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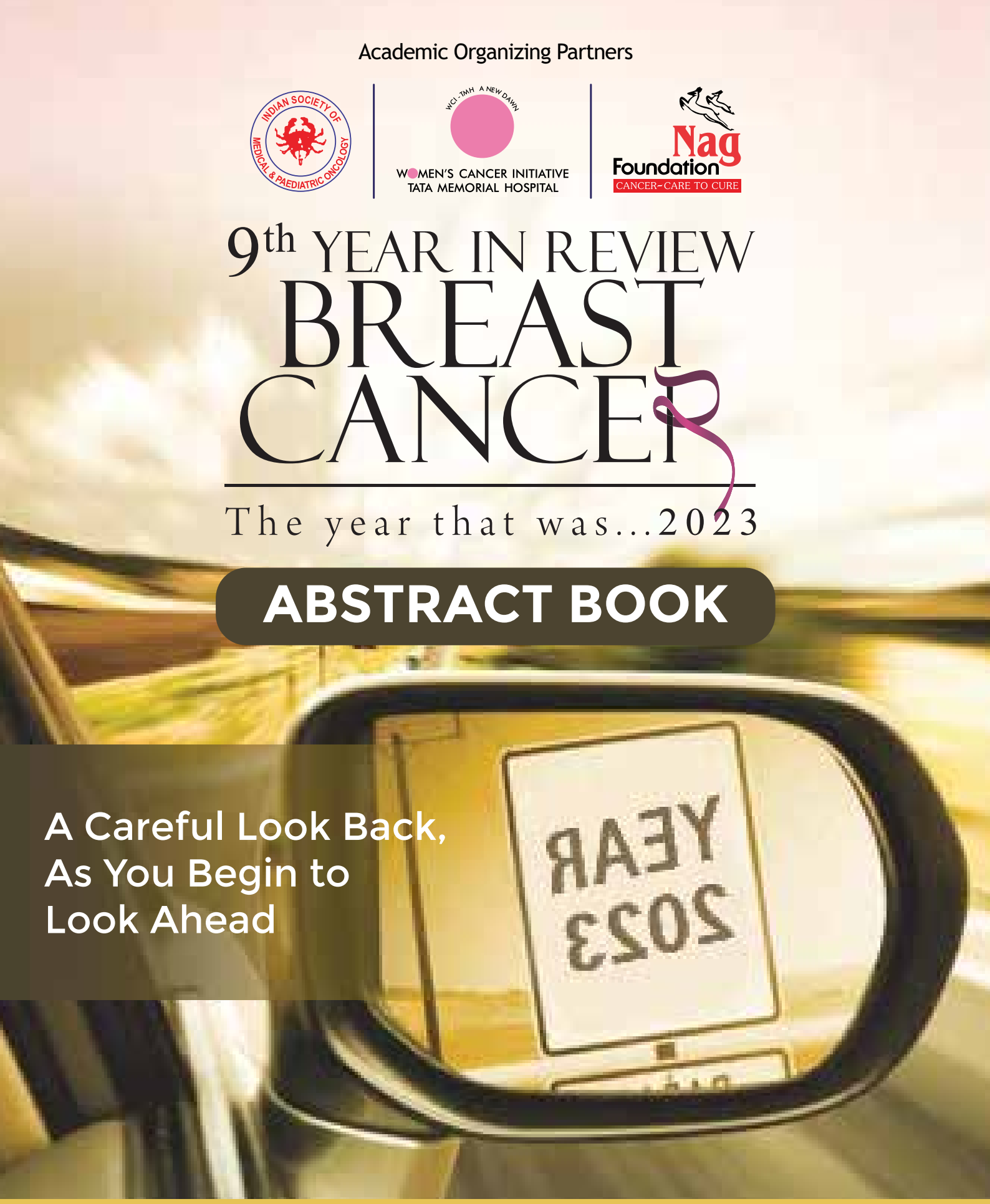
ABSTRACT BOOK



A Careful Look Back,
As You Begin to
Look Ahead

Fri - 12th, Sat - 13th & Sun - 14th | Jan-2024

**Venue: Prof. R.D. Choksi Auditorium,
Tata Memorial Hospital, Mumbai**

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LOCO-REGIONAL BREAST CANCER

Surgical Treatment of Women with Breast Cancer and a BRCA1 Mutation: An International Analysis of the Impact of Bilateral Mastectomy on Survival

Author: K. Metcalfe
Citation: SABCS 2023:GS02-04

Background: Women with breast cancer and a BRCA1 mutation face a high risk of contralateral breast cancer. For this reason, many women with a unilateral breast cancer opt for bilateral mastectomies. Some will have a contralateral prophylactic mastectomy as a second surgery. However, it is not clear to what extent this operation impacts breast cancer mortality. The objective of the current study was to evaluate the differences in survival by surgical treatment in an international cohort of women with a BRCA1 mutation and unilateral breast cancer.

Methods: Eligible participants were identified from a large international cohort of women with breast cancer and a BRCA1 mutation, from 26 collaborating centres. Patients with DCIS and stage IV breast cancer were excluded. Patients with synchronous bilateral cancer were excluded. Demographic data were patient reported and clinical and treatment data were collected from medical records. Women were followed from date of breast cancer diagnosis to either date of last follow-up or date of death.

Results: There were 2482 eligible participants from 26 centres from 11 countries. The mean age of breast cancer diagnosis was 43.1 years (range 18-70 years). Among those who had a unilateral mastectomy or lumpectomy, the risk of contralateral breast cancer at 20 years was 27.5%. After experiencing a contralateral cancer the hazard ratio for breast cancer death was 2.14 (95%CI 1.43-3.18), P=0.0002. The fifteen year breast cancer specific survival in the entire cohort was 82.9%. The survival was 78.7% for those who had a unilateral mastectomy, 86.2% for those who had a lumpectomy, and 88.7% for those

who had bilateral mastectomies. 529 of the women who initially underwent a unilateral surgery subsequently had a contralateral or bilateral preventive mastectomy in the follow up period. 529 of the women with unilateral surgery had a contralateral or bilateral preventive mastectomy in the follow up period. After adjusting for age of diagnosis, tumor size, nodal status, chemotherapy (yes/no) and preventive mastectomy (time dependent) the hazard ratio for breast cancer mortality for bilateral surgery versus unilateral surgery was 0.78 (95% CI 0.55-1.13), p = 0.19.

Discussion: Women with a BRCA1 mutation and breast cancer who develop a contralateral breast cancer have double the risk of mortality compared to women who do notdevelop contralateral breast cancer. We observed a small non-significant reduction in mortality for those who had bilateral mastectomies as initial treatment, but the cohort will require longer follow up for definitive results. Women with a BRCA1 mutation should be counselled on the risks of contralateral breast cancer and make surgical decisions with this knowledge.

Contralateral breast cancer risk in patients with breast cancer and a germline-BRCA1/2 pathogenic variant undergoing radiation

Author: Mark van Barele
Citation: JNCI: Journal of the National Cancer Institute, 2023, 115(11), 1318–1328

Background: Radiation-induced secondary breast cancer (BC) may be a concern after radiation therapy (RT) for primary breast cancer (PBC), especially in young patients with germline (g)BRCA–associated BC who already have high contralateral BC (CBC) risk and potentially increased genetic susceptibility to radiation. We sought to investigate whether adjuvant RT for PBC increases the risk of CBC in patients with gBRCA1/2-associated BC.

Methods: The gBRCA1/2 pathogenic variant carriers diagnosed with PBC were selected from the prospective International BRCA1/2 Carrier Cohort Study. We used multivariable Cox proportional hazards models to investigate the association between RT (yes vs no) and CBC risk. We further stratified for BRCA

status and age at PBC diagnosis (40years). Statistical significance tests were 2 sided.

Results: Of 3602 eligible patients, 2297 (64%) received adjuvant RT. Median follow-up was 9.6years. The RT group had more patient with stage III PBC than the non-RT group (15% vs 3%, P<.001), received chemotherapy more often (81% vs 70%, P<.001), and received endocrine therapy more often (50% vs 35%, P<.001). The RT group had an increased CBC risk compared with the non-RT group (adjusted hazard ratio [HR]=1.44; 95% confidence interval [CI] = 1.12 to 1.86). Statistical significance was observed in gBRCA2 (HR=1.77; 95% CI¼1.13 to 2.77) but not in gBRCA1 pathogenic variant carriers (HR=1.29; 95% CI=0.93 to 1.77; P= .39 for interaction). In the combined gBRCA1/2 group, patients irradiated when they were younger than or older than 40 years of age at PBC diagnosis showed similar risks (HR=1.38; 95% CI=0.93 to 2.04 and HR=1.56; 95% CI=1.11 to 2.19, respectively).

Conclusions: RT regimens minimizing contralateral breast dose should be considered in gBRCA1/2 pathogenic variant carriers.

Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial

Author: Oreste Davide Gentilini
Citation: JAMA Oncol. 2023 Nov 1;9(11):1557-1564.

Importance: Sentinel lymph node biopsy (SLNB) is the standard of care for axillary node staging of patients with early breast cancer (BC), but its necessity can be questioned since surgery for examination of axillary nodes is not performed with curative intent.

Objective: To determine whether the omission of axillary surgery is noninferior to SLNB in patients with small BC and a negative result on preoperative axillary lymph node ultrasonography.

Design, setting, and participants: The SOUND (Sentinel Node vs Observation After Axillary Ultra-Sound) trial was a prospective noninferiority phase 3 randomized clinical trial conducted in Italy, Switzerland, Spain, and Chile. A total of 1463 women of any age with BC up to 2 cm and a negative preoperative axillary ultrasonography result were enrolled and randomized between February 6, 2012, and June 30, 2017. Of those, 1405 were included in the intention-to-treat analysis. Data were analyzed from October 10, 2022, to January 13, 2023.

Intervention: Eligible patients were randomized on a 1:1 ratio to receive SLNB (SLNB group) or no axillary surgery (no axillary surgery group).

Main outcomes and measures: The primary end point of the study was distant disease-free survival (DDFS) at 5 years, analyzed as intention to treat. Secondary end points were the cumulative incidence of distant recurrences, the cumulative incidence of axillary recurrences, DFS, overall survival (OS), and the adjuvant treatment recommendations.

Results: Among 1405 women (median [IQR] age, 60 [52-68] years) included in the intention-to-treat analysis, 708 were randomized to the SLNB group, and 697 were randomized to the no axillary surgery group. Overall, the median (IQR) tumor size was 1.1 (0.8-1.5) cm, and 1234 patients (87.8%) had estrogen receptor-positive ERBB2 (formerly HER2 or HER2/neu), nonoverexpressing BC. In the SLNB group, 97 patients (13.7%) had positive axillary nodes. The median (IQR) follow-up for disease assessment was 5.7 (5.0-6.8) years in the SLNB group and 5.7 (5.0-6.6) years in the no axillary surgery group. Five-year distant DDFS was 97.7% in the SLNB group and 98.0% in the no axillary surgery group (log-rank P = .67; hazard ratio, 0.84; 90% CI, 0.45-1.54; noninferiority P = .02). A total of 12 (1.7%) locoregional relapses, 13 (1.8%) distant metastases, and 21 (3.0%) deaths were observed in the SLNB group, and 11 (1.6%) locoregional relapses, 14 (2.0%) distant metastases, and 18 (2.6%) deaths were observed in the no axillary surgery group.

