77 pts enrolled from June 2019 – February 2022, including 19 on Arm A, 16 on Arm B, and 42 on Arm C. Median age was 62 (range 32-88) and 65/77 pts (84%) received prior CDK4/6i (median no. of prior lines = 3, range 1-13). 56/77 pts (73%) had measurable disease at baseline and 50/77 pts (65%) had visceral metastases in the liver/lung (68% Arm A, 44% Arm B, 71% Arm C). Pts enrolled on Arms A and B received ipat at 400mg in combination with fulvestrant or an aromatase inhibitor, respectively. In Arm C, 27/42 pts enrolled into the dose escalation phase and received ipat + palbo at varying doses in combination with fulvestrant. Two DLTs were observed in the 300mg ipat + 125mg palbo cohort. Treatment was well tolerated in all arms. Grade 3 and 4 toxicities included neutropenia (39/77, 50.6%), leukopenia (15/77, 19.5%), diarrhea (11/77, 14/3%), transaminitis (7/77, 9.1%), lymphopenia (6/77, 7.8%), rash (6/77, 7.8%), and thrombocytopenia (3/77, 3.9%). As of 6/28/2022, 16/77 pts remain on treatment. The median treatment duration for all pts is estimated at 6 months (range 0.5-39). Among the 56 pts with measurable disease, 11 had partial response (PR) and 32 had stable disease (SD) as the best response. CBR, defined as percentage of pts who achieved PR or SD > 6 months, was 48% across the study (53% Arm A, 31% Arm B, 57% Arm C). The median PFS was 5.5 months (95% confidence interval [CI]: 3.8 – 7.4) and the median OS was 24.5 months (95% CI: 17.1 – 33.9). Conclusions: The combination of ipat with endocrine therapy +/- palbo is well tolerated in heavily pre-treated pts, with preliminary evidence of clinical activity. This trial demonstrates how molecular insights related to CDK4/6i resistance inform potential therapy combinations. Further studies are needed to evaluate AKTi-based combinations in pts with HR+ MBC.
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PD13-08 Phase 1 TROPION-PanTumor01 Study Evaluating Datopotamab Deruxtecan (Dato-DXd) in Unresectable or Metastatic Hormone Receptor–Positive/HER2–Negative Breast Cancer (BC)

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Background: Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I (Topo I) inhibitor payload via a stable, tumor-selective, tetrapeptide-based cleavable linker. Dato-DXd demonstrated compelling single-agent antitumor activity in heavily pretreated patients (pts) with metastatic triple-negative BC (Krop, SABCS 2021). This is the first report of results from the TROPION-PanTumor01 study in pts with unresectable or metastatic hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–low and HER2-zero) BC.

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 findings and exposure-response results from pts with NSCLC, Dato-DXd 6 mg/kg IV Q3W is being evaluated in pts with unresectable or metastatic HR+/HER2− BC that progressed on standard therapies. The primary objectives were safety and tolerability. Tumor responses, including ORR (complete response [CR] + partial response [PR]) and DCR (CR + PR + stable disease [SD]), were assessed per RECIST version 1.1 by blinded independent central review.

Results: As of the April 29, 2022, data cutoff, 41 pts had received Dato-DXd (median follow-up, 10.9 mo [range, 7-13]); 9 pts were ongoing. The primary cause of treatment discontinuation was disease progression (63%; progressive disease [PD] or clinical progression). Median age was 57 y (range, 33-75); 54% had de novo metastatic disease. Pts were heavily pretreated (Table) with a median of 5 (range, 3-10) prior regimens in the advanced setting; 95% had prior CDK4/6i (adjuvant/metastatic). Median time from initial treatment for metastatic disease to the first dose of Dato-DXd was 42.7 mo (range, 10.2-131.1). Treatment-emergent adverse events (TEAEs; all cause) were observed in 98% (any grade) and 41% (grade ≥3) of pts. Most common TEAEs (any grade, grade ≥3) were stomatitis (80%, 10%), nausea (56%, 0%), fatigue (46%, 2%), and alopecia (37%, 0%). Serious TEAEs were observed in 6 pts (15%); 1 pt died due to dyspnea, which was not considered to be treatment related. Dose reductions occurred in 5 pts due to stomatitis (n=3), fatigue (n=2), keratitis (n=1), and decreased appetite (n=1) (>1 AE per pt); 14 pts had treatment delayed due to stomatitis (n=8), retinopathy (n=1), dysphagia (n=1), fatigue (n=1), malaise (n=1), COVID-19 (n=1), cellulitis (n=1), urinary tract infection (n=1), decreased lymphocyte count (n=1), and nasal congestion (n=1; >1 AE per pt). Three pts discontinued treatment due to keratitis (n=1) and pneumonitis (n=2); 1 case of pneumonitis was adjudicated as grade 2 drug-related interstitial lung disease. The ORR was 29% (11 confirmed PRs; 1 pending confirmation), the DCR was 85% (35/41), and the clinical benefit rate (CR + PR (46%, 2%), and alopecia (37%, 0%). Serious TEAEs were observed in 6 pts (15%); 1 pt died due to dyspnea, which was not considered to be treatment related. Dose reductions occurred in 5 pts due to stomatitis (n=3), fatigue (n=2), keratitis (n=1), and decreased appetite (n=1) (>1 AE per pt); 14 pts had treatment delayed due to stomatitis (n=8), retinopathy (n=1), dysphagia (n=1), fatigue (n=1), malaise (n=1), COVID-19 (n=1), cellulitis (n=1), urinary tract infection (n=1), decreased lymphocyte count (n=1), and nasal congestion (n=1; >1 AE per pt). Three pts discontinued treatment due to keratitis (n=1) and pneumonitis (n=2); 1 case of pneumonitis was adjudicated as grade 2 drug-related interstitial lung disease. The ORR was 29% (11 confirmed PRs; 1 pending confirmation), the DCR was 85% (35/41), and the clinical benefit rate (CR + PR
Conclusions: Dato-DXd demonstrated a manageable safety profile and encouraging antitumor activity, with high disease control in heavily pretreated pts, the majority having received prior CDK4/6i. Based on these findings, the TROPION-Breast01 (NCT05104866) randomized phase 3 study comparing 2L+ Dato-DXd vs investigator’s choice chemotherapy is currently enrolling.

Prior Therapies in the Adjuvant or Metastatic Setting

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>% (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine and chemotherapy</td>
<td>98</td>
</tr>
<tr>
<td>CDK4/6i</td>
<td>95</td>
</tr>
<tr>
<td>≤12 months</td>
<td>44</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>51</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>83</td>
</tr>
<tr>
<td>Taxanes</td>
<td>59</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>54</td>
</tr>
<tr>
<td>(Neo)adjuvant chemotherapy</td>
<td>37</td>
</tr>
<tr>
<td>PI3KCAi</td>
<td>20</td>
</tr>
<tr>
<td>PARPi</td>
<td>15</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>7</td>
</tr>
<tr>
<td>Topo I inhibitor–based ADC therapy</td>
<td>0</td>
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</table>

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PD13-09 Clinical outcomes of patients with HR+ HER2- advanced breast cancer with early progression on CDK4/6 inhibitors

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Background: CDK4/6 inhibitors (CDK4/6i) paired with endocrine therapy (ET) are considered first-line (1L) therapy for patients (pts) with HR+ HER2- advanced breast cancer (aBC). A minority of pts will demonstrate primary resistance to CDK4/6i, as characterized by early progression. Thymidine kinase 1 (TK1) is a cell-cycle regulated enzyme downstream of CDK4/6 and involved in nucleotide metabolism during DNA synthesis. Prior studies have shown TK1 may serve as a biomarker of response to CDK4/6i, with early TK1 activity (TK1a) suppression after initiation of CDK 4/6i therapy associated with improved PFS. Lack of TK1a suppression may be associated with primary resistance to CDK4/6i. In this study, we aim to analyze response to subsequent lines of therapy and overall survival (OS) of pts with early progression on 1L CDK4/6i. Methods: Pts with HR+ HER2- aBC from a phase II trial of an alternative schedule of palbociclib (palbo alt dosing trial NCT 3007979) and from a retrospective palbociclib study were included in this analysis. Pts in the palbo alt dosing trial underwent baseline and C1D15 TK1a analysis after initiation on CDK4/6i. Pts in the retrospective palbociclib study included pts receiving palbo as part of their standard of care 1L therapy for HR+ HER2- aBC at Washington University in Saint Louis from 2016 to 2021. Clinical information, including treatment start and stop dates on each of the next-line therapies, were collected from the electronic medical record. PFS was estimated by the treatment duration on a specified treatment regimen. Early progression on CDK4/6i was defined as PFS < 6 mo. Best response was defined as next line of therapy with the numerically longest PFS. OS was defined as time to death from the initiation of CDK4/6i. Results: Of the 54 pts enrolled on the palbo alt dosing trial, 51 pts were evaluable for clinical
benefit and 46 pts were evaluable for TK1a suppression rate at C1D15. 7 pts (15.2%) were found without TK1a suppression at C1D15. This lack of TK1a suppression on palbo was associated with a significantly shorter PFS (median PFS=3.1 mo) compared to not reached in pts with TK1a suppression at C1D15. We conducted clinical analysis on N=26 pts who exhibited early progression on CDK4/6i which included 10 pts from the palbo alt dosing trial and 16 from the retrospective study. The average subsequent line of therapies in this cohort was 3, with the most common second line (2L) therapy being chemotherapy (N=17, 65.4%) and ET (N=8, 30.8%). The median PFS for pts receiving 2L chemotherapy and ET was 4.09 mo and 3.64 mo, respectively. 10 pts received both chemotherapy and ET with 7 (70.0%) achieving best response with chemotherapy compared to 3 pts (30.0%) who achieved best response with ET. The median OS for the cohort was 14.6 mo. Conclusions: Early progression on CDK4/6i is associated with a particularly poor prognosis. In our cohort, the median OS was far below the expected median OS for pts receiving 1L palbo as reported in the PALOMA-2 trial (14.6 mo vs 53.9 mo). Early progression on CDK4/6i is associated with more aggressive disease which may respond more favorably to chemotherapy, as demonstrated by best response to therapy. Further prospective studies are warranted to explore this treatment approach.

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PD13-10 Impact of Proton Pump Inhibitors (PPI) on Palbociclib (PAL) Outcomes in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer (HR+/HER2- ABC): Exploratory Analysis of the PARSIFAL Trial

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Background The use of PPI among cancer patients (pts) is quite frequent. PAL is an oral, cyclin-dependent kinase 4 and 6 inhibitor recommended to be taken under fed conditions. PAL showed a reduced solubility when gastric pH is >4.5, a level commonly achieved by PPI. Observational, retrospective studies on concomitant PPI with PAL or ribociclib showed a shorter progression-free survival (PFS) among PPI users than nonusers. In the randomized, phase 2 PARSIFAL trial, PAL plus fulvestrant demonstrated no improvement in PFS and overall survival (OS) versus PAL plus letrozole as frontline treatment in HR+/HER2- ABC pts (Llombart-Cussac et al, JAMA Oncol 2021). Here we assessed the impact of PPI on PAL efficacy and safety in pts included in the PARSIFAL study. Methods Pts with endocrine-sensitive HR+/HER2- ABC and no prior therapy in advanced setting were randomly assigned to received over the entire PAL-based regimen were defined as PPI users, or PPI naïve (N-PPI) if no PPI was administered over the whole study treatment. We carried out two analyses considering early PPI users (E-PPI) –composed by pts who were receiving PPI since the PAL-based regimen initiation– and long-term PPI users (LT-PPI) –composed by pts who received
based regimen. PPI users defined as neither E-PPI nor LT-PPI were excluded from the analysis to avoid biases due to the PPI limited exposition. PFS, OS, and safety were compared among groups. Landmark analysis at 3, 6, 12, 18, 24, and 30 months (mo) was used for survival estimates conditional on surviving to certain time points and adjust for immortality bias in comparison between N-PPI and PPI users. Analyses were adjusted by stratification factors and patient characteristics. Results Of 486 pts included in the study, 325 (66.9%) were N-PPI. Among 161 (33.1%) PPI users, 64 (13.2%) were E-PPI and 91 (18.7%) were LT-PPI. Omeprazole was the most prescribed PPI in 80.7% (130 of 161) of PPI users. Median exposition to PPI for PPI users, E-PPI, and LT-PPI was 13.6, 15.9, and 19.4 mo, respectively. Compared with N-PPI, E-PPI and LT-PPI were older (median age, 60.5 vs 66.5 vs 67.0 years, respectively; \( P < 0.001 \)) and had a worse functional status (ECOG PS of 0, 60.0% vs 34.0% vs 43.0%, respectively; \( P = 0.002 \)). Median follow-up for the whole population was 32 mo. Median PFS was 28.7 mo in N-PPI compared with 23.0 mo in E-PPI (HR 1.5; 95%CI 1.1–2.2; \( P = 0.024 \)) and 23.0 mo in LT-PPI (HR 1.4; 95%CI 1.0–1.9; \( P = 0.035 \)). Both PPI groups had poorer median PFS than N-PPI by landmark analysis at 3 and 12 mo. Subgroup analysis showed a consistent trend regardless of endocrine partner. Three-year OS rate was 81.1% in N-PPI compared with 63.5% in E-PPI (HR 2.2; 95%CI 1.3–3.7; \( P = 0.003 \)) and 62.0% in LT-PPI (HR 2.1; 95%CI 1.4–3.4; \( P = 0.001 \)). Both PPI groups had poorer 3-year OS rate than N-PPI by occurred in 71.7% (233 of 325 pts) of N-PPI compared with 57.8% (37 of 64 pts; \( P = 0.021 \)) of E-PPI and 54.9% (50 of 91 pts; \( P = 0.003 \)) of LT-PPI. Dose reductions and delays due to hematological AEs were reported in 70.8% (230 of 325 pts) of N-PPI compared with 56.3% (36 of 64 pts; \( P = 0.018 \)) of E-PPI and 52.7% (48 of 91 pts; \( P = 0.002 \)) of LT-PPI. At 3 mo, 45.8% (149 of 325 pts) of N-PPI required a dose reduction or delay due to hematological AEs compared with 39.1% (25 of 64 pts; \( P = 0.42 \)) of E-PPI. Conclusions Early and sustained coadministration of PPI with PAL and endocrine therapy were associated with lower efficacy, hematological toxicities, and dose modifications. Despite the post-hoc nature of the study, these findings suggest pharmacokinetic interactions between PPI and PAL capsules. Further confirmatory studies including the tablet formulation of PAL, which is expected to assure its optimal absorption, are needed.