Conclusions and relevance: In this randomized clinical trial, omission of axillary surgery was noninferior to SLNB in patients with small BC and a negative result on ultrasonography of the axillary lymph nodes. These results suggest that patients with these features can be safely spared any axillary surgery whenever the lack of pathological information does not affect the postoperative treatment plan.

Lymph Node Positivity of Axillary Reverse Mapping Lymph Nodes at the Time of Axillary Lymph Node Dissection: Two-Site Prospective Trial

Author: Molly M Benolken
Citation: Ann Surg Oncol. 2023 Oct;30(10):6042-6049.

Background: Axillary reverse mapping (ARM) was introduced in 2007 to identify and selectively preserve upper-extremity lymphatics during axillary lymph node surgery to decrease the risk of lymphedema. The patient population in which an ARM lymph node (LN) can be preserved during an axillary lymph node dissection (ALND) has not been established to date. This study aimed to determine the frequency of metastatic involvement of an ARM LN among patients undergoing ALND.

Methods: Patients undergoing ALND with or without immediate lymphatic reconstruction (ILR) were enrolled in a prospective trial at two institutional sites between April 2018 and Decemeber 2022. This report analyzes the ARM node positivity and total LN positivity rates during ALND for the cohort of patients enrolled in the ILR intervention arm of the study.

Results: The inclusion criteria were met by 139 patients, who made up the study population (133 with breast cancer and 6 with other disease). Of the breast cancer patients, 99.2% were female, 35.3% (47/133) were cT3 or greater, and 96.2% (128/133) had cN1 or greater disease. For 55 of the 133 patients (41.4%), the ARM nodes were marked and specified in the pathology report. Of the 55 patients, 39 (70.9%) had a positive LN at ALND. Of these 55 patients, 11 (20%) had positive ARM nodes. The ARM LN was the only positive node in 3 of the 11 patients.

Conclusion: In the contemporary patient population undergoing ALND, the positivity rate of the ARM LN was relatively high, suggesting that leaving ARM LNs in patients undergoing ALND may not be oncologically safe.

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials

Author: Early Breast Cancer Trialists' Collaborative Group (EBCTCG)
Citation: Lancet. 2023 Nov 25;402(10416):1991-2003.

Background: Radiotherapy has become much better targeted since the 1980s, improving both safety and efficacy. In breast cancer, radiotherapy to regional lymph nodes aims to reduce risks of recurrence and death. Its effects have been studied in randomised trials, some before the 1980s and some after. We aimed to assess the effects of regional node radiotherapy in these two eras.

Methods: In this meta-analysis of individual patient data, we sought data from all randomised trials of regional lymph node radiotherapy versus no regional lymph node radiotherapy in women with early breast cancer (including one study that irradiated lymph nodes only if the cancer was right-sided). Trials were identified through the EBCTCG's regular systematic searches of databases including MEDLINE, Embase, the Cochrane Library, and meeting abstracts. Trials were eligible if they began before Jan 1, 2009. The only systematic difference between treatment groups was in regional node radiotherapy (to the internal mammary chain, supraclavicular fossa, or axilla, or any combinations of these). Primary outcomes were recurrence at any site, breast cancer mortality, non-breast-cancer mortality, and all-cause mortality. Data were supplied by trialists and standardised into a format suitable for analysis. A summary of the formatted data was returned to trialists for verification. Log-rank analyses yielded first-event rate ratios (RRs) and confidence intervals.

Findings: We found 17 eligible trials, 16 of which had available data (for 14 324 participants), and one of which (henceforth excluded), had unavailable data (for 165 participants). In the eight newer trials (12 167 patients), which started during

1989-2008, regional node radiotherapy significantly reduced recurrence (rate ratio 0·88, 95% CI 0·81-0·95; p=0·0008). The main effect was on distant recurrence as few regional node recurrences were reported. Radiotherapy significantly reduced breast cancer mortality (RR 0·87, 95% CI 0·80-0·94; p=0·0010), with no significant effect on non-breast-cancer mortality (0·97, 0·84-1·11; p=0·63), leading to significantly reduced all-cause mortality (0·90, 0·84-0·96; p=0·0022). In an illustrative calculation, estimated absolute reductions in 15-year breast cancer mortality were 1·6% for women with no positive axillary nodes, 2·7% for those with one to three positive axillary nodes, and 4·5% for those with four or more positive axillary nodes. In the eight older trials (2157 patients), which started during 1961-78, regional node radiotherapy had little effect on breast cancer mortality (RR 1·04, 95% CI 0·91-1·20; p=0·55), but significantly increased non-breast-cancer mortality (1·42, 1·18-1·71; p=0·00023), with risk mainly after year 20, and all-cause mortality (1·17, 1·04-1·31; p=0·0067).

Interpretation: Regional node radiotherapy significantly reduced breast cancer mortality and all-cause mortality in trials done after the 1980s, but not in older trials. These contrasting findings could reflect radiotherapy improvements since the 1980s.

Radiotherapy or Surgery of the Axilla After a Positive Sentinel Node in Breast Cancer: 10-Year Results of the Randomized Controlled EORTC 10981-22023 AMAROS Trial

Author: Sanne A L Bartels
Citation: J Clin Oncol. 2023 Apr 20;41(12):2159-2165.

Purpose: The European Organisation for Research and Treatment of Cancer 10981-22023 AMAROS trial evaluated axillary lymph node dissection (ALND) versus axillary radiotherapy (ART) in patients with cT1-2, node-negative breast cancer and a positive sentinel node (SN) biopsy. At 5 years, both modalities showed excellent and comparable axillary control, with significantly less morbidity after ART. We now report the preplanned 10-year analysis of the

axillary recurrence rate (ARR), overall survival (OS), and disease-free survival (DFS), and an updated 5-year analysis of morbidity and quality of life.

Methods: In this open-label multicenter phase III noninferiority trial, 4,806 patients underwent SN biopsy; 1,425 were node-positive and randomly assigned to either ALND (n = 744) or ART (n = 681).

Results: Per intention-to-treat analysis, 10-year ARR cumulative incidence was 0.93% (95% CI, 0.18 to 1.68; seven events) after ALND and 1.82% (95% CI, 0.74 to 2.94; 11 events) after ART (hazard ratio [HR], 1.71; 95% CI, 0.67 to 4.39). There were no differences in OS (HR, 1.17; 95% CI, 0.89 to 1.52) or DFS (HR, 1.19; 95% CI, 0.97 to 1.46). ALND was associated with a higher lymphedema rate in updated 5-year analyses (24.5% v 11.9%; P < .001). Quality-of-life scales did not differ by treatment through 5 years. Exploratory analysis showed a 10-year cumulative incidence of second primary cancers of 12.1% (95% CI, 9.6 to 14.9) after ART and 8.3% (95% CI, 6.3 to 10.7) after ALND.

Conclusion: This 10-year analysis confirms a low ARR after both ART and ALND with no difference in OS, DFS, and locoregional control. Considering less arm morbidity, ART is preferred over ALND for patients with SN-positive cT1-2 breast cancer.

Five-year outcomes of the IDEA trial of endocrine therapy without radiotherapy after breast-conserving surgery for postmenopausal patients age 50-69 with genomically-selected favorable Stage I breast cancer

Author: Reshma Jagsi
Citation: SABCS 2023: GS02-08

Background: Multiple studies have shown a low risk of ipsilateral breast events (IBE) or other recurrences for selected patients age 65-70 or older with Stage I breast cancers treated with breast conserving surgery (BCS) and endocrine therapy (ET) without adjuvant radiotherapy (RT). We designed a prospective single-arm trial, IDEA (Individualized Decisions for Endocrine therapy Alone),

to see if younger postmenopausal patients could also be successfully treated without RT, adding a genomic assay to classic selection factors.

Methods: Postmenopausal patients aged 50-69 with pT1N0 unifocal invasive breast cancer with margins 2mm or wider after BCS whose tumors were ER+, PR+, and Her2- with Oncotype DX 21-gene recurrence score (RS) 18 or lower were eligible to avoid RT if they consented to take at least 5 years of ET and surveillance on study. The primary endpoint was the rate of breast cancer recurrence at 5 years of follow-up after BCS. A valid 5–year assessment was defined as a clinical assessment within 4 months prior to the 5-year anniversary or later. Follow-up time was calculated from the date of BCS until first recurrence [ipsilateral breast events (IBE) or regional or distant failures] or to last clinical follow-up. The time-to-event endpoint was calculated using the product-limit method of Kaplan and Meier measured from the date of BCS.

Results: 200 eligible patients were enrolled from 13 US institutions between June 2015 and October 2018. Median age was 63 years (IQR 58-66); mean RS was 11.2 (SD 4.8). Tumors were grade 1 in 85 patients, grade 2 in 109, and grade 3 in 6. Mean tumor size was 10mm (SD 4.6). Lymphovascular invasion was present in 16 tumors and an extensive intraductal component in 11. Median follow-up time was 5.21 years (IQR 5.01-5.97); 8 of 14 patients with less than 56 months of follow-up were lost to follow-up. Overall and breast cancer-specific survival rates at 5 years were both 100%; 2 deaths occurred later than 5 years. The 5-year freedom from recurrence was 99% (95% CI, 96%-100%). One of the two events occurring by 5 years was an isolated axillary recurrence at 21 months treated with axillary dissection and breast and regional nodal irradiation. The other was an IBE at 49 months, treated with repeat BCS. Both these patients had been compliant with ET. Six additional patients recurred later than 5 years after BCS (5 IBEs, 1 IBE plus regional recurrence). Crude rates of IBE for the entire follow-up period for patients aged 50-59 and 60-69 were 3.3% (2/60) and 3.6% (5/140), respectively; crude rates of overall relapse were 5.0% (3/60) and 3.6% (5/140).

Conclusions: This multicenter trial of ET without RT following BCS achieved a very low risk of relapse for postmenopausal patients with Stage I cancers using a genomic assay in combination with classic clinical and biologic features for treatment selection, including for patients younger than age 60. IDEA demonstrates a 5-year probability of recurrence consistent with or lower than the 4% risk estimated a priori, and the patients accrued were younger when compared to prior prospective trials (e.g., PRIME II, minimum age 65; CALGB 9343, minimum age 70; LUMINA, median age 67). The results of ongoing NRG BR007 trial, which randomly allocates women meeting these eligibility criteria to receive RT or not, and similar randomized and single-arm studies will help determine whether the option of avoiding initial RT can be offered to a broader group of women than current guidelines recommend. Long-term follow-up beyond the 5-year required period of ET will be important to determine if the risk of recurrence increases, particularly after discontinuation of ET.