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PD13-11
PD13-11 Final Overall Survival Analysis of Monarch 2: A Phase 3 trial of Abemaciclib Plus Fulvestrant in Patients with Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer

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Background Abemaciclib is approved for patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) with progression on prior endocrine therapy (ET). The MONARCH 2 trial showed a statistically significant benefit in progression-free survival (PFS) (hazard ratio [HR]: 0.553; 95% CI: 0.449-0.681; p < 0.001), overall survival (OS) (HR: 0.757; 95% CI: 0.606-0.945; p = 0.01) and a manageable safety profile for abemaciclib plus fulvestrant compared with fulvestrant alone. Here we report the pre-specified final overall survival (OS) analysis from the MONARCH 2 trial (NCT02107703). Methods MONARCH 2 was a global, randomized, placebo-controlled, double-blind phase 3 trial of abemaciclib or placebo, plus fulvestrant for treatment of pre-, peri- or postmenopausal women with CDK 4 & 6 inhibitor naïve HR+, HER2- ABC that progressed during ET. Pts were randomized 2:1 to receive abemaciclib or placebo, 150 mg twice daily, plus fulvestrant. Randomization was stratified based on site of metastasis (visceral, bone only, or other) and resistance to prior ET (primary versus secondary). OS and safety were key secondary endpoints, and chemotherapy-free survival was an exploratory endpoint defined as the time from randomization to initiation of chemotherapy or death, whichever occurs the earliest. Kaplan-Meier (KM) method was used to analyze time-to-event variables. A stratified Cox proportional hazards model was used to estimate treatment effect hazard ratio (HR). The prespecified final analysis was planned to occur based on approximately 441 OS events. Data cutoff was March 18, 2022. Results 669 women were randomized 2:1 to receive abemaciclib (n = 446) or placebo (n = 223), plus fulvestrant. Baseline characteristics have been previously reported (Sledge et. al., Jama Oncol 2020). The median follow-up time was approximately 80 months and at the time of the data cutoff, 11% of pts were still receiving study drug in the abemaciclib arm versus 2% in the placebo arm. 440 OS events were observed in the ITT population (abemaciclib arm: 283 events; placebo arm: 157 events). The median OS was 45.8 months in the abemaciclib arm and 37.2 months in the placebo arm (HR: 0.784; 95% CI: 0.644-0.955). The maintained separation of the KM curves beyond the medians is illustrated by the differences in the estimated 5- and 6-year OS rates between arms (5-year: 41.2% versus 29.2%; 6-year: 34.7% versus 23.7%; abemaciclib versus placebo respectively). While OS benefit was generally consistent across subgroups, a more pronounced benefit is noted in subgroups associated with a poorer prognosis such as visceral disease (HR: 0.643; 95% CI: 0.499-0.829), primary resistance to ET (HR: 0.634; 95% CI: 0.436-0.922) or negative progesterone receptor status (HR: 0.623; 95% CI: 0.405-0.959). Moreover, the addition of abemaciclib to fulvestrant deferred the initiation of chemotherapy (HR: 0.674; 95% CI: 0.562-0.809), with substantial difference in yearly chemotherapy-free survival rates (3 year: 42% vs 29.3%; 4 year: 37% vs 18.6%; 5 year: 32.4% vs 14.7%). Notably with longer exposure to abemaciclib, no new additional safety risks or cumulative toxicities were identified. Conclusions
At the prespecified final OS analysis of the MONARCH 2 trial, with a median follow-up of 6.5 years, the statistically significant benefit previously demonstrated was confirmed and maintained. OS benefit was generally consistent across subgroups, with numerically greater effect size observed among patients with poorer prognosis. Importantly, the survival benefit came with a substantial extension of the chemotherapy-free survival time, which is an important consideration for pts with ABC. The results also provide assurance of the safety of abemaciclib with longer-term use.

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PD13-12

PD13-12 Imlunestrant, an oral selective estrogen receptor degrader, in combination with abemaciclib with or without an aromatase inhibitor, in estrogen receptor-positive advanced breast cancer: Results from the phase 1a/b EMBER 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. Preclinically, imlunestrant has favorable efficacy and pharmacokinetic (PK) properties, including antitumor activity in ESR1-mutant models, along with enhanced efficacy when combined with abemaciclib. In dose escalation (Phase 1a) and dose expansion (Phase 1b) in the EMBER study, imlunestrant monotherapy was well tolerated with favorable safety, PK and encouraging antitumor activity in heavily pre-treated ER+, HER2- advanced breast cancer (aBC) patients (Jhaveri, ASCO 2022);

present the phase 1b dose expansion of imlunestrant with abemaciclib ± aromatase inhibitor (AI) in EMBER (NCT04188548).

Methods: Phase 1b enrolled patients with ER-positive (ER+), HER2-negative (HER2-) aBC

aBC but must not have received a prior CDK4/6 inhibitor]. Patients were randomized, based on menopausal status and presence of visceral metastases, to receive imlunestrant + abemaciclib OR imlunestrant + abemaciclib + Al. Men and premenopausal women received a concomitant GnRH agonist. Serial plasma samples were obtained for PK and ctDNA analysis. Key endpoints included safety and tolerability, PK, objective response rate (ORR) per RECIST v1.1 (ORR: complete response [CR] or partial response [PR]) in patients with measurable disease), and clinical benefit ra weeks prior to data cut.

Results: As of 26 May 2022, 85 patients have received imlunestrant [n=80 at 400 mg (RP2D); n=5 at 800 mg] in combination with abemaciclib (150mg twice daily) ± Al. Forty-eight (56%) patients had visceral disease and 9% had at least 1 ESR1 mutation detected in ctDNA at baseline. Patients were predominantly (75%) ET pre-treated, 51% with an AI; and 8% and 5%, respectively, had received prior chemotherapy or fulvestrant, for aBC. The most common treatment-emergent adverse events were diarrhea (87%), nausea (58%), fatigue (45%), neutropenia (39%) and abdominal pain (34%). The majority of treatment-related AEs (TRAEs)
g in 36% of patients. Most common TRAEs at RP2D (400mg) were diarrhea (81%), nausea (45%), fatigue (33%) and neutropenia (35%). No patient discontinued treatment due to an AE. Dose reductions were required of both imlunestrant and abemaciclib in 6 (7%) patients and of either imlunestrant in 3 (4%) or abemaciclib in 22 (26%) patients. Preliminary efficacy is presented in Table 1.

Conclusion: Imlunestrant in combination with abemaciclib ± AI showed acceptable safety and tolerability, comparable to the MONARCH 2 trial of fulvestrant + abemaciclib, along with evidence of clinical activity in ER+, HER2- aBC patients. These data suggest no additive toxicity of imlunestrant when administered in combination with abemaciclib, along with comparable clinical benefit to that observed in MONARCH 2. Further data will be presented at the meeting. The phase 3, EMBER-3 study is ongoing; evaluating imlunestrant, investigator's choice ET, and imlunestrant + abemaciclib in ET pre-treated ER+, HER2- aBC patients (NCT04975308).

Table 1. Preliminary efficacy in combination therapies in EMBER
Disclosure(s):

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12/8/2022
5:00 PM - 6:15 PM

Discussion 1 + Q&A: PD14-01, PD14-03, PD14-05, PD14-08, PD14-09

Presenting Author(s) and Co-Author(s):
Jennifer Caswell-Jin
Judith Mayer
12/8/2022
5:00 PM - 6:15 PM
Discussion 2 + Q&A: PD14-02, PD14-04, PD14-06, PD14-07
Presenting Author(s) and Co-Author(s):
Sarah Eskreis-Winkler
Judith Mayer
Poster Spotlight Discussion 14: Breast Cancer Risk Modeling

Presenting Author(s) and Co-Author(s):
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Background:

Breast cancer screening recommendations vary around the world, but most are based on age or inherited genetic risk factors. For instance, the American Cancer Society recommends annual mammography plus breast MRI starting at age 30yr for women at high risk of breast cancer based mainly on family history or high-risk genes. Women at average risk (no strong family history or high-risk genes) are recommended to have the option of annual mammography starting at age 40yr. Risk-based screening, which aims to personalise screening to an individual woman’s risk of breast cancer based on a more comprehensive risk assessment than just age, family history, or high-risk genes, might improve current screening strategies.

Methods:

We developed a deterministic model to estimate the incidence of advanced (node-positive) breast cancer (plus number of screens) for different risk-based screening strategies in a UK setting. The proportion of screen-detected and interval cancers was estimated for various...
screening intervals using a model developed by Launoy et al. and parameters for sensitivity (0.92) and annual transition rate from asymptomatic to symptomatic disease (0.25) from The Swedish Two-County Trial. The proportion of node-positive cancers was estimated for screen-detected (22%) and interval (53%) cancers, using data from the NHS Breast Screening Programme (England, 2015-18, women aged 47yr+).

Choice of mammography screening regimen was based on Tyrer-Cuzick 10yr risk (v8 including age, family history, reproductive factors, benign breast disease, SNPs and breast density). The proportion of women in each risk group was estimated from a UK cohort study investigating breast cancer risk at screening (PROCAS). In a hypothetical cohort of 3.45M women, 1M women would be identified as either high-risk (>8% 10yr risk; n=241,379) or low-risk (< 1.4% 10yr risk; n=758,621). In these 1M high/low-risk women, we evaluated two risk-based screening scenarios, comparing their effects with usual triennial screening starting at age 50yr (which was proposed for the 2.45M women at intermediate-risk (1.4-8% 10yr risk)).

Scenario (1): Changing screening interval based on risk (high-risk every 1yr; low-risk every 5yr) for screening between 50-70yr.

Scenario (2): Changing the starting age of screening based on risk (high-risk start annual screening at 45yr followed by triennial screening from 50yr; low-risk start triennial screening at 55yr); follow-up 45-55yr.

We assessed the trade-off between the decreased/increased number of node-positive breast cancers and increased/decreased number of screens with the high/low-risk regimens, respectively. A sensitivity analysis considered risk stratification without breast density.

Results:

Scenario (1): Changing screening interval based on risk reduced the number of node-positive cancers in high-risk women by 2,194 (with 3.14M additional mammograms) and increased the number of node-positive cancers in low-risk women by 910 (with 2.28M fewer mammograms) when compared with usual screening; a difference of 1,284 fewer node-positive cancers and 862,069 additional screens.

Scenario (2): Additional annual mammograms for high-risk women at 45-49yr reduced the number of node-positive cancers by 1,392 (with 2.28M fewer mammograms) when compared with usual screening; a difference of 1,284 fewer node-positive cancers and 862,069 additional screens.

Excluding breast density from risk assessment reduced the number identified as high or low-risk, and thus the number of advanced cancers prevented and screens required, but the overall findings were unchanged.

Conclusion:

Changing the starting age of screening based on risk of breast cancer is likely to be more effective per screen required at reducing the rate of advanced breast cancer than changing the screening interval based on risk.

Table 1: Results for Scenario (1)
Risk-based screening (changing screening interval based on risk: high-risk every 1 year; low-risk every 5 years) versus usual screening (every 3 years) between age 50-70 years (plus an additional 3 years of follow-up to adjust for the effect of screening on risk of breast cancer). N: Number; %: percentage; node+: Node-positive breast cancer; Δ: Difference; yr: Year; N/A: not applicable.