Development and Validation of a Genomic Profile for the Omission of Local Adjuvant Radiation in Breast Cancer

Author: Martin Sjöström
Citation: J Clin Oncol. 2023 Mar 10;41(8):1533-1540

Purpose: Adjuvant radiotherapy (RT) is used for women with early-stage invasive breast cancer treated with breast-conserving surgery. However, some women with low risk of recurrence may safely be spared RT. This study aimed to identify these women using a molecular-based approach.

Methods: We analyzed two randomized trials of women with node-negative invasive breast cancer to ± RT following breast-conserving surgery: SweBCG91-RT (stage I-II, no adjuvant systemic therapy) and Princess Margaret (age 50 years or older, T1-T2, adjuvant tamoxifen). Transcriptome-wide profiling was performed (Affymetrix Human Exon 1.0 ST microarray). Patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative tumors and with gene expression data were included. The SweBCG91-RT cohort was

divided into training (N = 243) and validation (N = 354) cohorts. A 16-gene signature named Profile for the Omission of Local Adjuvant Radiation (POLAR) was trained to predict locoregional recurrence (LRR) using elastic net regression. POLAR was then validated in the SweBCG91-RT validation cohort and the Princess Margaret cohort (N = 132).

Results: Patients categorized as POLAR low-risk without RT had a 10-year LRR of 6% (95% CI, 2 to 16) and 7% (0 to 27) in SweBCG91-RT and Princess Margaret cohorts, respectively. There was no significant benefit from RT in POLAR low-risk patients (hazard ratio [HR], 1.1 [0.39 to 3.4], P = .81, and HR, 1.5 [0.14 to 16], P = .74, respectively). Patients categorized as POLAR high-risk had a significant decreased risk of LRR with RT (HR, 0.43 [0.24 to 0.78], P = .0055, and HR, 0.25 [0.07 to 0.92], P = .038, respectively). An exploratory analysis testing for interaction between RT and POLAR in the combined validation cohort was performed (P = .066).

Conclusion: The novel POLAR genomic signature on the basis of LRR biology may identify patients with a low risk of LRR despite not receiving RT, and thus may be candidates for RT omission.

Overview of Axillary Treatment in Early Breast Cancer: patient-level meta-analysis of long-term outcomes among 20,273 women in 29 randomised trials

Author: G. Mannu
Citation: SABCS 2023:GS02-05

Background: In early breast cancer, the optimal management of the axilla is uncertain. To better understand the long-term benefits and risks of different approaches, we undertook an individual patient data meta-analysis of randomised trials comparing varying types of axillary treatment.

Methods: Information was available on 20,273 women in 29 trials of axillary surgery or axillary radiotherapy. The trial comparisons included in this overview are summarised in Table 1. Randomisation took place during 1958–2009. Median follow-up was 10.0 years (IQR 7.4–11.5).

Findings: In the trials of more extensive versus less extensive axillary treatment, the rate ratios (RR) for locoregional recurrence varied by site (p=0.003), however, 82% of these locoregional recurrences (552/670) occurred either in the breast or were of unspecified location (Table 2). Considering locoregional recurrence at any site, there was little difference in the risk from more versus less axillary treatment (10-year risk 4.3% vs 4.7%; RR 0.90 95% CI 0.77– 1.05; p = 0.20), even in women treated for node-positive disease (3.7% vs 3.6%; RR 1.01, 95% CI 0.74–1.36, p=0.97). There was, however, a substantial difference in lymphoedema for trials of more versus less axillary surgery (odds ratio (OR) 2.35, 95% CI 2.05–2.70; p< 0.00001) and for trials of axillary treatment (surgery or radiotherapy) compared with no further axillary treatment (OR 3.08, 95% CI 2.01–4.71; p< 0.00001). In the four trials comparing axillary node clearance to axillary radiotherapy, the risk of locoregional recurrence appeared to be somewhat reduced in women allocated to clearance (43 vs. 56 events, 10-year risk 4.4% vs. 6.9%; RR 0.64, 95% CI 0.43-0.96, p=0.03) whilst their risk of lymphoedema was increased (OR 1.79, 95% CI 1.42–2.27; p< 0.00001). The risks of distant recurrence, breast cancer, non-breast-cancer, or all-cause mortality did not differ significantly by extent of axillary treatment or when comparing axillary clearance to radiotherapy. Interpretation: This is the most comprehensive overview of axillary treatment to date. Less extensive surgery, such as sentinel lymph node biopsy, or using axillary radiotherapy, resulted in a substantial reduction in lymphoedema compared to axillary node clearance. While there was no evidence of a difference in locoregional recurrence, a moderate effect cannot be excluded. Funding: Cancer Research UK, British Heart Foundation, Medical Research Council.

Safety of Targeted Axillary Dissection After Neoadjuvant Therapy in Patients With Node-Positive Breast Cancer

Author: Sherko Kuemmel
Citation: JAMA Surg. 2023 Aug 1;158(8):807-815.

Importance: The increasing use of neoadjuvant systemic therapy (NST) has led to substantial pathological complete response rates in patients with initially node-positive, early breast cancer, thereby questioning the need for axillary lymph node dissection (ALND). Targeted axillary dissection (TAD) is feasible for axillary staging; however, data on oncological safety are scarce.

Objective: To assess 3-year clinical outcomes in patients with node-positive breast cancer who underwent TAD alone or TAD with ALND.

Design, setting, and participants: The SenTa study is a prospective registry study and was conducted between January 2017 and October 2018. The registry includes 50 study centers in Germany. Patients with clinically node-positive breast cancer underwent clipping of the most suspicious lymph node (LN) before NST. After NST, the marked LNs and sentinel LNs were excised (TAD) followed by ALND according to the clinician's choice. Patients who did not undergo TAD were excluded. Data analysis was performed in April 2022 after 43 months of follow-up.

Exposure: TAD alone vs TAD with ALND.

Main outcomes and measures: Three-year clinical outcomes were evaluated.

Results: Of 199 female patients, the median (IQR) age was 52 (45-60) years. A total of 182 patients (91.5%) had 1 to 3 suspicious LNs; 119 received TAD alone and 80 received TAD with ALND. Unadjusted invasive disease-free survival was 82.4% (95% CI, 71.5-89.4) in the TAD with ALND group and 91.2% (95% CI, 84.2-95.1) in the TAD alone group (P = .04); axillary recurrence rates were 1.4% (95% CI, 0-54.8) and 1.8% (95% CI, 0-36.4), respectively (P = .56). Adjusted

multivariate Cox regression indicated that TAD alone was not associated with an increased risk of recurrence (hazard ratio [HR], 0.83; 95% CI, 0.34-2.05; P = .69) or death (HR, 1.07; 95% CI, 0.31-3.70; P = .91). Similar results were obtained for 152 patients with clinically node-negative breast cancer after NST (invasive disease-free survival: HR, 1.26; 95% CI, 0.27-5.87; P = .77; overall survival: HR, 0.81; 95% CI, 0.15-3.83; P = .74).

Conclusions and relevance: These results suggest that TAD alone in patients with mostly good clinical response to NST and at least 3 TAD LNs may confer survival outcomes and recurrence rates similar to TAD with ALND.

Mammographic surveillance in early breast cancer patients aged 50 years or over: results of the Mammo-50 non-inferiority trial of annual versus less frequent mammography

Author: J. Dunn
Citations: SABCS 2023:GS03-02

Introduction: Annual surveillance mammograms for an unspecified period, after treatment for early breast cancer, are widely practised in USA and Europe and represent a significant healthcare cost. Current UK guidelines recommend annual mammograms up to 5 years, then reverts to 3 year screening without specified risk stratification. Further evidence is needed to determine the optimum frequency and duration of mammographic surveillance.

Methods: A multi-centre, randomised controlled, phase III trial of annual mammography versus 2-yearly for conservation surgery and 3-yearly mammograms for mastectomy patients up to 9 years. Women were eligible if aged 50 years or over at initial diagnosis of breast cancer (invasive or DCIS), and recurrence free 3 years post curative surgery.

Primary outcome was breast cancer specific survival (BCSS). Secondary outcomes include recurrence free interval (RFI) and overall survival (OS). BCSS event was defined as deaths from breast cancer and RFI as any locoregional or

distant invasive recurrence or new breast primary. 5000 women were needed to detect a 3% absolute non-inferiority (NI) margin for BCSS with 2.5% one-sided alpha and at least 85% power. Analyses were carried out on intention-to-treat basis.

Results: 5235 women were randomised between April 2014 and September 2018. 4347 (83%) women were aged 55-75 years, 4203 (80%) had undergone conservation surgery, 4564 (87%) had invasive disease, 1162 (22%) had node positive disease, 4330 (83%) had ER positive tumours and 3812 (73%) were taking hormone therapy at the time of randomisation. Patient characteristics were balanced across arms.

With a median of 5.4 years follow-up (interquartile range 4.6-5.9), 319 women have died; 104 of breast cancer (53 on annual arm; 51 on less frequent arm). BCSS at 5 years was 98.2% (95% CI 97.5-98.6%) on annual arm and 98.3% (95% CI 97.7-98.8%) on less frequent arm. Hazard ratio (HR) was 1.04 (95% CI 0.71 -1.54), demonstrating non-inferiority of less frequent mammograms at the 3% margin (NI p< 0.0001; critical value 2.71) and the 1% margin (NI p=0.02; critical value 1.56).

320 (6%) women had a new invasive breast cancer event (55 loco-regional recurrences, 85 new breast primaries, 139 distant recurrences and 41 with multiple invasive events); 164 on the annual arm compared to 156 on the less frequent arm. Five-year RFI was 94.2% (95% CI 93.2-95.1%) for the annual arm and 94.4% (95% CI 93.4-95.3%) for the less frequent arm; HR= 1.03; (95% CI 0.83-1.28) demonstrating non-inferiority at a 2% margin (NI p=0.006; critical value 1.36).

OS at 5 years was 94.9% (95% CI 93.9-95.7%) on the annual arm and 94.3% (95% CI 93.3-95.2%) on the less frequent arm. Hazard ratio (HR) was 1.18 (95% CI 0.94 -1.47), demonstrating non-inferiority of less frequent mammograms at the 3% margin (NI p=0.003; critical value 1.61) and the 2.5% margin (NI p=0.02; critical value 1.51).

A total of 14987 mammograms have been performed on the annual arm and 8047 on the less frequent arm. 1967 (75%) of 2618 women on the annual arm complied with their allocated schedule compared to 1775 (68%) of 2617 women on the less frequent arm. COVID-19 pandemic affected compliance; it is estimated that 345 (7%) women missed mammograms during the pandemic. A sensitivity analysis was performed on the 72% of women who fully complied with their scheduled mammograms as per protocol, and again NI was demonstrated for BCSS, RFI and OS.

Conclusions: For patients aged 50 or older and 3 years post diagnosis, Mammo-50 demonstrated that less frequent mammograms were no worse than annual mammograms. These results provide evidence for less frequent mammographic surveillance for this patient population.