**Table 2: Results for Scenario (2)**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk (48% Tyre-Cast 30yr risk; n=241,179): 24% of 1M high-risk</td>
<td>Number of node-positive breast cancers</td>
</tr>
<tr>
<td>Usual screening</td>
<td>2,741</td>
</tr>
<tr>
<td>Risk-based screening</td>
<td>1,949</td>
</tr>
<tr>
<td>Δ Number of nodes</td>
<td>-792</td>
</tr>
<tr>
<td>Risk-based vs. Usual screening</td>
<td>1,267</td>
</tr>
<tr>
<td>Low-risk (51% Tyre-Cast 30yr risk; n=278,621): 26% of 1M low-risk</td>
<td>Number of node-positive breast cancers</td>
</tr>
<tr>
<td>Usual screening</td>
<td>1,299</td>
</tr>
<tr>
<td>Risk-based screening</td>
<td>2,238</td>
</tr>
<tr>
<td>Δ Number of nodes</td>
<td>-841</td>
</tr>
<tr>
<td>Risk-based vs. Usual screening</td>
<td>-851</td>
</tr>
</tbody>
</table>

Risk-based screening (changing the starting age of screening based on risk: high-risk start annual screening at age 45-49 years followed by triennial screening from age 50 years; low-risk start triennial screening at age 55 years) versus usual screening (triennial screening starting at age 50 years), with follow-up from age 45-55 years. n: Number; 1M: 1 million; node+: Node-positive breast cancer; Δ: Difference; yr: Year.

**Table 3: Results for sensitivity analysis - Scenarios (1) and (2) with risk assessment including/excluding breast density**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Risk-based vs. Usual screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyre-Cast model with breast density</td>
<td>Tyre-Cast model without breast density</td>
</tr>
<tr>
<td>High-risk (48% Tyre-Cast 30yr risk)</td>
<td>Number of node-positive breast cancers</td>
</tr>
<tr>
<td>Scenario (1)</td>
<td>Δ Number of nodes</td>
</tr>
<tr>
<td>High-risk (48% Tyre-Cast 30yr risk)</td>
<td>-1,949</td>
</tr>
<tr>
<td>Low-risk (51% Tyre-Cast 30yr risk)</td>
<td>-841</td>
</tr>
<tr>
<td>Trade-off (High risk versus Low risk)</td>
<td>-1,241</td>
</tr>
<tr>
<td>Scenario (2)</td>
<td>Δ Number of nodes</td>
</tr>
<tr>
<td>High-risk (48% Tyre-Cast 30yr risk)</td>
<td>-1,949</td>
</tr>
<tr>
<td>Low-risk (51% Tyre-Cast 30yr risk)</td>
<td>-841</td>
</tr>
<tr>
<td>Trade-off (High risk versus Low risk)</td>
<td>-1,241</td>
</tr>
</tbody>
</table>

Scenario (1): Risk-based screening (changing screening interval based on risk: high-risk every 1 year; low-risk every 5 years) versus usual screening (every 3 years) between age 50-70 years (plus an additional 3 years of follow-up to adjust for the effect of screening on risk of breast cancer). Scenario (2): Risk-based screening (changing the starting age of screening based on risk: high-risk start annual screening at age 45-49 years followed by triennial screening from age 50 years; low-risk start triennial screening at age 55 years) versus usual screening.
screening (triennial screening starting at age 50 years), with follow-up from age 45-55 years. n: Number; node+: Node-

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Background: Artificial intelligence based, image-derived short-term risk models for breast cancer have shown high discriminatory performance compared to traditional lifestyle familial-based risk models. However, the long-term performance has not yet been investigated. Methods: In this study, we investigated the long-term performance for predicting breast cancer throughout 10 years using an image-based risk model and compared the results to a traditional lifestyle familial-based risk model. We performed a nested case-control study based on a mammography screening cohort conducted since 2010 in Sweden for women aged 40-74. Mammograms, age, lifestyle and familial risk factors were collected at study entry. In the breast cancer register update in 2022; 2,028 incident breast cancers were included together with 8,398 controls that were matched to the cases on year of prior baseline mammogram. The image-based model extracted mammographic features (density, microcalcifications, masses, left-right breast asymmetries of these features) and age from the baseline mammograms. Tyrer-Cuzick risk model used self-reported lifestyle and familial risk factors to estimate risk at study-entry. Absolute risks were estimated using the risk models. We estimated model performances using Area Under the receiver operating characteristic Curves (AUC) statistics of the absolute risks and, risk ratios of women classified as high-risk and low risk using NICE and USPSTF guidelines. Results: The AUCs of the image-derived risk model ranged from 0.76 (95%CI 0.72-0.81) to 0.66 (95%CI 0.65-0.67) for breast cancers developed 1-10 years after study-entry. The corresponding Tyrer-Cuzick AUCs were 0.68 (95%CI 0.63-0.73) to 0.62 (95%CI 0.60-0.63). For estrogen negative and symptomatic cancers, the AUCs for the image-density showed similar AUCs. Throughout the 10-years of follow-up, 20% of all women with cancers were deemed high risk at study-entry by the image-derived risk model compared to 6% of all women with cancers identified as high risk by the lifestyle familial-based model (p< 0.01). Conclusion: The image-derived model outperformed the lifestyle familial-based model both for short-term and long-term risk assessment and, could be used for identifying women who possibly could benefit from additional examinations and primary prevention.
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PD14-03

PD14-03 Reappraising the Fanconi Anemia DNA repair pathway in breast cancer risk and precision intervention: Insights and opportunities from the City of Hope INSPIRE study

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Background: Fanconi Anemia (FA) proteins facilitate homologous recombination (HR)-mediated repair of DNA interstrand cross-links. Germline monoallelic, pathogenic/likely pathogenic (P/LP) variants in the highly-penetrant (HP) breast cancer (BC) FA genes, BRCA1 (FANCS), BRCA2 (FANCD1) and PALB2 (FANCN), compromise HR and predispose to hereditary BC. The effects of monoallelic, pathogenic variants in other non-HP BC FA genes upon HR and BC predisposition remain less understood. In this investigation we report the germline mutational landscape of FA gene P/LP variants and somatic molecular consequences of patients with BC diagnoses from City of Hope’s (COH) INSPIRE (Implementing Next-generation Sequencing for Precision Intervention and Risk Evaluation) study.

Methods: COH-INSPIRE is a universal access study open to all patients at COH with a personal and/or family history of cancer. Patients undergo custom panel-based germline genetic testing to detect P/LP single nucleotide variants (SNVs), short insertions/deletions (indels) and exon-level deletions/duplications in 155 cancer-predisposition genes including the HP BC FA genes and 15 non-HP BC FA genes [FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCN, FANCO (RAD51C), FANCP, FANCU (XRCC2)]. Patients’ tumor specimens undergo somatic tumor (>400X)-normal (>180X) whole exome and transcriptome sequencing (>50 million reads). Somatic sequencing identifies P/LP SNVs, indels, copy number events, and fusions. Secondary analyses assessed somatic homologous recombination deficiency (HRD) by examining tumor mutational signatures, as well as an ensemble HRD score derived by combining individual genomic loss of heterozygosity, telomeric allelic imbalance and large-scale molecular transition scores. Reference comparison of germline and somatic features to current FDA therapeutic guidelines and NIH clinical trials registrations determined eligibility for precision therapeutic intervention and clinical trial enrollment.

Results: Of 7,584 patients enrolled in COH-INSPIRE, 1,651 (21.8%) patients had a BC diagnosis. Germline panel testing of BC patients identified 204 (12.4%) with germline P/LP variant in a FA gene. Greater than one third of FA gene-altered BC patients (37.7%) carried a P/LP variant in a non-HP BC FA gene. We observed that BC patients with a non-HP BC FA gene variant may demonstrate HR compromise as evidenced by presence of a Signature 3 mutational profile or an elevated combined HRD score (> 33 and/or > 42). (Table 1) Further, we identified ostensible segregation of triple negative BC in a family harboring a germline pathogenic variant in FANCG. With regard to precision clinical actionability (i.e. qualification for targeted therapeutic intervention [PARP inhibitor (PARPi)] and/or clinical trial) for patients with advanced stage BC: All patients with germline P/LP HP BC FA gene variant and 20.7% (N=16) of patients with a P/LP FA non-HPBC FA gene variant met criteria for treatment with on/off-label PARPi. 100% of patients with advanced BC with germline P/LP HP BC or non-HPBC FA gene variant qualified for a clinical trial.

Conclusions: Patients with BC often carry a germline monoallelic, P/LP FA gene variant; in more than one third, the FA gene alteration occurs in a non-HP BC FA gene. BC patients harboring a monoallelic germline non-HP BC P/LP FA gene may exhibit somatic mutational signatures and HRD scoring consistent with compromise of HR. Somatic tumor evaluation of BC patients with germline P/LP non-HP BC FA gene variants expands opportunities for precision therapeutic intervention and clinical trial enrollment. Continued appraisal will clarify emerging questions of germline non-HP P/LP FA gene-associated autosomal dominant BC risk and management as well as facilitate optimization of precision BC care.

Table 1 Summary Molecular Features of BC patients with P/LP Variants in FA gene from COH-INSPIRE
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Kevin McDonnell, MD, PhD: No financial relationships to disclose
Joseph Bonner, PhD, MS: No financial relationships to disclose
Kevin K. Tsang, MS: No financial relationships to disclose
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Stephen Gruber, MD, PhD, MPH: Astra Zeneca: Research gift (Terminated, December 31, 2020)
To efficiently capture data from mammographic breast images and classify long-term risk of breast cancer, we developed FLIP, a novel Cox regression-based framework that fully utilizes data in the mammograms beyond current density measures. FLIP uses the extensive existing data that are currently ignored in the context of breast cancer risk stratification. More than 20 studies support texture features add value to risk prediction beyond breast density. However, the entire mammogram imaging data has a high dimension of pixels (~13 million per image), greatly exceeding the number of women in a cohort. FLIP was fitted and cross-validated within the Joanne Knight Breast Health Cohort excluding cases diagnosed in the first 6 months of entry.

The Joanne Knight Breast Health Cohort is comprised of over 10,000 women undergoing repeated mammography screening at Siteman Cancer Center and followed since 2010. All women had baseline mammogram at entry, provided a blood sample and completed a risk factor questionnaire. Mammograms are all using the same technology (Hologic). During follow-up through October 2020, we identified 246 incident breast cancer cases (pathology confirmed) and matched them to controls from the perspective cohort based on month of mammogram and age at entry.

We obtained an AUC of 0.68 (SE 0.03) including the whole mammogram image, age and BI-RADS (4th edition) density category; and AUC of 0.72 (SE 0.04) by adding in BMI and menopausal status to this model. These 5-year prediction performances exceed that of well-developed models based on epidemiologic risk factors (P < 0.001). FLIP offers standard statistical solutions and removes barriers to wider clinical use without prohibitive training data and extensive computational requirements, providing a transparent workflow ensuring high reproducibility. It should be accessible anywhere mammograms are used.

We conclude that using full mammogram images for breast cancer risk prediction captures additional information on breast tissue characteristics that relate to cancer risk, and improves prediction classification. This prediction algorithm can run efficiently in real time (in seconds) with processing of digital mammograms. Thus, this model can be easily implemented in mammography screening services and other clinical settings to guide real-time risk stratification to improve precision prevention of the leading cancer in women worldwide. Further analysis will quantify the value of adding other breast cancer risk factors, including polygenic risk scores. Addition of repeated mammogram images over time should further increase classification...
performance. This approach has the potential to improve risk classification by using data already available for the vast majority of women already having repeated screening mammograms.

Schema overview of FLIP

The raw images are in the form of .dcm files before entering into FLIP. After automated processing and image alignment, the two CC-views (left and right) are average between the two breasts for characterization. The inputted 2D mammograms are first characterized with bivariate splines over triangulation to preserve spatial distribution of pixels and accommodate the irregular semi-circular breast boundary. The characterization is further optimized (see Supplemental Material) which provides a unique and closed-form solution. b. A simple Cox proportional hazards model is adopted using well-established risk factors (RF), including age, breast density (BI-RADS), BMI, menopausal status, parity, family history, and history of benign breast disease. The mammogram image acts as an additional risk factor in the Cox regression accompanied with a 2D coefficient surface. All inferential procedures with Cox regression are applicable to FLIP which provides a transparent workflow ensuring high reproducibility. c. Women who are diagnosed with breast cancer within the first 6 month of their mammogram date have been removed from this analysis and we focus on the 5-year risk. Discriminatory performance is assessed with AUC and validated via a 10-fold cross-validation.

Disclosure(s):
Shu Jiang, n/a: No financial relationships to disclose
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PD14-05 Prospective longitudinal validation of a breast cancer risk prediction model in a cohort of 130,058 women

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Background: Personalized breast cancer (BC) risk assessment depends on known traditional risk factors, specific germline mutations, and genome-wide polygenic risk scores (PRS). PRS explains a substantial proportion of genetic BC susceptibility. Accuracy of BC risk prediction may be improved by combining a PRS with traditional risk factors. We recently developed and validated a 149-SNP PRS for women of diverse ancestries using ancestry-informative genetic markers and combined this with version 7 of the Tyrer-Cuzick (TC) model to generate a Combined Risk Score (CRS). Here, we describe a pre-specified prospective longitudinal clinical validation of CRS as a predictor of BC risk.

Methods: Women in the U.S. who were referred for clinical genetic testing between January 2017 and February 2019 were matched to medical and hospital claims in an anonymized dataset. Women with a pathogenic mutation in a BC-related gene were excluded from analysis. Follow-up began 4 months after testing and extended to the earliest date of BC diagnosis, censoring at the time of BC preventive treatment, or November 1, 2019. Incident BC events were determined by an ICD10 code of C50.* and confirmed by relevant treatment codes. CRS calibration was evaluated by the ratio of observed (O) to expected (E) incident BCs for the full cohort, and for women split into event-based 5-year CRS risk deciles. Cox proportional hazards models were used to evaluate discriminatory accuracy in terms of hazard ratios (HR) with 95% confidence intervals (CI) and p-values from likelihood ratio chi-squared statistics.
Kaplan-Meier analysis was used to examine risk for women split into high- or low-risk groups according to a 3% 5-year CRS risk threshold.

Results: 130,058 women with 148,349 total patient years met study eligibility criteria and were matched to claims data. Over a median (range) follow-up of 12.1 (4.0-29.5) months, 340 incident BC events were observed. The CRS was well calibrated in the overall cohort with an O/E ratio of 1.11 (95% CI=0.99-1.23) and within deciles of predicted risk (Table). Importantly, in the highest risk decile, the O/E was 0.91 (95% CI=0.63-1.27) with CRS, but 0.67 (95% CI=0.46-0.94) with TC alone, illustrating the superior calibration of CRS. In a Cox model adjusted for age at testing, PRS had an HR per standard deviation (SD) of 1.48 (95% CI=1.33-1.64, p=2.55×10-13); the HR/SD was 1.43 (95% CI=1.29-1.59, p=1.61×10-11) after adjusting for family history. In a bivariate analysis using both CRS and TC to predict time to BC, CRS added significantly to the model after accounting for TC (HR/SD=2.89, 95% CI=2.12-3.94, p=1.20×10-11), whereas TC did not add significant information after accounting for CRS. 15,986 (12.3%) women were above the CRS high-risk threshold, including 123 with events. A total of 10,248 (7.9%) women were reclassified by the CRS model compared to the TC model. Among women who were classified as high-risk by TC, 32.6% were reclassified as low-risk by CRS; among those classified as low-risk by TC, 4.3% were reclassified as high-risk by CRS. The CRS high-risk group experienced events at over three times the rate of the low-risk group (HR=3.75, 95% CI=3.00-4.68, p=6.39×10-27).

Conclusion: The CRS was well-calibrated in predicting BC and significantly improved upon a traditional risk factor model. Clinical use of the CRS may lead to improved BC prevention and screening strategies.

Table: Absolute risk calibration by 5-year risk decile

<table>
<thead>
<tr>
<th>Risk decile</th>
<th>Expected incidence</th>
<th>Observed incidence (95% CI)</th>
<th>O/E (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.68%</td>
<td>0.55</td>
<td>1.00 (0.69-1.40)</td>
<td>1.83 (1.27-2.56)</td>
</tr>
<tr>
<td>0.68-1.04%</td>
<td>1.52</td>
<td>2.24 (1.55-3.13)</td>
<td>1.48 (1.02-2.06)</td>
</tr>
<tr>
<td>1.04-1.37%</td>
<td>2.21</td>
<td>2.93 (2.03-4.10)</td>
<td>1.33 (0.92-1.86)</td>
</tr>
<tr>
<td>1.37-1.70%</td>
<td>2.86</td>
<td>3.50 (2.42-4.89)</td>
<td>1.22 (0.85-1.71)</td>
</tr>
<tr>
<td>1.70-2.29%</td>
<td>3.74</td>
<td>2.76 (1.91-3.86)</td>
<td>0.74 (0.51-1.03)</td>
</tr>
<tr>
<td>2.29-2.80%</td>
<td>4.84</td>
<td>4.92 (3.41-6.87)</td>
<td>1.02 (0.70-1.42)</td>
</tr>
<tr>
<td>2.80-3.34%</td>
<td>5.91</td>
<td>6.61 (4.58-9.23)</td>
<td>1.12 (0.77-1.56)</td>
</tr>
<tr>
<td>3.34-4.04%</td>
<td>7.13</td>
<td>7.83 (5.43-10.95)</td>
<td>1.10 (0.76-1.53)</td>
</tr>
<tr>
<td>4.04-5.26%</td>
<td>9.00</td>
<td>9.00 (6.23-12.58)</td>
<td>1.00 (0.69-1.40)</td>
</tr>
<tr>
<td>&gt;5.26%</td>
<td>13.59</td>
<td>12.38 (8.57-17.30)</td>
<td>0.91 (0.63-1.27)</td>
</tr>
</tbody>
</table>

Incidence is reported per 1,000 women-years. 34 breast cancers were observed per decile.

Disclosure(s):
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We recently derived an absolute breast cancer risk prediction model, the Black Women’s Health Study (BWHS) model, for breast cancer in U.S. Black women using data from three large case-control studies and validated it in independent prospective data from the Black Women’s Health Study (Palmer 2021). The BWHS model includes epidemiologic risk factors as well as family history of breast cancer and family history of prostate cancer. It does not include genetic variants because at the time of model development breast cancer polygenic risk scores performed poorly in women of predominantly African ancestry, primarily due to differences in allele frequency and linkage disequilibrium. More recently, Gao et al. (2022) developed and tested a polygenic risk score (PRS) using 56,943 SNPs for breast cancer in women of African ancestry (AA) based on 9,235 breast cancer cases and 10,184 controls from a large pooled analysis of studies from African American and African women; the c-statistic from cross-validation was 0.581, considerably better than in previous efforts. We evaluated whether adding this AA-PRS to the BWHS risk prediction model would improve risk stratification. We conducted a nested case-control study of 901 breast cancer cases and 1,576 controls matched on age and most recent questionnaire completed from among BWHS participants for whom genome-wide association data were available and who had not been included in the collaboration from which the PRS was derived and tested. We examined discriminatory accuracy, estimated by the area under the receiver operating characteristic curve (AUC), for the risk prediction model alone, the PRS alone, and the combination of risk prediction model and PRS, controlling for the matching factor “questionnaire cycle”. We conducted the analyses within strata of 5-year age and then combined results using inverse-variance weighting. In preliminary analyses, the AUC was 0.579 for the risk prediction model alone and 0.600 for the AA-PRS alone. When the AA-PRS and the BWHS risk prediction model were both used as predictors in a logistic regression model, the AUC increased from 0.579 to 0.622. This improvement in risk stratification is similar to what Kachuri et al. (2020) obtained in an analysis of U.K. Biobank data, where adding a PRS to epidemiologic and personal risk factors showed an improvement from 0.572 to 0.635 in women of European ancestry. The present study provides external validation of a recently derived AA PRS and demonstrates the potential for improving risk stratification for U.S. Black women by adding a PRS to a breast cancer risk prediction model that already includes family history of breast cancer.

Disclosure(s):
Gary R. Zirpoli, PhD: No financial relationships to disclose
PD14-07

**PD14-07 Associations of Breast Cancer Risk Level and Prediction of Tumor Aggressiveness in the Athena Breast Health Network**

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Background: The Athena Breast Health Network (Athena) is a University of California (UC) initiative integrating clinical care and research to drive improvements in breast cancer screening. Through standardized, self-reported clinical intake forms, a patient’s breast health status and information regarding their breast cancer risk is captured before each mammography appointment. Breast cancer risk models provide a level of risk to develop breast cancer but do not take into account aggressiveness of breast cancer. Here, we evaluated outcome data of a large screening cohort for association between risk level and aggressiveness at diagnosis. Methods: We calculated Breast Cancer Surveillance Consortium (BCSC) risk scores for a cohort of 8,923 consented UCSF Athena participants from the years 2012-2018 with a median follow-up of 5-years. To identify those who developed invasive breast cancer on or after completing an Athena intake form, we performed a cancer linkage with the San Francisco Mammography Registry (SFMR), a local registry that regularly collects cancer data from the California Cancer Registry. We classified tumors as aggressive if they met one or more of the following criteria: hormone receptor (HR)-negative, HER2-positive, grade 3. All other tumors were classified as non-aggressive. We used student's t-tests to examine associations between BCSC 5-year risk score, the development of invasive breast cancer, and tumor aggressiveness among cases. To account for the association between older age and higher BCSC risk score (as well as HR-positive subtypes), we stratified by percentiles of BCSC risk by age (top 2.5% vs. bottom 97.5%). The top 2.5% by age threshold consistently identifies women with lifetime risk of 23–28% and was chosen as high-risk threshold to trigger annual screening in the WISDOM study (Dreher: PMID34843026). Results: Of 8,923 participants, 170 (2%) developed breast cancer during the follow-up period. The average 5-year BCSC risk score for women with breast cancer was 1.81% and 1.47% for those without (p< 0.001). Among women with breast cancer, 123 (72%) developed non-aggressive cancers and 47 (28%) developed aggressive cancers. The average 5-year BCSC risk score for women with non-aggressive and aggressive cancers was 1.89% and 1.60%, respectively (p=0.13). In analyses stratified by percentile of BCSC risk by age, 521 (6%) participants had a BCSC 5-year risk score in the top 2.5% by age and 8,402 (94%) participants had a BCSC 5-year risk score in the bottom 97.5%. A higher percentage of women with non-aggressive cancers vs healthy women (controls) were in the top 2.5% by age (p = 0.001), but the percentage of aggressive cancers vs healthy women in the top 2.5% by age was similar (p = 0.61). Conclusion: Through this study we confirmed that higher 5-year BCSC risk scores are associated with higher overall breast cancer development. Interestingly, participants with the highest 5-year BCSC risk scores (top 2.5% by age), are more likely to develop cancers with non-aggressive features (low grade, hormone positive). This suggests that the BCSC model may preferentially predict less aggressive tumors, and those with the highest 5-year BCSC risk may be more likely to benefit from endocrine risk reduction therapy. There remains a gap in our ability to identify those at risk for aggressive cancers. Our findings highlight the need for screening programs to better understand who is at risk for what type of breast cancer. Current work is focused on developing models tailored to risk prediction of aggressive cancers.

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Yiwey Shieh, M.D., M.A.S.: No financial relationships to disclose
Laura J. Esserman, M.D., M.B.A.: Blue Cross/Blue Shield: Consulting Fees (e.g., advisory boards) (Ongoing); Merck: Contracted Research (Ongoing)
Laura Van ‘t Veer, MSc PhD: Agendia NV: Ownership Interest (stocks, stock options, patent or other intellectual property or other ownership interest excluding diversified mutual funds) (Ongoing), Salary (Ongoing)
12/8/2022
5:00 PM - 6:15 PM
PD14-08 WITHDRAWN
PD14-09 The effect of timing of TP53 genetic testing on treatment and outcomes among women with Li-Fraumeni syndrome and breast cancer

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Background: Li-Fraumeni syndrome (LFS) is a pan-cancer predisposition syndrome caused by pathogenic germline TP53 variants. Breast cancer (BC) is the most prevalent tumor in women with LFS. The risk of secondary malignancies, including multiple primary BCs, other LFS-related cancers, radiation-induced sarcomas, and local recurrences are important clinical concerns in the LFS setting. The diagnosis of LFS may influence treatment decisions and outcomes. Methods: In this international multicenter study, we analyzed women with pathogenic or likely pathogenic germline TP53 variants and BC (DCIS or invasive breast carcinoma) diagnosed 2002-2022 from three retrospective LFS cohorts (Dana Farber Cancer
Institute, USA; Institut Gustave Roussy, France; Hospital Sírio-Libanês, Brazil). We excluded carriers of TP53 unconfirmed possibly mosaic variants, carriers of a 2nd pathogenic variant in another BC susceptibility gene, and those with missing data related to timing of genetic testing (TGT) or date of 1st BC diagnosis (dx). The overall cohort was divided in two groups: genetic

B). In cases with synchronous bilateral BC, we included the tumor of higher risk of recurrence (invasive, higher stage, more aggressive tumor biology) and excluded the other. The chi-square test was used to measure the association between TGT and other categorical variables.