Post-diagnosis weight trajectories and mortality among women with breast cancer

Author: Leah S Puklin
Citation: NPJ Breast Cancer. 2023 Dec 2;9(1):98. doi: 10.1038 s41523-023-00603-5.

Weight gain after breast cancer diagnosis is associated with adverse health outcomes. Yet, few studies have characterized post-diagnosis weight change in the modern treatment era or populations most at risk for weight changes. Among women diagnosed with stages I–III breast cancer in the Smilow Care Network (2013–2019; N = 5441), we abstracted demographic and clinical characteristics from electronic health records and survival data from tumor registries. We assessed if baseline characteristics modified weight trajectories with nonlinear multilevel mixed-effect models. We evaluated body mass index (BMI) at diagnosis and weight change 1-year post-diagnosis in relation to all-cause and breast cancer-specific mortality with Cox proportional hazard models. Women had 34.4 ± 25.5 weight measurements over 3.2 ± 1.8 years of follow-up. Weight gain was associated with ER/PR–, HER2+ tumors, BMI ≤ 18.5 kg/m^2, and age ≤ 45 years (+4.90 kg (standard error [SE] = 0.59), +3.24 kg (SE = 0.34), and

+1.75 kg (SE = 0.10), respectively). Weight loss was associated with BMI ≥ 35 kg/m^2 and age ≥ 70 years (−4.50 kg (SE = 0.08) and −4.34 kg (SE = 0.08), respectively). Large weight loss (≥10%), moderate weight loss (5–10%), and moderate weight gain (5–10%) 1-year after diagnosis were associated with higher all-cause mortality (hazard ratio [HR] = 2.93, 95% confidence interval [CI] = 2.28–3.75, HR = 1.32, 95% CI = 1.02–1.70 and HR = 1.39, 95% CI = 1.04–1.85, respectively). BMI ≥ 35 kg/m^2 or BMI ≤ 18.5 kg/m^2 at diagnosis were also associated with higher all-cause mortality. Weight change after a breast cancer diagnosis differed by demographic and clinical characteristics highlighting subgroups at-risk for weight change during a 5-year period post-diagnosis. Monitoring and interventions for weight management early in clinical care are important.

Recurrence-free survival following sentinel node-positive breast cancer without completion axillary lymph node dissection – first results from the international randomized SENOMAC trial.

Author: J. de Boniface
Citation: SABCS 2023: GS02-06

Background: The omission of a completion axillary lymph node dissection (cALND) after a positive sentinel lymph node (SLN) biopsy in patients with clinically node-negative breast cancer has been demonstrated to yield survival outcomes non-inferior to routine cALND in breast-conserving surgery followed by whole-breast irradiation (ACOSOG Z0011 and IBCSG 23-01 trials), and to axillary radiotherapy (RT) regardless of breast surgery (EORTC AMAROS trial). Mainly due to the under-representation of mastectomy patients, and a limited number of observed events compromising statistical power, the international randomized SENOMAC trial was initiated in 2015. The main aim of this non-inferiority trial was to address knowledge gaps relating to individuals treated by mastectomy, those with larger tumors and those with SLN extracapsular extension.

Method: The SENOMAC trial (NCT 02240472) enrolled patients with cT1-3cN0 primary breast cancer and 1-2 SLN macrometastases at 67 sites in five countries between January 27, 2015, and December 31, 2021. Participants were randomized 1:1 between cALND (standard) and omission of cALND (intervention). Stratification was per country. Breast-conserving surgery and mastectomy were eligible surgical interventions. Preoperative axillary ultrasound was mandatory; patients with non-palpable suspicious axillary lymph nodes, even if proven metastatic by biopsy, were eligible. SLN extracapsular extension was allowed. Adjuvant radiotherapy was dictated by national guidelines and not by the trial protocol. Statistical sample size calculation was based on the primary outcome overall survival. Non-inferiority was defined as a 5-year overall survival not worsened by more than 2.5% when refraining from cALND after the observation of 190 all-cause deaths in a target sample size of 3000 included patients. In the present analysis, the pre-specified secondary outcome of recurrence-free survival is reported.

Results: Out of 2766 randomized individuals, 2539 comprised the per-protocol population: 1204 in the standard and 1335 in the intervention group. Median follow-up was 37.1 months (1.5-75.0) and median age at inclusion 61 years (range 20-94). Most tumors belonged to the luminal subtype (93.6%); tumor stage was T1 in 1358 (53.5%), T2 in 1034 (40.7%) and T3 in 146 participants (5.8%). Out of 347 participants with suspicious lymph nodes on ultrasound, 36 had confirmed non-palpable metastasis. SLN extracapsular extension was reported in 866 (34.1%). The breast was conserved in 1621 (63.8%) and a mastectomy performed in 918 (36.2%) patients. Most patients (2127, 83.8%) received radiotherapy including nodal target volumes. In 34.1% of the standard group, additional non-SLN metastases were identified on cALND. Overall, 104 recurrences were reported, 54 (4.5%) in the standard and 50 (3.7%) in the intervention group. Of these, 11 recurrences were found in the ipsilateral axilla: 5 (0.4%) and 6 (0.5%), respectively. Recurrence-free survival did not differ between groups (country-adjusted HR 0.89, 95% CI 0.65-1.20).

Conclusion: Despite extended inclusion criteria, there was no difference in recurrence-free survival whether cALND was omitted (intervention) or not (standard). Patients undergoing mastectomy will specifically be addressed in subgroup analyses. Long-term follow-up is crucial considering the high proportion of luminal cancers

Local Recurrence After Breast-Conserving Therapy in Patients With Multiple Ipsilateral Breast Cancer: Results From ACOSOG Z11102 (Alliance)

Author: Judy C. Boughey
Citation: Journal of Clinical Oncology 41, no. 17 (June 10, 2023) 3184-3193.

Purpose: Breast-conserving therapy (BCT) is the preferred treatment for unifocal breast cancer (BC). The oncologic safety of BCT for multiple ipsilateral breast cancer (MIBC) has not been demonstrated in a prospective study. ACOSOG Z11102 (Alliance) is a phase II, single-arm, prospective trial designed to evaluate oncologic outcomes in patients undergoing BCT for MIBC.

Patients and Methods: Women age 40 years and older with two to three foci of biopsy-proven cN0-1 BC were eligible. Patients underwent lumpectomies with negative margins followed by whole breast radiation with boost to all lumpectomy beds. The primary end point was cumulative incidence of local recurrence (LR) at 5 years with an a priori rate of clinical acceptability of <8%.

Results: Among 270 women enrolled between November 2012 and August 2016, there were 204 eligible patients who underwent protocol-directed BCT. The median age was 61 years (range, 40-87 years). At a median follow-up of 66.4 months (range, 1.3-90.6 months), six patients developed LR for an estimated 5-year cumulative incidence of LR of 3.1% (95% CI, 1.3 to 6.4). Patient age, number of sites of preoperative biopsy–proven BC, estrogen receptor status and human epidermal growth factor receptor 2 status, and pathologic T and N categories were not associated with LR risk. Exploratory analysis showed that the 5-year LR rate in patients without preoperative magnetic resonance imaging (MRI; n = 15) was 22.6% compared with 1.7% in patients with a preoperative MRI (n = 189; P = .002).

Conclusion: The Z11102 clinical trial demonstrates that breast-conserving surgery with adjuvant radiation that includes lumpectomy site boosts yields an acceptably low 5-year LR rate for MIBC. This evidence supports BCT as a reasonable surgical option for women with two to three ipsilateral foci, particularly among patients with disease evaluated with preoperative breast MRI.

Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer

Author: Timothy J Whelan
Citation: N Engl J Med. 2023 Aug 17;389(7):612-619.

Background: Adjuvant radiotherapy is prescribed after breast-conserving surgery to reduce the risk of local recurrence. However, radiotherapy is inconvenient, costly, and associated with both short-term and long-term side effects. Clinicopathologic factors alone are of limited use in the identification of women at low risk for local recurrence in whom radiotherapy can be omitted. Molecularly defined intrinsic subtypes of breast cancer can provide additional prognostic information.

Methods: We performed a prospective cohort study involving women who were at least 55 years of age, had undergone breast-conserving surgery for T1N0 (tumor size <2 cm and node negative), grade 1 or 2, luminal A-subtype breast cancer (defined as estrogen receptor positivity of ≥1%, progesterone receptor positivity of >20%, negative human epidermal growth factor receptor 2, and Ki67 index of ≤13.25%), and had received adjuvant endocrine therapy. Patients who met the clinical eligibility criteria were registered, and Ki67 immunohistochemical analysis was performed centrally. Patients with a Ki67 index of 13.25% or less were enrolled and did not receive radiotherapy. The primary outcome was local recurrence in the ipsilateral breast. In consultation with radiation oncologists and patients with breast cancer, we determined that if the upper boundary of the two-sided 90% confidence interval for the

cumulative incidence at 5 years was less than 5%, this would represent an acceptable risk of local recurrence at 5 years.

Results: Of 740 registered patients, 500 eligible patients were enrolled. At 5 years after enrollment, recurrence was reported in 2.3% of the patients (90% confidence interval [CI], 1.3 to 3.8; 95% CI, 1.2 to 4.1), a result that met the prespecified boundary. Breast cancer occurred in the contralateral breast in 1.9% of the patients (90% CI, 1.1 to 3.2), and recurrence of any type was observed in 2.7% (90% CI, 1.6 to 4.1).

Conclusions: Among women who were at least 55 years of age and had T1N0, grade 1 or 2, luminal A breast cancer that were treated with breast-conserving surgery and endocrine therapy alone, the incidence of local recurrence at 5 years was low with the omission of radiotherapy.

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Author: Ian H Kunkler
Citation: N Engl J Med.2023 Feb 16;388(7):585-594.

Background: Limited level 1 evidence is available on the omission of radiotherapy after breast-conserving surgery in older women with hormone receptor-positive early breast cancer receiving adjuvant endocrine therapy.

Methods: We performed a phase 3 randomized trial of the omission of irradiation; the trial population included women 65 years of age or older who had hormone receptor-positive, node-negative, T1 or T2 primary breast cancer (with tumors ≤3 cm in the largest dimension) treated with breast-conserving surgery with clear excision margins and adjuvant endocrine therapy. Patients were randomly assigned to receive whole-breast irradiation (40 to 50 Gy) or no irradiation. The primary end point was local breast cancer recurrence. Regional recurrence, breast cancer-specific survival, distant recurrence as the first event, and overall survival were also assessed.