Results: 209 patients (pts) met criteria for this analysis. The median age of 1st BC dx was 35-42). BC was the 1st cancer dx in 87.5% of the pts. Among 1st breast tumors, 38 were DCIS, 147 were early-stage BC (61 I, 49 II, 37 III) and 7 stage IV (17 missing). There were no differences between groups A and B regarding staging at dx. Missense TP53 variants were the most common type of germline mutation (n=154, 73.6%), with 60.4% (n=93) in the DNA-binding domain and 38.9% (n=60) in the tetramerization domain. Median follow-up from 1st BC dx was 6 years (IQR, 3-10). 53.1% of pts (n=111) underwent TP53 germline testing only after 1st BC dx. Family history of BC < 50 and non-BC malignancy prior to or synchronous with 1st BC dx were not associated with TGT (p=0.3 and p=0.2, respectively). 35.4% of pts developed a second primary BC (25 ipsilateral; 49 contralateral). Among pts without synchronous bilateral BC or metastatic BC at dx, 97 pts underwent contralateral risk reducing mastectomy (CRRM), 56.7% (55/97) as part of treatment surgery for the 1st BC. CRRM uptake was associated with TGT (A 70.3% vs B 41.6%, p=0.001). Of 194 pts with detailed data on surgical treatment (1st BC), 146 underwent mastectomies and 48 breast conserving surgery (BCS). Group A had more mastectomies (79.5% vs 61.2%, p=0.001) and less radiation therapy (10.2% vs 45.9%, p<0.001). Among the irradiated pts, 9.8% (n=5) developed sarcomas in the irradiated field. Thirty-eight pts had BC recurrence: 21 loco-regional (A 6 vs B 15, p< 0.05), mostly in-breast, and 17 distant relapses. There was a significant statistical association between TGT and type of BC surgery (p=0.001), radiation-therapy (p< 0.001), CRRM uptake (p=0.001) and local relapses (p< 0.05). Conclusion: This analysis of BC in our sizable cohort of LFS patients with treatment data confirms that, timing of genetic testing affects some treatment options and outcomes, including surgical procedures and use or avoidance of radiation. These decisions appear to influence the risk of local recurrence or additional primary BC and radiation-induced sarcoma. Recognition of germline TP53 variants in breast cancer patients as part of genetic testing at diagnosis appears to have implications for treatment options and outcomes.

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Renata Sandoval, MD, PhD: No financial relationships to disclose
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5:00 PM - 6:15 PM
Discussion 1 + Q&A: PD15-01, PD15-02, PD15-03 & PD15-11
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Tracy Ann Moo
Discussion 2 + Q&A: PD15-04, PD15-05, PD15-06 & PD15-07

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5:00 PM - 6:15 PM
Discussion 3 + Q&A: PD15-08, PD15-09, PD15-10 & PD15-12
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Poster Spotlight Discussion 15: Local Regional/Management of the Axilla

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PD15-01
PD15-01 AXILLARY NODAL RECURRENCE IS RARE IN PATIENTS WITH NODE-POSITIVE BREAST CANCER UNDERGOING SLNB FOLLOWING NEOADJUVANT CHEMOTHERAPY: EARLY RESULTS OF THE NEOSENTITURK-TRIAL/MF-18-03

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Background:
Whether axillary lymph node dissection (ALND) following sentinel lymph node biopsy (SLNB) could be spared in patients with initially clinically positive axilla after neoadjuvant chemotherapy (NAC) is still controversial even though recent studies indicate that axillary recurrence seems to be a rare event. Our aim is to find out whether omitting ALND could be oncologically safe in patients undergoing SLNB after NAC.

Material and Methods
Of patients presented with cT1-4N1-3M0 disease, those undergoing SLNB after NAC were included in the prospective multicentre registry trial "MF18-03/BHWG" (ClinicalTrials.gov/NCT04250129). Cases with inflammatory breast cancer, distant metastases, pregnancy, bilateral breast cancer, or other cancers and those without adjuvant nodal radiotherapy were excluded from the study. The end points of the present report are the axillary nodal recurrence (AR) and locoregional recurrence (LRR) rates at a median follow-up more than 2 years, and determine factors associated with AR and LRR. The locoregional recurrences included ipsilateral, and contralateral axillary recurrences, infra- and supraclavicular recurrences, and recurrences in the mammaria interna region.

Results
Between January 2018 to January 2021, 2358 patients with cN(+) disease, who became cN0 after NAC, and underwent SLNB, were analyzed. Median age was 47 (range, 21-86). Of those, the majority of patients had cT1-2 (80.5%) and N1 (80.3%) disease. Following NAC, half of the patients (50%) had breast conserving surgery, whereas the remaining half had mastectomy (50%). Of 2358 patients, 908 (38.5%) had ALND following SLN (ypN+, 85%) and 1450 (61.5%) underwent SLNB alone (ypN0, 72%). SLNB was performed by using the blue dye technique-alone in 66.6% of patients and by targeted axillary dissection in 659 patients (27.9%). Of those, 819 (34.8%) were HER2(+) and 373 (15.8%) were triple negative. The pCR rates for the axilla, breast and both for the axilla and breast were 50%, 35% and 28%, respectively. At a median follow-up time of 28 months (range, 12-62), the LRR, AR and isolated AR rates were 0.6% (n=14), 0.25% (n=6) and 0.13% (n=3), respectively. Furthermore, no significant difference could be found in LRR- and AR-rates between SLNB-alone and ALND groups regardless of the definitive nodal pathology (Table 1). Nodal recurrences were seen at a median of 12 months after the surgery. Of 6 cases with AR, 3 had synchronous local recurrences in breast, and 2 of them also had lung metastases in addition to local recurrence. All patients with AR were interestingly found to have HER2(+) or triple negative breast cancer at the initial diagnosis, and had residual invasive cancer in the breast surgical specimen. Logistic regression analyses revealed that patients with AR were significantly more likely to be younger than 45 (RR=7.81; 95% CI, 0.91-66.91) and have a cN2-3 (RR=4.1; 95% CI, 0.83-20.38), and non-luminal breast cancer (RR=12.47; 95% CI, 1.45-106.9) at the initial diagnosis (Table 2). Similarly, patients with LRR were more likely to present with cN2-3 disease (RR=3.09; 95% CI, 1.07-8.94) and non-
luminal pathology (RR=6.27; 95%CI, 1.96-20.06).

Conclusion: This large prospective registry data also suggest that nodal recurrences can be detected at very low rates within 3 years after surgery in patients with clinically node-positive disease following NAC regardless of the extent of axillary surgery or nodal pathology as long as regional nodal radiation is provided. Since patients with early nodal recurrences have an aggressive tumor biology with a potential of systemic recurrences, effective adjuvant systemic therapies should be considered in those with HER2(+) or triple negative residual breast cancer after surgery following adjuvant nodal radiation.

Table 1. Local, locoregional and systemic recurrences in cT1-4N1-3 patients with ypNO ypN(+) disease (n=2358)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n=2358)</th>
<th>SLNB (n=1450)</th>
<th>ALND (n=908)</th>
<th>SLNB(+) (n=1042)</th>
<th>SLNB(+) (n=408)</th>
<th>AD(+) (n=137)</th>
<th>AD(+) (n=771)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence after BCT*</td>
<td>0.999*</td>
<td>0.458*</td>
<td>0.999*</td>
<td>0.384*</td>
<td>0.999*</td>
<td>0.364*</td>
<td>0.346*</td>
</tr>
<tr>
<td>Yes</td>
<td>13(1.1)</td>
<td>9(1.1)</td>
<td>4(1.1)</td>
<td>8(1.3)</td>
<td>10(5)</td>
<td>0(0)</td>
<td>4(1.3)</td>
</tr>
<tr>
<td>No</td>
<td>1173(98.9)</td>
<td>805(98.9)</td>
<td>368(98.9)</td>
<td>593(98.7)</td>
<td>213(99.5)</td>
<td>57(100)</td>
<td>311(98.7)</td>
</tr>
<tr>
<td>Chest wall recurrence after mastectomy</td>
<td>0.245*</td>
<td>0.999*</td>
<td>0.364*</td>
<td>0.682*</td>
<td>0.564*</td>
<td>0.990*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13(1.1)</td>
<td>5(0.8)</td>
<td>8(1.5)</td>
<td>4(0.9)</td>
<td>10(5)</td>
<td>0(0)</td>
<td>8(1.8)</td>
</tr>
<tr>
<td>No</td>
<td>1159(98.9)</td>
<td>631(99.2)</td>
<td>528(98.5)</td>
<td>437(99.1)</td>
<td>194(99.5)</td>
<td>80(100)</td>
<td>448(98.2)</td>
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<td>Locoregional recurrence*</td>
<td></td>
<td></td>
<td></td>
<td>0.245*</td>
<td>0.999*</td>
<td>0.346*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>140(6.0)</td>
<td>60(4.0)</td>
<td>80(9.0)</td>
<td>5(0.5)</td>
<td>10(2.2)</td>
<td>2(1.5)</td>
<td>60(8.0)</td>
</tr>
<tr>
<td>No</td>
<td>2344(94.0)</td>
<td>1444(96.0)</td>
<td>900(91.0)</td>
<td>1037(99.5)</td>
<td>407(99.8)</td>
<td>125(98.5)</td>
<td>765(99.2)</td>
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<td>Ipsilateral Axillary recurrence</td>
<td>0.682*</td>
<td>0.564*</td>
<td>0.990*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60(2.5)</td>
<td>30(2.1)</td>
<td>30(3.3)</td>
<td>3(0.3)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>30(4.0)</td>
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<td>No</td>
<td>2352(97.5)</td>
<td>1447(97.9)</td>
<td>905(99.7)</td>
<td>1038(99.7)</td>
<td>408(100)</td>
<td>137(100)</td>
<td>768(99.6)</td>
</tr>
</tbody>
</table>

*BCT=Breast Conserving Therapy

**=Axilla, infraclavicular, supraclavicular, mammary interna and contralateral axillary metastases

p<0.05, *=Fisher’s Exact Test, $=Pearson Chi-Square Test, $=Pearson Chi-Square Test,
Table 2. Factors associated with axillary and locoregional recurrences (AR=axillary recurrences, LRR=locoregional recurrences, pCR= pathologic complete response)

<table>
<thead>
<tr>
<th></th>
<th>AR (n=6) (%)</th>
<th>Patients without AR (%)</th>
<th>p</th>
<th>LRR (N=14) (%)</th>
<th>Patients without LRR (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>5 (0.5)</td>
<td>919 (99.5)</td>
<td>0.037*</td>
<td>7 (0.76)</td>
<td>917 (99.24)</td>
<td>0.421</td>
</tr>
<tr>
<td>≥45</td>
<td>1 (0.07)</td>
<td>1433 (99.9)</td>
<td></td>
<td>7 (0.5)</td>
<td>1427 (99.5)</td>
<td></td>
</tr>
<tr>
<td>Tumor pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCR (Breast)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>0/0</td>
<td>820/100</td>
<td>0.098</td>
<td>0/0</td>
<td>820/100</td>
<td>0.003*</td>
</tr>
<tr>
<td>(-)</td>
<td>6/0</td>
<td>1532/99.6</td>
<td>14/0.9</td>
<td>1524/99.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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PD15-02 Long Term Outcome in Patients with Nodal-Positive Breast Cancer Treated with Sentinel Lymph Node Biopsy Alone After Neoadjuvant Chemotherapy

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Importance:
The use of neoadjuvant chemotherapy (NAC) in the clinical care of breast cancer patients has increased considerably over recent years especially in node positive cases. For patients who have axillary nodal metastases prior to NAC, the prevailing standard of care is to undergo an axillary lymph node dissection (ALND), regardless of response to therapy. Sentinel lymph node biopsy (SLNB) has yet to be accepted as the standard staging procedure in patients who had clinical complete response in the axilla following NAC. This is due to the presumed high false negative rate associated with SLNB in such scenario. But there are limited data on the long term outcome of these patients who are only treated with SLNB alone.

Aim:
A retrospective cohort study comparing the long term outcome of breast cancer patients with clinically node positive disease (N1) but turned clinically node negative (N0) following NAC, receiving SLNB alone versus ALND.

Methods:
Patients who had pathologic proven N1 breast cancer (before NAC) treated with NAC and turned clinically N0 from January 2009 to December 2014 were identified from Asan Medical Center breast cancer database in South Korea. Primary endpoint was axillary recurrence rate (ARR) and secondary endpoints were disease-free survival (DFS) and overall survival (OS). These outcomes were reported for patients who had SLNB alone versus ALND.

Results:
561 patients with clinically stage N1 (cN1) cancer treated with NAC and turned clinically stage N0 (cN0) were identified. 253 (45.1%) patients received SLNB only while 308 (54.9%) patients had ALND. The clinicopathological features of these patients were illustrated in Table 1. Majority of these patients received adjuvant radiotherapy, 81.2% in the SLNB group and 76.5% in the ALND group. In the pathologically stage N0 (ypN0) group, at a median follow up of 69 months, ARR was 3.0% in the SLNB only group and 1.7% in the ALND group (p=0.704). DFS and OS were not significantly different between patients with SLNB alone versus ALND (p=0.561 and 0.810 respectively). Median number of SLN harvested in the SLNB only group is 5 (range 1 -17).

In the pathologically stage N1 (ypN1) group with only 1-2 lymph node positive for metastasis, at a median follow up of 66 months, ARR was 5.8% in the SLNB group and 4.7% in the ALND group (p=0.768). There was no significant difference in DFS and OS between the SLNB and ALND group (p=0.537 and 0.645). In the SLNB only group, the median number of positive lymph node was 1 (range 1-2), the median number of sentinel lymph node was 6 (range 2-18).

Conclusion:
In cN1 breast cancer patients who were converted to cN0 following NAC, axillary recurrences were rare. No statistically significant differences were noted in DFS and OS between patients with SLNB or ALND. Our findings suggest that these patients may be safely treated with SLNB only, even when there are up to 2 positive SLNs.

Table 1 Clinicopathological features of breast cancer patients with nodal disease and NAC

<table>
<thead>
<tr>
<th>Variable</th>
<th>SLNB (n=253)</th>
<th>ALND (n=308)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (months)</td>
<td>60</td>
<td>60</td>
<td>0.1533</td>
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<tr>
<td>Age</td>
<td>50-70</td>
<td>50-70</td>
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<tr>
<td>Menopausal status</td>
<td>42.8%</td>
<td>42.8%</td>
<td>0.9956</td>
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<td>Primary site</td>
<td>39.6%</td>
<td>40.6%</td>
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<td>T stage</td>
<td>20%</td>
<td>20%</td>
<td>0.9956</td>
</tr>
<tr>
<td>T1</td>
<td>62%</td>
<td>62%</td>
<td>0.9956</td>
</tr>
<tr>
<td>T2</td>
<td>38%</td>
<td>38%</td>
<td>0.9956</td>
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<tr>
<td>N stage</td>
<td>50%</td>
<td>50%</td>
<td>0.9956</td>
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<tr>
<td>N0</td>
<td>49%</td>
<td>49%</td>
<td>0.9956</td>
</tr>
<tr>
<td>N1</td>
<td>51%</td>
<td>51%</td>
<td>0.9956</td>
</tr>
<tr>
<td>Number of positive nodes</td>
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<td>1</td>
<td>0.9956</td>
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<tr>
<td>Median number of SLN</td>
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<td>5</td>
<td>0.9956</td>
</tr>
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Disclosure(s):
Sue Zann Lim, n/a: No financial relationships to disclose
Tae-Kyung Yoo, M.D.: No financial relationships to disclose
Sae Byul Lee, M.D., Ph.D.: No financial relationships to disclosure
Jisun Kim, M.D., Ph.D.: No financial relationships to disclose
Il-Yong Chung, M.D.: No financial relationships to disclose
Beom Seok Ko, M.D., Ph.D.: No financial relationships to disclose
Jong Won Lee, M.D., Ph.D.: No financial relationships to disclose
Byung Ho Son, M.D., Ph.D.: No financial relationships to disclose
Sei Hyen Ahn, M.D., Ph.D.: No financial relationships to disclose
Hee Jeong Kim, M.D., Ph.D.: No financial relationships to disclose
Background
It is of substantial importance to tailor axillary surgery after neoadjuvant chemotherapy (NAC) based on tumor biology and response to treatment. This study aimed to determine the accuracy of repeated core needle biopsy (RCNB) in breast to predict nodal response after NAC.

Methods
Eligible patients with clip insertment into pathologically-proven positive node underwent RCNB during NAC. Targeted fine needle aspiration (TFNA) of clipped lymph node (CLN) was performed in a subset of patients after NAC. All patients ultimately underwent axillary surgery. RCNB and TFNA results were compared with surgical pathology.

Results
Data from 189 eligible patients were analyzed. The overall axillary pCR was 57.1%. The false-negative rate (FNR) of RCNB across the whole cohort was 12.1% (95% CI, 5.3%–18.9%), and exploratory subgroup analysis revealed an excellent ability to predict the presence of residual nodal disease in estrogen receptor-positive breast cancer with a low FNR of 1.6% (95% CI, 0.0%–4.9%) (Table 1). Adopting a strategy where only patients with negative RCNB undergo targeted axillary dissection (TAD) would potentially reduce the FNR of TAD from 9.3% to 2.3%. Furthermore, combination of RCNB and TFNA demonstrated a FNR of 2.2% (95% CI, 0.0%–6.6%), and negative predictive value of 94.1% (95% CI, 81.6%–100.0%) (N = 87) (Table 2). The proposed algorithm based on RCNB and TFNA is helpful in optimizing axillary surgery by avoiding 25 unnecessary attempts as well as 2 false-negative cases in TAD and conferring 10 patients omission of axillary surgery.

Conclusions
Combination of RCNB and TFNA allows for an accurate assessment of nodal response after NAC. These results may facilitate reliable identification of suitable candidates for de-escalation or elimination in axillary surgery.

Table 1. Overall Cohort Diagnostic Accuracy of Repeated Core Needle Biopsy to Predict Nodal Response (N = 189)
Abbreviations: ER, estrogen receptor; HER2, human epidermal factor receptor 2; NPV, negative predictive value; PPV, positive predictive value.

Table 2. Diagnostic Accuracy of Repeated Core Needle Biopsy in Breast, Targeted Fine Needle Aspiration and the Combination in Cohort 2 (N = 87)

<table>
<thead>
<tr>
<th></th>
<th>% (95%CI)</th>
<th>% (95%CI)</th>
<th>% (95%CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>All subtypes (n = 189)</strong></td>
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<td></td>
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</tr>
<tr>
<td>Accuracy</td>
<td>70.4% (63.8-76.9)</td>
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<tr>
<td>Sensitivity</td>
<td>87.9% (81.1-94.7)</td>
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<tr>
<td>Specificity</td>
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<tr>
<td>NPV</td>
<td>82.8% (73.3-92.3)</td>
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<tr>
<td>PPV</td>
<td>64.0% (55.5-72.5)</td>
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<tr>
<td><strong>ER+HER2- (n = 53)</strong></td>
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<tr>
<td>Accuracy</td>
<td>84.9% (74.9-94.9)</td>
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<tr>
<td>Sensitivity</td>
<td>100.0% (100.0-100.0)</td>
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<tr>
<td>Specificity</td>
<td>38.5% (7.9-69.1)</td>
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<tr>
<td>NPV</td>
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<tr>
<td>PPV</td>
<td>83.3% (72.4-94.3)</td>
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<tr>
<td><strong>ER+HER2+ (n = 50)</strong></td>
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<tr>
<td>Accuracy</td>
<td>70.0% (56.8-83.2)</td>
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<tr>
<td>Sensitivity</td>
<td>95.2% (85.3-100.0)</td>
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<tr>
<td>Specificity</td>
<td>51.7% (32.4-71.1)</td>
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<tr>
<td>NPV</td>
<td>93.8% (80.4-100.0)</td>
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<tr>
<td>PPV</td>
<td>58.8% (41.4-76.3)</td>
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<tr>
<td><strong>ER-HER2- (n = 52)</strong></td>
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<tr>
<td>Accuracy</td>
<td>61.5% (47.9-75.2)</td>
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<tr>
<td>Sensitivity</td>
<td>56.3% (28.9-83.6)</td>
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<tr>
<td>Specificity</td>
<td>63.9% (47.4-80.4)</td>
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<tr>
<td>NPV</td>
<td>76.7% (60.6-92.7)</td>
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<tr>
<td>PPV</td>
<td>40.9% (18.6-63.2)</td>
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<tr>
<td><strong>ER-HER2+ (n = 34)</strong></td>
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<tr>
<td>Accuracy</td>
<td>61.8% (44.6-79.0)</td>
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<tr>
<td>Sensitivity</td>
<td>84.6% (61.9-100.0)</td>
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<tr>
<td>Specificity</td>
<td>50.0% (26.0-74.0)</td>
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<tr>
<td>NPV</td>
<td>47.6% (24.3-70.9)</td>
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<tr>
<td>PPV</td>
<td>52.4% (29.1-75.7)</td>
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</tr>
</tbody>
</table>

Table 2. Diagnostic Accuracy of Repeated Core Needle Biopsy in Breast, Targeted Fine Needle Aspiration and the Combination in Cohort 2 (N = 87)
Abbreviations: NPV, negative predictive value; PPV, positive predictive value; RCNB, repeated core needle biopsy; TFNA, targeted fine needle aspiration.

Disclosure(s):
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Guangyu Liu, n/a: No financial relationships to disclose
Background Breast conserving surgery with adjuvant radiotherapy (BCS+RT) and mastectomy are currently offered as oncologically equivalent options for the surgical management of early breast cancer based on findings from randomised controlled trials (RCTs) conducted over four decades ago. Since then, locoregional and systemic breast cancer treatments have improved significantly and several recent observational studies suggest a survival advantage in patients receiving BCS+RT compared to those having mastectomy. If BCS+RT is oncologically superior to mastectomy, this may dramatically impact surgical treatment recommendations. The aim of this systematic review was to identify, critically appraise and summarise the contemporary literature comparing survival following BCS+RT and mastectomy to inform surgical decision-making for patients with early breast cancer. Methods A systemic search of MEDLINE, Cochrane Central Register of Controlled Trials and Embase identified studies published between 1st January 2000 to 22nd September 2021. Included were primary research studies published in English comparing overall survival in women undergoing primary surgery with either BCS+RT or mastectomy for unilateral stage I to III breast cancer. Excluded were studies evaluating neoadjuvant chemotherapy; rare breast cancer subtypes (e.g. mucinous) or in specific patient populations (e.g. pregnancy associated breast cancer) and those that completed recruitment before 1st January 1990. We used the ROBINS-I tool to assess the risk of bias in study results and GRADE to assess the overall certainty of evidence. All papers without critical risk of bias were included in a quantitative meta-analysis. Where more than one study reported outcomes in overlapping population-based registry cohorts, the study with the most recent data on the largest cohort was selected for analysis. The primary analysis was a random effects meta-analysis with a fixed effect model undertaken as sensitivity analysis. A
secondary meta-analysis was performed for studies only including triple negative breast cancers. All analyses were conducted using STATA17. Results 10,876 abstracts were screened and 157 full-text papers assessed for eligibility, of which 93 (17 multi-centre observational studies, 30 were single-centre observational studies and 46 registry-based studies) met the inclusion criteria for the review. 25 papers were excluded from meta-analysis due to an overall critical risk of confounder bias and 27 were excluded due overlapping study populations. 36 studies (34 with serious risk of bias and 2 with moderate risk of bias) reporting survival outcomes on 1,321,291 patients (729,789 undergoing BCS+RT and 591,502 undergoing mastectomy) were included in the meta-analysis. The pooled hazard ratio was 0.72 (95% CI 0.64– 0.81, p< 0.001, I2 97.6%) demonstrating improved overall survival for patients undergoing BCS+RT compared with those receiving mastectomy. The sensitivity analysis, using a fixed effect model, showed a hazard ratio of 0.88 (95% CI 0.87 – 0.89, p< 0.001, I2 97.6%) for survival in women undergoing BCS+RT compared with mastectomy. Meta-analysis of 8 studies reporting survival in 17,181 patients with triple negative breast cancer showed a hazard ratio of 0.73 (95% CI 0.68 – 0.79, p< 0.001, I2 34.7%) for those receiving BCS+RT versus mastectomy. Discussion This meta-analysis provides further, albeit very low certainty evidence, that overall survival is improved following BCS+RT compared with mastectomy in a contemporary cohort of patients treated for early-stage breast cancer. These results should be interpreted with caution due to the heterogeneity of included studies and the high risk of bias associated with observational data. As future RCTs will not be feasible, well-designed large-scale prospective observational studies are needed to provide better evidence to support surgical decision-making in early-stage breast cancer.

Disclosure(s):
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Chris Holcombe, MD FRCS: No financial relationships to disclose
Shelley Potter, PhD FHEA FRCS: No financial relationships to disclose
PD15-05 Breast Conserving Therapy Has Improved Survival Without An Increased Risk Of Locoregional Recurrence Compared To Mastectomy In Both Clinically Node Positive And Node Negative Patients.

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   Country: United States

Elaine Mckevitt, Clinical Professor, Breast Surgeon - University of British Columbia
   Country: United States

Background:
Randomized trials demonstrated equivalent survival between breast conserving surgery (BCS) combined with radiotherapy (Breast conserving therapy, BCT) and mastectomy (MT). Subsequent meta-analysis confirmed no difference in survival, despite higher rates of local recurrence with BCT. Advances in early detection, systemic therapy, and expanded indications for radiotherapy have led to improved survival from breast cancer, and in turn, contemporary studies show improved survival with BCT. These studies use pathological stage of the primary tumor and the nodal status for the analysis, yet this information is unknown to the surgeon at
the time of deciding between MT and BCS. To mimic real-world surgical decision-making and its influence on outcomes, this study assesses overall survival (OS), breast cancer specific survival (BCSS), and locoregional recurrence (LRR) in a modern population-based cohort in patients with clinically node-positive and node-negative breast cancer.

Methods:
Female patients aged 18-69 treated with BCT or MT with or without adjuvant radiation in 2006-2016 for T1-3N0-3M0 breast cancer were identified from our prospective provincial database. Patients treated with neoadjuvant chemotherapy were excluded. The cohort was stratified based on clinical nodal status and multivariable logistic regression was used to assess the effect of local treatment type on OS, BCSS, and LRR for both strata. Comprehensive sensitivity analyses were performed using imputation to assess cases with missing variables. In the node-negative cohort, where pathological nodal stage was upgraded, receipt of nodal irradiation was accounted for in the final model.

Results:
A total of 13,914 patients met inclusion criteria: 8,228 had BCT and 5,686 had MT. Baseline characteristics were not balanced, with higher risk clinical and pathological factors seen in the MT group. Median follow up for both groups was between 7.8-8.5 years.