Results: A total of 1326 women were enrolled; 658 were randomly assigned to receive whole-breast irradiation and 668 to receive no irradiation. The median follow-up was 9.1 years. The cumulative incidence of local breast cancer recurrence within 10 years was 9.5% (95% confidence interval [CI], 6.8 to 12.3) in the no-radiotherapy group and 0.9% (95% CI, 0.1 to 1.7) in the radiotherapy group (hazard ratio, 10.4; 95% CI, 4.1 to 26.1; P<0.001). Although local recurrence was more common in the group that did not receive radiotherapy, the 10-year incidence of distant recurrence as the first event was not higher in the no-radiotherapy group than in the radiotherapy group, at 1.6% (95% CI, 0.4 to 2.8) and 3.0% (95% CI, 1.4 to 4.5), respectively. Overall survival at 10 years was almost identical in the two groups, at 80.8% (95% CI, 77.2 to 84.3) with no radiotherapy and 80.7% (95% CI, 76.9 to 84.3) with radiotherapy. The incidence of regional recurrence and breast cancer-specific survival also did not differ substantially between the two groups.

Conclusions: Omission of radiotherapy was associated with an increased incidence of local recurrence but had no detrimental effect on distant recurrence as the first event or overall survival among women 65 years of age or older with low-risk, hormone receptor-positive early breast cancer.

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases: The FAST-01 Nonrandomized Trial

Author: Anthony E Mascia
Citation: JAMA Oncol.2023 Jan 1;9(1):62-69.

Importance: To our knowledge, there have been no clinical trials of ultra-high-dose-rate radiotherapy delivered at more than 40 Gy/sec, known as FLASH therapy, nor first-in-human use of proton FLASH.

Objectives: To assess the clinical workflow feasibility and treatment-related toxic effects of FLASH and pain relief at the treatment sites.

Design, setting, and participants: In the FAST-01 non-randomized trial, participants treated at Cincinnati Children's/UC Health Proton Therapy Center underwent palliative FLASH radiotherapy to extremity bone metastases. Patients 18 years and older with 1 to 3 painful extremity bone metastases and life expectancies of 2 months or more were eligible. Patients were excluded if they had foot, hand, and wrist metastases; metastases locally treated in the 2 weeks prior; metal implants in the treatment field; known enhanced tissue radiosensitivity; and implanted devices at risk of malfunction with radiotherapy. One of 11 patients who consented was excluded based on eligibility. The end points were evaluated at 3 months posttreatment, and patients were followed up through death or loss to follow-up for toxic effects and pain assessments. Of the 10 included patients, 2 died after the 2-month follow-up but before the 3-month follow-up; 8 participants completed the 3-month evaluation. Data were collected from November 3, 2020, to January 28, 2022, and analyzed from January 28, 2022, to September 1, 2022.

Interventions: Bone metastases were treated on a FLASH-enabled (≥40 Gy/sec) proton radiotherapy system using a single-transmission proton beam. This is consistent with standard of care using the same prescription (8 Gy in a single fraction) but on a conventional-dose-rate (approximately 0.03 Gy/sec) photon radiotherapy system.

Main outcome and measures: Main outcomes included patient time on the treatment couch, device-related treatment delays, adverse events related to FLASH, patient-reported pain scores, and analgesic use.

Results: A total of 10 patients (age range, 27-81 years [median age, 63 years]; 5 [50%] male) underwent FLASH radiotherapy at 12 metastatic sites. There were no FLASH-related technical issues or delays. The average (range) time on the treatment couch was 18.9 (11-33) minutes per patient and 15.8 (11-22) minutes per treatment site. Median (range) follow-up was 4.8 (2.3-13.0) months. Adverse events were mild and consistent with conventional radiotherapy. Transient pain flares occurred in 4 of the 12 treated sites (33%). In 8 of the 12 sites (67%)

patients reported pain relief, and in 6 of the 12 sites (50%) patients reported a complete response (no pain).

Conclusions and relevance: In this non-randomized trial, clinical workflow metrics, treatment efficacy, and safety data demonstrated that ultra-high-dose-rate proton FLASH radiotherapy was clinically feasible. The treatment efficacy and the profile of adverse events were comparable with those of standard-of-care radiotherapy. These findings support the further exploration of FLASH radiotherapy in patients with cancer.

Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial

Author: Charlotte E Cole
Citation: Lancet.2023 Jun 24;401(10394):2124-2137.

Background: A tumour-bed boost delivered after whole-breast radiotherapy increases local cancer-control rates but requires more patient visits and can increase breast hardness. IMPORT HIGH tested simultaneous integrated boost against sequential boost with the aim of reducing treatment duration while maintaining excellent local control and similar or reduced toxicity.

Methods: IMPORT HIGH is a phase 3, non-inferiority, open-label, randomised controlled trial that recruited women after breast-conserving surgery for pT1-3pN0-3aM0 invasive carcinoma from radiotherapy and referral centres in the UK. Patients were randomly allocated to receive one of three treatments in a 1:1:1 ratio, with computer-generated random permuted blocks used to stratify patients by centre. The control group received 40 Gy in 15 fractions to the whole breast and 16 Gy in 8 fractions sequential photon tumour-bed boost. Test group 1 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions concomitant photon boost to the tumour-bed volume. Test group 2 received 36 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 53 Gy in

15 fractions concomitant photon boost to the tumour-bed volume. The boost clinical target volume was the clip-defined tumour bed. Patients and clinicians were not masked to treatment allocation. The primary endpoint was ipsilateral breast tumour relapse (IBTR) analysed by intention to treat; assuming 5% 5-year incidence with the control group, non-inferiority was predefined as 3% or less absolute excess in the test groups (upper limit of two-sided 95% CI). Adverse events were assessed by clinicians, patients, and photographs. This trial is registered with the ISRCTN registry, ISRCTN47437448, and is closed to new participants.

Findings: Between March 4, 2009, and Sept 16, 2015, 2617 patients were recruited. 871 individuals were assigned to the control group, 874 to test group 1, and 872 to test group 2. Median boost clinical target volume was 13 cm^3 (IQR 7 to 22). At a median follow-up of 74 months there were 76 IBTR events (20 for the control group, 21 for test group 1, and 35 for test group 2). 5-year IBTR incidence was 1·9% (95% CI 1·2 to 3·1) for the control group, 2·0% (1·2 to 3·2) for test group 1, and 3·2% (2·2 to 4·7) for test group 2. The estimated absolute differences versus the control group were 0·1% (-0·8 to 1·7) for test group 1 and 1·4% (0·03 to 3·8) for test group 2. The upper confidence limit for test group 1 versus the control group indicated non-inferiority for 48 Gy. Cumulative 5-year incidence of clinician-reported moderate or marked breast induration was 11·5% for the control group, 10·6% for test group 1 (p=0·40 vs control group), and 15·5% for test group 2 (p=0·015 vs control group).

Interpretation: In all groups 5-year IBTR incidence was lower than the 5% originally expected regardless of boost sequencing. Dose-escalation is not advantageous. 5-year moderate or marked adverse event rates were low using small boost volumes. Simultaneous integrated boost in IMPORT HIGH was safe and reduced patient visits.

Effect of different quilting techniques on seroma formation after breast surgery: retrospective study

Author: Lotte J van Zeelst
Citation: BJS Open. 2023 Apr; 7(2): zrac171. Published online 2023 Mar 18.

Background: Quilting, a technique in which skin flaps are sutured to the underlying muscle, reduces seroma after mastectomy and/or axillary lymph node dissection. The aim of this study was to assess the effect of different quilting techniques on the formation of clinically significant seroma.

Methods: This was a retrospective study including patients undergoing mastectomy and/or axillary lymph node dissection. Four breast surgeons applied the quilting technique based on their own discretion. Technique 1 was performed using Stratafix in 5–7 rows placed at 2–3 cm distance. Technique 2 was performed using Vicryl 2–0 in 4–8 rows placed at 1.5–2 cm distance. Technique 3 was performed using Vicryl 0/1 in 3 rows placed at 3–4 cm distance. Technique 4 was performed using Vicryl 0 in 4–5 rows placed at 1.5 cm distance. The primary outcome was clinically significant seroma.

Results: A total of 445 patients were included. Clinically significant seroma incidence was 4.1 per cent (six of 147) for technique 1, which was significantly lower than that for the other techniques (25.0 per cent (29 of 116), 29.4 per cent (32 of 109), and 33 per cent (24 of 73) for techniques 2, 3, and 4 ($P < 0.001$) respectively). The duration of surgery was not significantly longer for technique 1 compared with the other three techniques. The length of hospital stay, number of additional visits to the outpatient clinic, and reoperations did not differ significantly between the four techniques.

Conclusion: Quilting using Stratafix and placing 5–7 rows with 2–3 cm distance between the stitches associates with low clinically significant seroma incidence without adverse effects.

A Comparative Study Between Mastectomy Flap Quilting Sutures with Axillary Drain Versus Conventional Sutures with Axillary and Pectoral Drain in Reducing Post-Modified Radical Mastectomy Seroma Formation

Author: Mohit Bhagchandani
Citation: Indian Journal of Surgery (IF 0.4) Pub Date: 2023-04-06.

The aim of this study was to compare quilting suture with axillary drain versus conventional sutures with axillary and pectoral drain on the formation of seroma after modified radical mastectomy with axillary lymph node dissection. The study was undertaken among 90 female patients with breast cancer who were candidates for modified radical mastectomy with axillary clearance. The intervention group (N = 43) with quilting and axillary drain placement and the control group (N = 33) without quilting with axillary and pectoral drain placement. All the patients were followed up for complications pertaining to this procedure. There were no significant differences between the two groups with regard to demographic characteristics, comorbidities, pre-operative chemotherapy, post-operative pathological findings, lymph node involvement or clinical staging. The incidence of seroma formation on follow-up was significantly lower in the intervention group than that in the control group (23% versus 58%; $p < 0.05$) whereas there was no significant difference with respect to flap necrosis, superficial skin necrosis and wound gaping between the two groups. Furthermore, it took a shorter duration for seroma to resolve in the intervention group (4 days versus 9 days; $p < 0.001$) with a smaller duration of hospital stay (4 days versus 9 days; $p < 0.001$). The use of quilting sutures for flap fixation in order to obliterate dead space post-modified radical mastectomy with placement of axillary drain significantly reduced seroma formation along with shorter duration of wound drainage and a smaller hospital stay with only slightly increased operative time. Therefore, we recommend quilting of flap as a routine step after mastectomy.

Effect of Peritumoral Infiltration of Local Anesthetic Before Surgery on Survival in Early Breast Cancer

Author: Rajendra A Badwe
Citation: J Clin Oncol.2023 Jun 20;41(18):3318-3328.

Purpose: Preventing metastases by using perioperative interventions has not been adequately explored. Local anesthesia blocks voltage-gated sodium channels and thereby prevents activation of prometastatic pathways. We conducted an open-label, multicenter randomized trial to test the impact of presurgical, peritumoral infiltration of local anesthesia on disease-free survival (DFS).

Methods: Women with early breast cancer planned for upfront surgery without prior neoadjuvant treatment were randomly assigned to receive peritumoral injection of 0.5% lidocaine, 7-10 minutes before surgery (local anesthetics [LA] arm) or surgery without lidocaine (no LA arm). Random assignment was stratified by menopausal status, tumor size, and center. Participants received standard postoperative adjuvant treatment. Primary and secondary end points were DFS and overall survival (OS), respectively.