In the clinically node-positive group, 485 patients had BCT with a median tumor size of 2.5 cm (IQR: 1.8-3.0) and 892 had MT with a median tumor size of 3.0 cm (IQR: 2.2-4.5). BCT patients had radiation only to the chest in 8.9% patients and 91.1% had both chest and regional nodal irradiation. 84% of MT patients had radiation, with 1.1% only to the chest, and 83% to both chest and regional nodes. On multivariable analysis, BCT was associated with improved OS (HR 1.46, p=0.002) and BCSS (HR 1.44, p=0.008), while locoregional recurrence was 6.6% after BCT and 6.7% after mastectomy, HR 0.89 (p=0.7).

For patients that were clinically node-negative, 7,743 had BCT with a median tumor size of 1.5 cm (IQR: 1.0-2.1) and 4,794 had MT with a median tumor size of 2.0 cm (IQR: 1.2-3.0). After surgery, 79% of BCT patients and 62% of MT patients remained node-negative. All BCT patients had radiation, with 80% only to the chest, and 20% to both chest and regional nodes. 38% of MT patients had radiation, with 5.4% radiation to only the chest and 33% to both chest and regional nodes. On multivariable analysis, BCT was associated with improved OS (HR 1.37, p< 0.001) and BCSS (HR 1.32, p< 0.001), while locoregional recurrence was 3.8% after BCT and 4.3% after MT, HR 0.84 (p=0.1).

Conclusion:
For women with both clinically node-positive and clinically node-negative breast cancer, BCT offers better survival than mastectomy without an increased risk of loco-regional recurrence. When feasible, BCT should be recommended to patients with breast cancer.
Table 1. Breast Cancer Specific Survival Multivariable Analysis.

<table>
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<tr>
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<th>Node-negative</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
<td>HR</td>
</tr>
<tr>
<td>Procedure</td>
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<tr>
<td>BCS</td>
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<td>Mastectomy</td>
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<td>1.1, 1.6</td>
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<td>1.0, 1.0</td>
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<td>1.2, 1.3</td>
<td>&lt;0.001</td>
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<td>0.7, 1.6</td>
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Disclosure(s):
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Pathologic complete response and breast-conserving surgery are associated with improved prognosis in patients with early-stage triple-negative breast cancer treated with neoadjuvant chemotherapy

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Background: Neoadjuvant chemotherapy (NACT) is standard of care for patients with triple-negative breast cancer (TNBC). Treatment response, especially pathologic complete response (pCR), is a strong predictive factor for treatment outcome. In the setting of up-front surgery, retrospective data have suggested improved outcome in patients with early TNBC that received breast-conserving surgery with adjuvant radiotherapy (BCT) as compared to mastectomy.

Methods: We identified 2632 patients with early TNBC from the German Breast Group meta-database. Patients with cT1-2 cN0 and ypN0, available surgery and follow-up data were eligible for this project. A total of 1074 patients from 8 prospective NACT trials were analyzed. Endpoints of interest were locoregional recurrence as first site of relapse (LRR, other sites of recurrence were considered competing events), disease-free survival (DFS) and overall survival (OS); analyses were performed using univariate and multivariate Fine-Gray (for LRR) and Cox models including study, age, cT, surgery type and pCR. For the analyses including pCR as covariable, only patients at risk at the landmark time were evaluated. Results: Median age was 48 years, 69.6% of patients had cT2 tumors and 85.3% underwent BCS. Of the 1074 analyzed patients, 48.8% achieved pCR. After a median follow-up of 64 months, there were 94 (8.8%) locoregional events as first site of relapse. Upon univariate analysis, absence of pCR (hazard ratio [HR]=2.28; 95%CI 1.44-3.61; p< 0.001) and ypT-stage (ypT0/is vs. ypT1-3, HR=0.61; 95%CI 0.40-0.95; p=0.028) were significantly associated with LRR, while type of surgery, age and cT-stage were not. Upon multivariate analysis, absence of pCR was the only factor associated with increased risk of LRR (HR=2.22; 95%CI 1.38-3.58; p=0.001). Patients that underwent mastectomy (N=158) were significantly younger (age ≤ 50 years 72.8% vs. 59.9% for BCT [N=916]; p=0.002) DFS and OS was significantly better in patients who underwent BCT compared to mastectomy (DFS: HR=0.47; 95%CI 0.34-0.66; p< 0.001 and OS: HR=0.40; 95%CI 0.26-0.63; p< 0.001). In multivariate analysis, BCT was associated with a significantly better DFS and OS as compared to mastectomy (DFS: HR=0.51; 95%CI 0.36-0.72; p< 0.001; and OS HR=0.43; 95%CI 0.27-0.68; p< 0.001), whereas absence of pCR was associated with significantly worse DFS and OS (DFS: HR=2.43; 95%CI 1.78-3.31; p< 0.001; and OS: HR=3.15; 95%CI 1.94-5.10; p< 0.001). Conclusions: In this retrospective analysis from the GBG meta-database, treatment response, e.g. pCR, was the main determinant of locoregional recurrence in patients with early stage TNBC treated with NACT. BCT was associated with improved DFS and OS compared to mastectomy, which may at least in part reflect favorable patient selection.

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PD15-07

PD15-07 7-gene predictive biosignature improves risk stratification for breast ductal carcinoma in situ patients compared to clinicopathologic criteria, identifying a low risk group not clinically benefiting from adjuvant radiotherapy

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   Country: United States
Background: Prognostic and predictive tools are needed to optimize treatment for women diagnosed with ductal carcinoma in situ (DCIS). While radiotherapy (RT) is standard of care for DCIS after breast conserving surgery (BCS), those at low-risk for ipsilateral breast recurrence (IBR) risk may be treated without RT. Low-risk has been defined as the absence of high risk clinicopathologic (CP) factors, including larger (>2 cm), palpable, or high nuclear grade (NG) tumors, and younger age (< 50 yrs). However, prospective trials have failed to identify low risk patients (pts) who do not clinically benefit from RT after BCS (RTOG 9804). DCISionRT® (PreludeDxTM, CA) is a 7-gene predictive biosignature providing a validated score (DS) to assess the 10-yr IBR risk and RT benefit, using individual tumor biology and CP factors. This study assessed total 10-yr IBR rates, RT benefit, and number needed to treat (NNT) for risk groups defined by biosignature and CP criteria.

Methods: DCIS patients (n=926) from four international cohorts (median follow up 8.5 yrs, 1-3rd quartile 5.8 – 10.2 yrs) treated with BCS (negative margins), with (n=641) and without RT (n=335), had formalin-fixed paraffin-embedded tissues analyzed at a CLIA lab (PreludeDx, Laguna Hills, CA) for DCISionRT with a Residual Risk subtype (RRt). A biosignature Low Risk group (DS≤2.8 without RRt) was contrasted to a High Risk group comprising Elevated Risk (DS>2.8 without RRt) and Residual Risk (DS>2.8 with RRt) groups. Low-risk CP groups were RTOG 9804-like (NG1-2, non-palpable, negative margins, screening detected) or (age >50 and NG 1-2). Total 10-yr IBR rates were evaluated using Cox Proportional Hazards and Kaplan Meier analysis by treatment, biosignature and CP risk groups. NNT was determined with 10-yr IBR rate differences with RT.

Results: The biosignature classified 37% (n=338) of women as Low Risk and 63% (n=588) as High Risk. Among women who did not receive RT, biosignature Low Risk pts had lower IBR than biosignature High Risk pts (5.6% vs. 25.7%, p<.001). About half of pts defined as CP low-risk by 9804-like (NG1-2, non-palpable, negative margins, screening detected) or (age >50 and NG 1-2). Total 10-yr IBR rates were evaluated using Cox Proportional Hazards and Kaplan Meier analysis by treatment, biosignature and CP risk groups. NNT was determined with 10-yr IBR rate differences with RT.
groups, RT reduced IBR by 0%. Overall, RT did not significantly reduce IBR rate for biosignature Low Risk patients \((p=0.71, n=338)\), with a 0.8% absolute 10-yr IBR rate difference and a NNT of ~100.

Conclusion: In a large multicenter population, DCISionRT was a better predictor of 10-yr prognosis and RT benefit than CP criteria alone. Pts with biosignature Low Risk disease, comprising about 1/3 of CP high-risk pts, had no significant RT benefit. Whereas pts with biosignature High Risk disease, comprising about 1/2 of CP low-risk pts, significantly benefited from RT, highlighting the lack of accuracy of these CP factors in assessing RT benefit.

<table>
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<tr>
<th>Clinical-Pathologic Groups</th>
<th>Biosignature Low Risk group (DS≤2.8 without RR)</th>
<th>Biosignature High Risk group (Combined Elevated/Residual Risk, DS&gt;2.8 without or with RR)</th>
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<tr>
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<td>10-year IBR risk</td>
<td>10-year IBR risk</td>
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<tr>
<td>Overall</td>
<td>588 (65%)</td>
<td>0.8 (0.3, 3.3)</td>
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<td>0.8 (0.3, 3.3)</td>
<td>0.3 (0.1, 0.7)</td>
</tr>
<tr>
<td>RTOG 9804-like*</td>
<td>232 (49%)</td>
<td>5.5% (3.1, 12.9)</td>
</tr>
<tr>
<td>'good-risk' (Low-risk)</td>
<td>5.5% (3.1, 12.9)</td>
<td>0.96 (0.3, 3.3)</td>
</tr>
<tr>
<td></td>
<td>4.8 (0.3, 14.9)</td>
<td>0.3 (0.1, 0.7)</td>
</tr>
<tr>
<td>RTOG 9804-like*</td>
<td>106 (23%)</td>
<td>5.9% (2.2, 22.9)</td>
</tr>
<tr>
<td>'High-risk'</td>
<td>5.9% (2.2, 22.9)</td>
<td>0.5 (0.1, 3.8)</td>
</tr>
<tr>
<td></td>
<td>30.5% (21.4, 43.7)</td>
<td>8.7 (6.1, 14.8)</td>
</tr>
<tr>
<td>Age ≥50 and Grade 1 or 2</td>
<td>190 (42%)</td>
<td>6.3% (3.1, 14.9)</td>
</tr>
<tr>
<td>(Low-risk)</td>
<td>6.3% (3.1, 14.9)</td>
<td>0.9 (0.3, 3.0)</td>
</tr>
<tr>
<td></td>
<td>18.4% (11.3, 30.3)</td>
<td>7.2% (4.1, 13.1)</td>
</tr>
<tr>
<td>Age &lt;50 or Grade 3</td>
<td>148 (31%)</td>
<td>4.4% (1.1, 17.9)</td>
</tr>
<tr>
<td>(High-risk)</td>
<td>4.4% (1.1, 17.9)</td>
<td>0.7 (0.1, 4.0)</td>
</tr>
<tr>
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<td>34.3% (26.4, 48.8)</td>
<td>8.5% (5.1, 14.8)</td>
</tr>
</tbody>
</table>

Table 1. Ten-Year Risk of Ipsilateral Breast Recurrence (IBR)

* RTOG 9804-like criteria (Nuclear Grade 1 or 2, non-Palpable, Screening Detected, Negative Margins)

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Rachel Rabinovitch, MD: PreludeDx: Contracted Research (Ongoing)
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PD15-08

PD15-08 Brazilian Randomized Study - BREAST-MRI Trial - Impact of Preoperative Magnetic Resonance in the Evaluation for Breast Cancer Conservative Surgery: Local recurrence and surgical outcomes

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Introduction: Breast magnetic resonance imaging (MRI) has high sensitivity in detecting invasive neoplasms. However, controversy remains as to whether preoperative staging with breast MRI impacts surgical outcomes and local recurrence. Materials and Methods: BREAST-MRI is a randomized, open-label trial including female breast cancer patients older than 18 years old, with stage 0-III disease, eligible for BCS. We performed a 1:1 stratified randomization by breast density according to ACR-BIRADS to divide patients into two groups; one in which preoperative MRI was used and the control group where the MRI was not used. The primary outcome was local relapse-free survival (LR). Secondary outcomes were overall survival (OS), repeat operation, and the proportion of patients whose surgical management was modified to mastectomy. Results: 524 were randomized, 257 included in the MRI group, and 267 in the control group. The baseline characteristics were similar between groups, except for chemotherapy use (table 1). The survival analysis showed a 6-year local recurrence-free survival was 99.2% in MRI group versus 98.9% in the control group, p=0.702, overall survival of 95.3% in the MRI group versus 96.3% in the control group, p=0.481. No difference was found in reoperation rates, 22 (8.7%) in the MRI group versus 23 (8.7%) in the control group (p=0.85)(table2). Surgical management changed in 21 ipsilateral breasts in the MRI group; 21 (8.3%) had mastectomies versus 1 in the control group (p< 0.01). Conclusion: Preoperative MRI evaluation increased the mastectomy rates by 8%. The use of preoperative MRI did not influence local relapse-free survival, overall survival, or reoperation rates. Keywords: breast magnetic resonance imaging; breast cancer; conservative surgery; MRI accuracy, surgical outcomes, randomized clinical trial