Results: Excluding eligibility violations, 1,583 of 1,600 randomly assigned patients were included in this analysis (LA, 796; no LA, 804). At a median follow-up of 68 months, there were 255 DFS events (LA, 109; no LA, 146) and 189 deaths (LA, 79; no LA, 110). In LA and no LA arms, 5-year DFS rates were 86.6% and 82.6% (hazard ratio [HR], 0.74; 95% CI, 0.58 to 0.95; P = .017) and 5-year OS rates were 90.1% and 86.4%, respectively (HR, 0.71; 95% CI, 0.53 to 0.94; P = .019). The impact of LA was similar in subgroups defined by menopausal status, tumor size, nodal metastases, and hormone receptor and human epidermal growth factor receptor 2 status. Using competing risk analyses, in LA and no LA arms, 5-year cumulative incidence rates of locoregional recurrence were 3.4% and 4.5% (HR, 0.68; 95% CI, 0.41 to 1.11), and distant recurrence rates were 8.5% and 11.6%, respectively (HR, 0.73; 95% CI, 0.53 to 0.99). There were no adverse events because of lidocaine injection.

Conclusion: Peritumoral injection of lidocaine before breast cancer surgery significantly increases DFS and OS. Altering events at the time of surgery can prevent metastases in early breast cancer

Impact of 18F-Labeled Fluorodeoxyglucose Positron Emission Tomography - Computed Tomography Versus Conventional Staging in Patients With Locally Advanced Breast Cancer

Author: Ian S Dayes
Citation: J Clin Oncol.2023 Aug 10;41(23):3909-3916.

Purpose: Patients with locally advanced breast cancer (LABC) typically undergo staging tests at presentation. If staging does not detect metastases, treatment consists of curative intent combined modality therapy (neoadjuvant chemotherapy, surgery, and regional radiation). Positron emission tomography-computed tomography (PET-CT) may detect more asymptomatic distant metastases, but the evidence is based on uncontrolled studies.

Methods: For inclusion, patients had histological evidence of invasive ductal carcinoma of the breast and TNM stage III or IIb (T3N0, but not T2N1). Consenting patients from six regional cancer centers in Ontario were randomly assigned to 18F-labeled fluorodeoxyglucose PET-CT or conventional staging (bone scan, CT of the chest/abdomen and pelvis). The primary end point was upstaging to stage IV. A key secondary outcome was receiving curative intent combined modality therapy (ClinicalTrials.gov identifier: NCT02751710).

Results: Between December 2016 and April 2022, 184 patients were randomly assigned to whole-body PET-CT and 185 patients to conventional staging. Forty-three (23%) PET-CT patients were upstaged to stage IV compared with 21 (11%) conventional staged patients (absolute difference, 12.3% [95% CI, 3.9 to 19.9]; P = .002). Consequently, treatment was changed in 35 (81.3%) of 43 upstaged PET-CT patients and 20 (95.2%) of the 21 upstaged conventional patients. Subsequently, 149 (81%) patients in the PET-CT group received combined modality treatment versus 165 (89.2%) patients in the conventional staging group (absolute difference, 8.2% [95% CI, 0.1 to 15.4]; P = .03).

Conclusion: In patients with LABC, PET-CT detected more distant metastases than conventional staging, and fewer PET-CT patients received combined modality therapy. Our randomized trial demonstrates the utility of the PET-CT staging strategy.

Effect of preoperative chemotherapy on the outcome of women with operable breast cancer

Author: B Fisher
Citation: Journal of Clinical Oncology 41, no. 10 (April 01, 2023) 1795-1808.

Purpose: To determine, in women with primary operable breast cancer, if preoperative doxorubicin (Adriamycin) and cyclophosphamide (Cytoxan; AC) therapy yields a better outcome than postoperative AC therapy, if a relationship exists between outcome and tumor response to preoperative chemotherapy, and if such therapy results in the performance of more lumpectomies.

Patients and Methods: Women (1,523) enrolled onto National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 were randomly assigned to preoperative or postoperative AC therapy. Clinical tumor response to preoperative therapy was graded as complete (cCR), partial (cPR), or no response (cNR). Tumors with a cCR were further categorized as either pathologic complete response (pCR) or invasive cells (pINV). Disease-free survival (DFS), distant disease-free survival (DDFS), and survival were estimated through 5 years and compared between treatment groups. In the preoperative arm, proportional-hazards models were used to investigate the relationship between outcome and tumor response.

Results: There was no significant difference in DFS, DDFS, or survival (P = .99, .70, and .83, respectively) among patients in either group. More patients treated preoperatively than postoperatively underwent lumpectomy and radiation therapy (67.8% v 59.8%, respectively). Rates of ipsilateral breast tumor recurrence (IBTR) after lumpectomy were similar in both groups (7.9% and 5.8%, respectively; P = .23). Outcome was better in women whose tumors

showed a pCR than in those with a pINV, cPR, or cNR (relapse-free survival [RFS] rates, 85.7%, 76.9%, 68.1%, and 63.9%, respectively; P < .0001), even when baseline prognostic variables were controlled. When prognostic models were compared for each treatment group, the preoperative model, which included breast tumor response as a variable, discriminated outcome among patients to about the same degree as the postoperative model.

Conclusion: Preoperative chemotherapy is as effective as postoperative chemotherapy, permits more lumpectomies, is appropriate for the treatment of certain patients with stages I and II disease, and can be used to study breast cancer biology. Tumor response to preoperative chemotherapy correlates with outcome and could be a surrogate for evaluating the effect of chemotherapy on micrometastases; however, knowledge of such a response provided little prognostic information beyond that which resulted from postoperative therapy.

Hormonal Contraception and the Risk of Breast Cancer in Women of Reproductive Age: A Meta-Analysis

Author: Luz Angela Torres-de la Roche
Citation: Cancers (Basel). 2023 Dec; 15(23): 5624.

This study aims to summarize evidence from observational studies about the lifetime use of HC and the risk of BC in women of reproductive age. The PubMed, Cochrane, and EMBASE databases were searched for observational studies published from 2015 to February 2022. Meta-analyses were performed using adjusted odds ratios and relative risks with a random-effects model using the I^2 statistic to quantify the heterogeneity among studies. Of the 724 studies identified, 650 were screened for title/abstract selection, 60 were selected for full-text revision, and 22 were included in the meta-analysis. Of these, 19 were case-control studies and 3 were cohort studies. The results of the meta-analysis indicate a significantly higher risk of developing BC in ever users of HC (pooled OR = 1.33; 95% CI = 1.19 to 1.49). This effect is larger in the subgroups of case-control studies (pooled OR = 1.44, 95% CI = 1.21 to 1.70) and in the subgroup of studies that strictly define menopausal status (pooled OR = 1.48; 95% CI,

1.10 to 2.00). Although our meta-analysis of observational studies (cohort and case-control) suggests a significantly increased overall risk of BC in users or ever-users of modern hormonal contraceptives, the high heterogeneity among studies (>70%) related to differences in study design, measurement of variables, confounders, among other factors, as well as publication biases should be considered when interpreting our results.

Global Stage Distribution of Breast Cancer at Diagnosis: A Systematic Review and Meta-Analysis

Author: Javier David Benitez Fuentes
Citation: JAMA Oncol . 2023 Nov 9:e234837..

Importance: Stage at diagnosis is a key prognostic factor for cancer survival.

Objective: To assess the global distribution of breast cancer stage by country, age group, calendar period, and socioeconomic status using population-based data.

Data sources: A systematic search of MEDLINE and Web of Science databases and registry websites and gray literature was conducted for articles or reports published between January 1, 2000, and June 20, 2022.

Study selection: Reports on stage at diagnosis for individuals with primary breast cancer (C50) from a population-based cancer registry were included.

Data extraction and synthesis: Study characteristics and results of eligible studies were independently extracted by 2 pairs of reviewers (J.D.B.F., A.D.A., A.M., R.S., and F.G.). Stage-specific proportions were extracted and cancer registry data quality and risk of bias were assessed. National pooled estimates were calculated for subnational or annual data sets using a hierarchical rule of the most relevant and high-quality data to avoid duplicates.

Main outcomes and measures: The proportion of women with breast cancer by (TNM Classification of Malignant Tumors or the Surveillance, Epidemiology, and End Results Program [SEER]) stage group.

Results: Data were available for 2.4 million women with breast cancer from 81 countries. Globally, the proportion of cases with distant metastatic breast cancer at diagnosis was high in sub-Saharan Africa, ranging from 5.6% to 30.6% and low in North America ranging from 0.0% to 6.0%. The proportion of patients diagnosed with distant metastatic disease decreased over the past 2 decades from around 3.8% to 35.8% (early 2000s) to 3.2% to 11.6% (2015 onwards), yet stabilization or slight increases were also observed. Older age and lower socioeconomic status had the largest proportion of cases diagnosed with distant metastatic stage ranging from 2.0% to 15.7% among the younger to 4.1% to 33.9% among the oldest age group, and from 1.7% to 8.3% in the least disadvantaged groups to 2.8% to 11.4% in the most disadvantaged groups.

Conclusions and relevance: Effective policy and interventions have resulted in decreased proportions of women diagnosed with metastatic breast cancer at diagnosis in high-income countries, yet inequality persists, which needs to be addressed through increased awareness of breast cancer symptoms and early detection. Improving global coverage and quality of population-based cancer registries, including the collection of standardized stage data, is key to monitoring progress.

ER Positive Breast Cancer

Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer

Author: Nicholas C Turner
Citation: N Engl J Med.2023 Jun 1;388(22):2058-2070.

Background: AKT pathway activation is implicated in endocrine-therapy resistance. Data on the efficacy and safety of the AKT inhibitor capivasertib, as an addition to fulvestrant therapy, in patients with hormone receptor-positive advanced breast cancer are limited.

Methods: In a phase 3, randomized, double-blind trial, we enrolled eligible pre-, peri-, and postmenopausal women and men with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer who had had a relapse or disease progression during or after treatment with an aromatase inhibitor, with or without previous cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy. Patients were randomly assigned in a 1:1 ratio to receive capivasertib plus fulvestrant or placebo plus fulvestrant. The dual primary end point was investigator-assessed progression-free survival assessed both in the overall population and among patients with AKT pathway-altered (PIK3CA, AKT1, or PTEN) tumors. Safety was assessed.

Results: Overall, 708 patients underwent randomization; 289 patients (40.8%) had AKT pathway alterations, and 489 (69.1%) had received a CDK4/6 inhibitor previously for advanced breast cancer. In the overall population, the median progression-free survival was 7.2 months in the capivasertib-fulvestrant group, as compared with 3.6 months in the placebo-fulvestrant group (hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.51 to 0.71; P<0.001). In the AKT pathway-altered population, the median progression-free survival was 7.3 months in the capivasertib-fulvestrant group, as compared with 3.1 months in the placebo-fulvestrant group (hazard ratio, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The most frequent adverse events of grade 3 or higher in patients

receiving capivasertib-fulvestrant were rash (in 12.1% of patients, vs. in 0.3% of those receiving placebo-fulvestrant) and diarrhea (in 9.3% vs. 0.3%). Adverse events leading to discontinuation were reported in 13.0% of the patients receiving capivasertib and in 2.3% of those receiving placebo.

Conclusions: Capivasertib-fulvestrant therapy resulted in significantly longer progression-free survival than treatment with fulvestrant alone among patients with hormone receptor-positive advanced breast cancer whose disease had progressed during or after previous aromatase inhibitor therapy with or without a CDK4/6 inhibitor.

Pooled ctDNA analysis of MONALEESA phase III advanced breast cancer trials

Author: F André
Citation: Ann Oncol.2023 Nov;34(11):1003-1014.

Background: The phase III MONALEESA trials tested the efficacy and safety of the cyclin-dependent kinase (CDK)4/6 inhibitor ribociclib with different endocrine therapy partners as first- or second-line treatment of hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer (ABC). Using the largest pooled biomarker dataset of the CDK4/6 inhibitor ribociclib in ABC to date, we identified potential biomarkers of response to ribociclib.

Patients and methods: Baseline circulating tumour DNA from patients in the MONALEESA trials was assessed using next-generation sequencing. An analysis of correlation between gene alteration status and progression-free survival (PFS) was carried out to identify potential biomarkers of response to ribociclib.

Results: Multiple frequently altered genes were identified. Alterations in ERBB2, FAT3, FRS2, MDM2, SFRP1, and ZNF217 were associated with a greater PFS benefit with ribociclib versus placebo. Patients with high tumour mutational burden (TMB) and with ANO1, CDKN2A/2B/2C, and RB1 alterations exhibited decreased sensitivity to ribociclib versus placebo.

Conclusions: Although exploratory, these results provide insight into alterations associated with the improved response to ribociclib treatment and may inform treatment sequencing in patients with actionable alterations following progression on CDK4/6 inhibitors. Validation of potential biomarkers identified here and development of prospective trials testing their clinical utility are warranted.

Efficacy of Oral SERDs in the treatment of ER+, HER2 - metastatic breast cancer, a stratified analysis of the ESR1 wild type and mutant subgroups

Author: N Z H Wong
Citation: Ann Oncol.2023 Oct 21:S0923-7534(23)043284.

Background: Oral SERDs are a novel drug class that have been developed to counteract resistance due to ESR1 mutations. Several SERDs have emerged from phase 2 and 3 trials, with the FDA limiting approval for Elacestrant to patients with ESR1mt tumours despite PFS benefit in the overall population. However, questions remain on whether patients with ESR1wt tumours stand to benefit from oral SERDs.

Patients and methods: Manuscripts and conference presentations of Randomised Controlled Trials were extracted after a systematic search of Embase, PubMed and Cochrane from inception until January 21,2023. RCTs investigating the efficacy of oral SERDs versus endocrine therapy for ER positive, HER2 negative advanced breast cancer, and which reported the Kaplan Meier (KM) curves of PFS in the overall and ESR1 mutant (ESR1mt) population were selected. A graphical reconstructive algorithm was applied to estimate time-to-event outcomes from reported KM curves in all overall and ESR1mt cohorts. A bipartite matching algorithm, KMSubtraction, was used to derive survival data for unreported (ESR1wt) subgroups. An individual patient data (IPD) meta-analysis was then pursued, pooling data by ESR1 mutation status in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Guidelines for IPD.

Results: The randomized clinical trials ACELERA, AMEERA-3, EMERALD and SERENA-2 were included, totalling 1290 patients. In the pooled analysis of the overall cohort, PFS benefit was observed with oral SERDs when compared with treatment of physicians choice (TPC) (HR 0.783, 95%CI 0.681-0.900, p<0.001). In the ESR1mt subgroup, oral SERDs demonstrated improved PFS (HR 0.557, 95%CI 0.440-0.705, p<0.001) compared to TPC. In the ESR1wt subgroup, oral SERDs demonstrated no significant PFS benefit (HR 0.944, 95%CI 0.783-1.138, p=0.543) when compared to TPC.

Conclusions: The results of this IPD meta-analysis suggests that PFS benefit in the overall population is mainly driven by the ESR1mt subgroup.

Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial

Author: Kevin Kalinsky
Citation: J Clin Oncol.2023 Aug 20;41(24):4004-4013.

Purpose: Cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) with endocrine therapy (ET) improves progression-free survival (PFS) and overall survival (OS) in hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). Although preclinical and clinical data demonstrate a benefit in changing ET and continuing a CDK4/6i at progression, no randomized prospective trials have evaluated this approach.

Methods: In this investigator-initiated, phase II, double-blind placebo-controlled trial in patients with HR+/HER2- MBC whose cancer progressed during ET and CDK4/6i, participants switched ET (fulvestrant or exemestane) from ET used pre-random assignment and randomly assigned 1:1 to the CDK4/6i ribociclib versus placebo. PFS was the primary end point, defined as time from random assignment to disease progression or death. Assuming a median PFS of 3.8 months with placebo, we had 80% power to detect a hazard

ratio (HR) of 0.58 (corresponding to a median PFS of at least 6.5 months with ribociclib) with 120 patients randomly assigned using a one-sided log-rank test and significance level set at 2.5%.

Results: Of the 119 randomly assigned participants, 103 (86.5%) previously received palbociclib and 14 participants received ribociclib (11.7%). There was a statistically significant PFS improvement for patients randomly assigned to switched ET plus ribociclib (median, 5.29 months; 95% CI, 3.02 to 8.12 months) versus switched ET plus placebo (median, 2.76 months; 95% CI, 2.66 to 3.25 months) HR, 0.57 (95% CI, 0.39 to 0.85); P = .006. At 6 and 12 months, the PFS rate was 41.2% and 24.6% with ribociclib, respectively, compared with 23.9% and 7.4% with placebo.

Conclusion: In this randomized trial, there was a significant PFS benefit for patients with HR+/HER2- MBC who switched ET and received ribociclib compared with placebo after previous CDK4/6i and different ET.

Invasive disease–free survival (iDFS) across key subgroups from the phase III NATALEE study of ribociclib (RIB) + a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2- early breast cancer (EBC)

Author: Aditya Bardia
Citation: Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

Background: The NATALEE trial demonstrated a statistically significant iDFS benefit with RIB + NSAI vs NSAI alone in a broad population of pts with stage II or III HR+/HER2– EBC at risk of recurrence (Slamon D, et al. ASCO 2023. Oral LBA500). Evaluating iDFS outcomes in clinically relevant subgroups is important for understanding treatment (tx) benefit in specific pts. Here we present a prespecified exploratory subgroup analysis of iDFS in pts enrolled in NATALEE.

Methods: Pts with HR+/HER2– EBC were randomized 1:1 to RIB for 3 y (400 mg/d for 3 wk on/1 wk off) + NSAI for ≥5 y (letrozole 2.5 mg/d or anastrozole 1 mg/d) or NSAI alone. Premenopausal women and men received goserelin

every 28 d. NATALEE included pts with anatomical stage IIA (N0 requiring additional risk factors or N1 [1-3 axillary lymph nodes]) and all pts with stage IIB or III disease per AJCC's Cancer Staging Manual (8th ed). iDFS was evaluated by Kaplan-Meier methods. iDFS analysis was performed according to anatomical stage, menopausal status, nodal status, age, and Ki-67 score (locally tested). This prespecified analysis was not powered for statistical significance.

Results: A total of 5101 pts were included in this analysis (data cutoff: 11 Jan 2023; median follow-up for iDFS, 27.7 mo in both arms). Overall, the iDFS benefit with RIB + NSAI vs NSAI alone was consistent across all clinically relevant subgroups (Table), which in turn was consistent with that observed in the overall trial population.

Conclusions: The iDFS benefit with RIB + NSAI was generally consistent with that in the intent-to-treat population of NATALEE and was not driven by any particular subgroup. The results further support RIB + NSAI as a new tx of choice in a broad population of pts with HR+/HER2– EBC. Table: LBA23

	Tx, n	3-y iDFS rate, %	HR (95% CI)
Menopausal status Premenopausal women & men Postmenopausal women	RIB + NSAI, 1126 NSAI alone, 1132 RIB + NSAI, 1423 NSAI alone, 1420	91 89 90 86	0.72 (0.53-0.98) 0.78 (0.61-1.00)
Anatomical stage II III	RIB + NSAI, 1011 NSAI alone, 1034 RIB + NSAI, 1528 NSAI alone, 1512	94 91 87 84	0.76 (0.53-1.10) 0.74 (0.59-0.93)
Nodal status N0 N1-N3	RIB + NSAI, 285 NSAI alone, 328 RIB + NSAI, 2261 NSAI alone, 2219	94 89 90 87	0.63 (0.34-1.17) 0.77 (0.63-0.94)
Age <65 y ≥65 y	RIB + NSAI, 2142 NSAI alone, 2186 RIB + NSAI, 407 NSAI alone, 366	90 87 90 86	0.77 (0.62-0.94) 0.72 (0.46-1.14)
Ki-67 ≤20% >20%	RIB + NSAI, 1199 NSAI alone, 1236 RIB + NSAI, 920 NSAI alone, 938	92 90 89 84	0.80 (0.59-1.08) 0.75 (0.56-1.00)

Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2– early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial

Author: G. Hortobagyi
Citation: SABCS 2023-GS03-03

Background: Interim results from the phase 3 NATALEE trial demonstrated that adding RIB to standard-of-care adjuvant NSAI had a statistically significant iDFS benefit in patients with stage II and III HR+/HER2– early breast cancer at risk of recurrence, including those with nodenegative disease (Slamon et al, ASCO 2023). We present the final protocol-specified analysis of the primary endpoint of iDFS.

Methods: A total of 5101 pre-/postmenopausal women and men underwent 1:1 randomization to receive RIB (400 mg/day; 3 weeks on/1 week off for 36 months) + NSAI (letrozole 2.5 mg/day or anastrozole 1 mg/day for ≥60 months) or NSAI alone. Men and premenopausal women received goserelin (3.6 mg once every 28 days). Patients were required to have anatomic stage IIA (either N0 with additional risk factors or N1), IIB, or III breast cancer per the AJCC (8th edition). Patients remained on trial as long as they were continuing on NSAI (≤5 years), regardless of RIB discontinuation. The primary endpoint was iDFS according to STEEP v1.0 criteria, and the secondary efficacy endpoints were recurrence-free survival (RFS), distant disease–free survival (DDFS), and overall survival (OS). This final analysis was planned after approximately 500 iDFS events. iDFS was evaluated by the Kaplan-Meier method, and statistical comparison was made by a stratified log-rank test. P values were not corrected for multiple comparisons.