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Introduction: Women considering immediate breast reconstruction (IBR) after mastectomy for breast cancer require high-quality information about the short and long-term outcomes of different procedure types to allow them to make informed decisions about their surgical options. Long-term multicentre patient-reported outcomes (PROs) comparing the patients’ perspectives of different techniques is currently lacking. The UK Brighter study aimed to compare the long-term patient-reported outcomes of different types of IBR to support informed decision-making. Methods: Women who underwent unilateral mastectomy and/or breast reconstruction for invasive breast cancer or ductal carcinoma in situ (DCIS) in England between 1 April 2008 and 31 March 2009 were identified from National Health Service (NHS) Hospital Episode Statistics...
(HES), and current contact information for the surviving cohort were provided by the NHS Personal Demographic Service. Women were sent a letter inviting them to complete three validated patient report questionnaires, the BREAST Q, EQ-5D5L and ICECAP-A, electronically or by post at a minimum of 12 years following their index surgery. Results: 11,977 women were invited to participate of whom 4,207 (35.1%) completed the questionnaires. Of these, 1,236 (29.4%) received IBR with 343 (27.8%) expander/implant (EI) reconstructions, 629 (50.9%) latissimus dorsi (LD) procedures with or without an implant, and 264 (21.4%) abdominal flap (AF) reconstructions. The mean age at index surgery was 52.1 years, standard deviation (SD) 9.5. The majority of respondents were white (n=1,179, 97.4%) and predominantly from areas of the lowest socioeconomic deprivation. The mean body mass index (BMI) was 24.6 (SD 3.9). 141 (11.6%) women actively smoked at the time of surgery and 227 (19.0%) had a complication requiring further surgery. Women undergoing AFs reported significantly higher ‘Satisfaction with Breasts’ (mean 67.7, SD 20.4) than those undergoing LD (mean 58.9, SD 21.1), or EI reconstructions (mean 54.7, SD 19.2), (p< 0.001). ‘Satisfaction with Breasts’ was also greater in women undergoing index surgery over 50 years of age (p=0.02) and in those who did not smoke (p=0.03) whereas experiencing post-operative complications was strongly associated with poorer ‘Satisfaction with Breasts’ in the multivariable analysis (p=0.001). Women receiving AF also reported better ‘Physical Well-being’ (mean 87.8, SD 16.04) than women undergoing LD flap (mean 79.5, SD 20.5) or EI procedures (mean 82.1, SD 18.2), (p< 0.001). Overall, women undergoing AFs were more likely to rate the outcome of their surgery as ‘excellent’ or ‘very good’ (189/256, 73.8%) compared with those receiving other reconstruction types (LD - 386/610, 63.3%; EI - 175/331, 52.9%, p< 0.001). Conclusion: Women undergoing abdominal flap reconstruction report significantly better outcomes 12 years following IBR than women receiving other reconstruction types. These findings should be shared with women considering breast reconstruction to help them make informed decisions about their surgical options.

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Introduction: Women considering immediate breast restoration (IBR) after mastectomy for breast cancer need high-quality information about the short and long-term clinical outcomes of different procedure types, including the need for further surgery, to allow them to make fully informed decisions about their breast restoration options. Long-term outcome data is currently lacking. The UK Brighter population-based cohort study aimed to compare the need for revisional surgery and secondary reconstruction by type of IBR at a minimum of 12 years following the index procedure to support informed decision-making. Methods: Women who underwent unilateral mastectomy and IBR for invasive breast cancer or ductal carcinoma in situ.
(DCIS) in England between 1 April 2008 and 31 March 2009 were identified using National Health Service (NHS) Hospital Episode Statistics (HES). Lists of procedure codes indicating revisional surgery, defined as operations performed to the same site as the index reconstruction and/or the donor site (if appropriate), excluding a single planned implant exchange in the expander group, or secondary reconstruction, defined as the replacement of one reconstruction with another, with or without a period of being flat, were iteratively developed and refined. Numbers of revision procedures and secondary reconstructions were compared by type of index reconstruction. Multivariable regression was used to control for potential confounders. Results: 2,260 women underwent IBR during the study period including 742 (32.8%) expander/implant (EI), 1,146 (50.7%) latissimus dorsi (LD) flap reconstructions with (n=649) and without (n=497) an implant and 372 (16.5%) abdominal free-flap (AFF) procedures. Women receiving reconstructions involving implants were significantly more likely to require more revisions over time, with 201/742 (27.1%) patients undergoing EI reconstruction and 154/649 (23.7%) those receiving an implant-assisted LD reconstruction requiring two or more post-reconstruction revision procedures compared with 77/497 (15.5%) patients undergoing autologous LD and 59/372 (15.9%) patients receiving AFF procedures (p< 0.001). Undergoing primary reconstructive surgery before the age of 50, and region of residence at the time of the mastectomy were factors influencing revisional surgery in the multivariable regression analysis. By 12 years, 128/742 (17.3%) of women who initially underwent an expander/implant reconstruction had received a secondary reconstruction compared with 34/1146 (3.0%) patients who had initially received an LD +/- implant procedure and 11/372 (3.0%) patients initially undergoing an AFF reconstruction (p< 0.001). Conclusions: The need for revisional surgery in women electing to undergo IBR involving implants is significantly greater than that for women electing to receive autologous reconstructions and almost 1 in 5 women undergoing primary EI reconstruction required a secondary reconstruction by 12 years. These findings should be shared with women considering IBR to support informed decision making and with healthcare providers and commissioners to support the provision of high-quality, evidence-based reconstructive care.

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PD15-11 Axillary dissection to determine nodal burden to inform systemic therapy recommendations in patients with clinically node-positive breast cancer: Pre-planned substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101)

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Introduction: Chemotherapy is recommended for patients with luminal breast cancer and more than three positive nodes. In addition, recent landmark trials raised the question if the exact number of positive nodes is required to indicate genomic testing. In the neoadjuvant setting, response-driven therapy is increasingly used and may be influenced by surgical staging of the axilla. The present study addressed the role of axillary lymph node dissection (ALND) as decision aid for systemic therapy in a contemporary cohort of patients with clinically node-positive breast cancer in the adjuvant and neoadjuvant setting. Methods: The study was preplanned in the international multicenter phase-III OPBC-03/TAXIS trial (ClinicalTrials.gov Identifier: NCT03513614). The first 500 patients with clinically node-positive breast cancer who were randomized after tailored axillary surgery (TAS) to undergo ALND or axillary radiotherapy (ART) without ALND in the context of extended regional irradiation were included from August 2018 to June 2022. Clinically node-positive breast cancer was defined by confirmed nodal disease at the time of initial diagnosis; in case of neoadjuvant therapy, the finding of residual nodal disease was mandatory for randomization. TAS consisted of removal of palpably suspicious findings and the sentinel nodes with the option of image guidance. In the ART arm, the total number of positive nodes was not known. We analyzed the impact of ALND on rate and type of systemic therapy. Results: A total of 500 patients with a median age of 57 years (IQR: 48-69 years) were included at 44 breast centers from six European countries. Subtype was hormone receptor (HR) positive (+) and human epidermal growth factor receptor 2 (HER2) negative (-) in 393 (80.0%), HR+/HER2+ in 52 (10.6%), HR-/HER2+ in 5 (1.0%) and HR-/HER2- in 34 (6.9%) patients. Of 343 patients (68.6%) who were treated in the adjuvant setting, 297 had HR+/HER2- disease. Of these 297 patients, 145 (48.8%) underwent ART without ALND and 152 (51.2%) underwent ALND after TAS. In the ART arm, the median number of lymph nodes removed was five (IQR 4-8), three (IQR 1-4) of which were positive and in the ALND arm, the number was 19 (IQR 14-26), four (IQR 2-9) of which were positive (p < 0.001). The use of ALND had no significant impact on the rate of patients with HR+/HER2- disease undergoing adjuvant chemotherapy (51.0% in the ART and 57.9% in the ALND arm, p=0.2), and there were no significant differences in type of systemic therapy with the exception of tamoxifen, which was 18.4% with ALND versus 9.0% without (p=0.018). A total of 143 patients (28.6%) underwent neoadjuvant chemotherapy, 13 had neoadjuvant antihormonal treatment and one had neoadjuvant double HER2-blockade without chemotherapy. Of the 143 patients who received neoadjuvant chemotherapy, 71 (49.7%) underwent ART without ALND and 72 (50.3%) underwent ALND. In the ART arm, the median number of lymph nodes removed was four (IQR 3-6), one (IQR 1-3) of which was positive and in the ALND arm, the number was 16 (IQR 12-19), two (IQR 1-5) of which were positive (p < 0.001). The use of ALND in patients after neoadjuvant treatment had no significant impact on the rate of adjuvant systemic therapy (71.8% in the ART and 65.3% in the ALND arm, p=0.4), with no significant differences in type of chemotherapy (e.g., capecitabine: 11.3% vs 12.5%, p=0.8; T-DM1: 11.3% vs. 11.1%, p>0.9) or antihormonal therapy (e.g., aromatase inhibitors: 49.3% vs. 41.7%, p=0.4; tamoxifen: 11.3% vs. 5.6%, p=0.2). Discussion: This study showed that although ALND significantly increased the number of positive nodes removed in the adjuvant and neoadjuvant setting, it had no relevant impact on rate and type of adjuvant systemic therapy.

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PD15-12
A pre-surgical window trial of oral tamoxifen versus transdermal 4-hydroxytamoxifen gel in women with estrogen receptor positive duct carcinoma in situ (DCIS)

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Background: Adjuvant oral tamoxifen (TAM) benefits women with DCIS, but toxicity concerns have limited its acceptance. Transdermal therapy with 4-hydroxy tamoxifen (4-OHT) gel applied to the breast skin is a possible solution. Previous pilot data suggest equivalent anti-proliferative efficacy of TAM and 4-OHT gel, but minimal systemic exposure with transdermal therapy. We report a prospective double blinded randomized phase 2 trial comparing TAM to 4-OHT gel in women with DCIS. Methods: 107 women with estrogen receptor positive (≥10%) DCIS were randomized to TAM (20 mg/day + placebo gel) or 4-OHT gel (2mg 4-OHT gel/breast, bilaterally + oral placebo), for 4-10 weeks prior to surgery. The primary endpoint was reduction in DCIS Ki67 labeling index (LI). Secondary endpoints included the 12-gene DCIS Score assay (Exact Sciences), breast tissue and plasma concentrations of 4-OHT and endoxifen, TAM-responsive circulating proteins, and patient reported symptoms (Breast Eight Symptom Scale). We estimated that 80 evaluable participants would provide 80.5% power to establish non-inferiority of 4-OHT, defined as relative Ki67-LI decline >35% and absolute decline >2.6%, with one-sided
\(\alpha=0.10\). Non-inferiority of 4-OHT gel for Ki67-LI reduction was tested using an ANCOVA model. Statistical comparisons within- and between-arms were calculated with paired t-test and Welch Two Sample t-test, respectively. Results: 72 of 87 women adhered to the protocol, and were evaluable for the primary endpoint (39 TAM and 33 4-OHT gel). Mean treatment duration was 47 days for TAM and 44 days for 4-OHT gel (\(p=0.2\)). The median absolute decline in Ki67 labeling index was significant in the oral TAM (-3.7%, \(p<0.001\)) but not in 4-OHT gel arm (-1.3%, \(p=0.2\)) (\(p=0.002\)). Ki67 results following menopausal stratification also favored the TAM arm: (-1.3%; \(p=0.06\) in 37 premenopausal women and -3.7%; \(p=0.02\) in 35 postmenopausal women). Similarly, DCIS score showed a significantly greater reduction in the TAM (-14, \(p<0.001\)) but not in the 4-OHT gel arm (-4, \(p=0.1\)). Tissue 4-OHT concentrations were non-significantly higher in the TAM arm and were similar between superficial and deep sampling locations (superficial 6.1 and 4.2 ng/g for TAM and 4-OHT gel, respectively, \(p=0.55\); deep 5.7 and 3.8 ng/g, respectively, \(p=0.06\)), whereas plasma 4-OHT concentration was markedly lower in the gel group (2 ng/mL and 0.24 ng/mL for TAM and 4-OHT gel, respectively, \(p<0.001\)).

Endoxifen was abundant in plasma (11 ng/mL) and deep tissue (13 ng/g) of the TAM arm, but present in trace amounts in the 4-OHT gel arm (undetectable in plasma and 0.31 ng/g in tissue; \(p<0.001\)). Circulating TAM responsive markers (insulin like growth factor 1, sex hormone binding globulin, von Willebrand factor, and protein S total) and vasomotor symptoms were significantly and unfavorably modulated by TAM, but not by 4-OHT gel therapy. Conclusions: The non-inferiority of transdermal 4-OHT gel to Tam in terms of anti-proliferative effect in DCIS lesions was not demonstrated at the doses used for this study. DCIS Score analysis gave similar results. Tissue 4-OHT concentration in 4-OHT gel and Tam-treated subjects was roughly similar. However, endoxifen exposure was higher with oral TAM therapy and may partially explain the observed differences in major endpoints. In future studies, use of higher 4-OHT gel doses, longer duration of treatment, or different formulation may overcome these.

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