Results: At the data cutoff (July 21, 2023), among the 2549 patients in the RIB + NSAI arm, 1091 (42.8%) completed 3 years of RIB treatment, and 905 (35.5%) discontinued RIB or RIB + NSAI early and 528 patients (20.7%) remained on RIB. 1748 patients (68.5%) remain on treatment in the NSAI arm. Median follow-up for iDFS was 33.3 months, an additional 5.6 months from the previous interim analysis. A total of 509 iDFS events were observed, 226 (8.9%) in the RIB + NSAI arm and 283 (11.1%) in the NSAI alone arm. RIB + NSAI demonstrated a significant iDFS benefit over NSAI alone (HR, 0.749; 95% CI, 0.628-0.892; P=.0006). The 3-year iDFS rates were 90.7% (95% CI, 89.3%-91.8%) vs 87.6% (95% CI, 86.1%-88.9%). A consistent benefit was observed across patient subgroups, including those with node-negative, stage II, or stage III disease (Table). Secondary endpoints of DDFS and RFS favored RIB + NSAI over NSAI alone (Table). OS data were immature, with 84 (3.3%) and 88 (3.4%) total events in the RIB + NSAI and NSAI alone arms, respectively. No new safety signals were observed since the prior interim analysis. Discontinuation of RIB due to adverse events was observed in 19.5% of patients (a <1% increase from the prior interim analysis).

Conclusion: With a substantial proportion of patients completing 3 years of RIB treatment, NATALEE continues to demonstrate a significant iDFS improvement with RIB + NSAI over NSAI alone. Efficacy results confirm continued improvement in benefit across subgroups, including stage II disease. Safety findings support the manageable toxicity profile of RIB at the 400-mg starting dose in early breast cancer.

Table

	RIB + NSAI n = 2549	NSAI alone n = 2552
iDFS in ITT population		
HR (95% CI)	0.749 (0.628-0.892)	
P value[a]	.0006	
3-Year iDFS rate, %	90.7	87.6
iDFS in clinically relevant subgroups		
Node negative		
HR (95% CI)	0.723 (0.412-1.268)	
3-Year iDFS rate, %	93.2	90.6
Stage II		
HR (95% CI)	0.700 (0.496-0.986)	
3-Year iDFS rate, %	94.2	92.6
Stage III		
HR (95% CI)	0.755 (0.616-0.926)	
3-Year iDFS rate, %	88.1	83.8
Secondary efficacy endpoints in ITT population		
RFS		
HR (95% CI)	0.727 (0.602-0.877)	
3-Year RFS, %	92.1	89.1
DDFS		
HR (95% CI)	0.749 (0.623-0.900)	
3-Year DDFS, %	92.9	90.2
OS		
HR (95% CI)	0.892 (0.661-1.203)	
3-Year OS, %	97.0	96.1

ITT, intent to treat.

[a] One-sided *P* value.

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2– early breast cancer: Primary results from the phase III NATALEE trial.

Author: Dennis J. Slamon
Citation: J Clin Oncol 41, 2023 (suppl 17; abstr LBA500)

Background: RIB + ET has demonstrated significant survival benefits in pre- and postmenopausal pts with HR+/HER2– metastatic BC. To investigate whether RIB + ET also improves outcomes in early BC (EBC), the Phase III NATALEE trial (NCT03701334) evaluated adjuvant RIB + ET in a broad population of pts with stage II or III HR+/HER2– EBC at risk for recurrence, including pts with no nodal involvement (N0). As extended duration of tx is crucial to prolong cell cycle arrest and drive more tumor cells into senescence or death, a 3-y duration of RIB tx at a dose of 400 mg was chosen to improve tolerability while maintaining efficacy. Results from a prespecified interim analysis of invasive disease–free survival (iDFS; primary endpoint) are presented.

Methods: Men and pre- or postmenopausal women were randomized 1:1 to RIB (400 mg/day; 3 wk on/1 wk off for 3 y) + ET (letrozole 2.5 mg/day or anastrozole 1 mg/day, for ≥ 5 y) or ET alone. Men and premenopausal women also received goserelin. Eligible pts had an ECOG PS of 0-1 and BC anatomic stage IIA (either N0 with additional risk factors or 1-3 axillary lymph nodes [N1]), stage IIB, or stage III per AJCC (8th ed); prior (neo)adjuvant ET was allowed if initiated ≤ 12 mo before randomization. Stratification factors were menopausal status, disease stage, prior (neo)adjuvant chemotherapy, and geographic region. This prespecified interim analysis of iDFS, defined per STEEP criteria, was planned after ≈ 425 iDFS events (≈ 85% of planned total events). iDFS was evaluated by Kaplan-Meier methods, and statistical comparison was made by a stratified log-rank test, with a protocol-defined Lan-DeMets (O'Brien-Flemming) stopping boundary of a 1-sided P < .0128 for superior efficacy.

Results: From 10 Jan 2019 to 20 April 2021, 5101 pts were randomized (RIB+ET, n = 2549; ET alone, n = 2552). As of the data cutoff (11 Jan 2023), median follow-up was 34 mo (min, 21 mo). 3- and 2-y RIB tx was completed by 515 pts (20.2%) and 1449 pts (56.8%), respectively; 3810 (74.7%) remained on study tx (RIB+ET, n = 1984; ET alone, n = 1826). iDFS was evaluated after 426 events (RIB + ET, n = 189; ET alone, n = 237). RIB + ET demonstrated significantly longer iDFS than ET alone (HR, 0.748; 95% CI, 0.618-0.906; P = .0014); 3-y iDFS rates were 90.4% vs 87.1%. iDFS benefit was generally consistent across stratification factors and other subgroups. Secondary endpoints of overall survival, recurrence-free survival, and distant disease–free survival consistently favored RIB. RIB at 400 mg had a favorable safety profile with no new signals.

Conclusions: Ribociclib added to standard-of-care ET demonstrated a statistically significant, clinically meaningful improvement in iDFS with a well-tolerated safety profile. The NATALEE results support ribociclib + ET as the treatment of choice in a broad population of pts with stage II or III HR+/HER2– EBC, including pts with N0 disease

Effects of ovarian ablation or suppression on breast cancer recurrence and survival: Patient-level meta-analysis of 14,993 pre-menopausal women in 25 randomized trials.

Author: Richard G. Gray
Citation: ASC0 2023 Abstract 503

Background: Suppressing ovarian function of women with breast cancer may improve outcome by preventing estrogenic stimulation of any residual cancer, particularly for pre-menopausal women with estrogen receptor (ER)-positive tumors. We report a collaborative meta-analysis of individual participant data from randomized trials of ovarian ablation or suppression.

Methods: Data were sought from randomized trials that compared ovarian ablation or suppression versus not. Primary analyses included only premenopausal women age < 55 with ER-positive or unknown tumors, stratified into those who received no chemotherapy, or remained premenopausal following chemotherapy, and those whose menopausal status following chemotherapy was not ascertained. Standard log-rank methods estimated ER-weighted annual event rate ratios (RR).

Results: Individual patient data were provided for 25 of 27 relevant trials, comprising 14,993 (98.7%) of 15,195 women randomized. Overall, fewer breast cancer recurrences were seen with ovarian ablation/suppression than control (RR = 0·82, 95% CI 0·77–0·88; p < 0·0001). Recurrence reductions were significantly (p = 0.0003) larger among women (n = 7,213) known to be premenopausal prior to ovarian suppression (RR = 0·70, 0·63–0·78; p = 0·0003) than among those (n = 7,786) whose menopausal status was uncertain after chemotherapy (RR = 0·91, 0·83–0·99; p = 0·03). For known premenopausal women, 15-year risk of recurrence was improved by 12·1% (28·9% vs 41·0%; p < 0·0001. 15-year breast cancer and all-cause mortality were improved by 8·0% (20·9% vs 28·9%; RR 0·69, 0·60–0·80; p < 0·0001) and 7.2% (26·0% vs 33·1%; RR = 0·73, 0·64–0·82; p < 0·0001), respectively, with no increase in deaths without recurrence (RR = 0·88, 0·67–1·14; p = 0·33). Recurrence reductions were significantly (p = 0·003) larger among premenopausal women aged under 45 (RR = 0·63, 0·55–0·72; p < 0·0001) than among those aged 45-54 (RR = 0·84, 0·70–1.00; p = 0·045), but did not differ significantly by other recorded patient or tumor characteristics.

Conclusions: For premenopausal women aged under 45, ovarian ablation or suppression substantially reduces the 15-year risk of recurrence and death from breast cancer without increasing mortality from other causes.

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC).

Author: Gabe S. Sonke
Citation: ASCO 2023:LBA1000

Background: The phase-3, randomized, investigator-initiated, nationwide SONIA trial is evaluating the efficacy, safety and cost-effectiveness of CDK4/6i added to either first- or second-line endocrine therapy (ET) in patients with HR+, HER2- ABC who have received no prior therapy for ABC. The addition of CDK4/6i to ET improves progression-free (PFS) and overall survival (OS) in HR+, HER2- ABC, as initial treatment (first-line) and after prior endocrine monotherapy (second-line). Most international guidelines advice first-line use, despite prolonged toxicity and a steep increase in costs compared to use in second-line. Evidence of superiority of first-line use over second-line based on a head-to-head comparison is lacking.

Methods: Pre- and postmenopausal women (N=1050), who received no prior therapy for ABC, with measurable or evaluable disease and WHO performance status 0-2 were enrolled in 74 Dutch hospitals. (Neo)adjuvant therapy was allowed (disease-free interval after non-steroidal aromatase inhibitor (NSAI) >12 months). Patients were randomized 1:1 to receive strategy A (first-line treatment with an NSAI + CDK4/6i, followed on progression by fulvestrant (F)) or strategy B (first-line treatment with an NSAI, followed on progression by F + CDK4/6i). Choice between one of the available CDK4/6i (abemaciclib, palbociclib, ribociclib) was a stratification factor and left to the discretion of the treating physician. The primary endpoint is time from randomization to second objective disease progression, as assessed by local investigators, or death (PFS2). Secondary endpoints include OS, safety, quality of life, and cost-effectiveness.

Results: After a median follow-up of 37.3 months (data cut-off 1 December 2022), median PFS2 was 31.0 months in strategy A versus 26.8 months in strategy B (hazard ratio 0.87; 95% confidence interval, 0.74 to 1.03; P=0.10). The treatment effect was consistent across the levels of pre-defined subgroups. The safety profile was characteristic for ET + CDK4/6i. Median time on CDK4/6i was 24.64 months in strategy A and 8.08 months in strategy B (Δ 16.56 months). The number of grade ≥3 adverse events was 2782 for strategy A and 1620 for strategy B.

Conclusions: First-line use of CDK4/6i + ET does not provide statistically significant, nor clinically meaningful PFS benefit compared to second-line use in women with HR+, HER2- ABC. Use in first-line prolongs the time on CDK4/6i by 16.56 months and increases toxicity and costs. Second-line use may thus be a preferred option for the majority of patients.

Neoadjuvant chemotherapy combined with endocrine therapy for hormone receptor-positive breast cancer: A systematic review and meta-analysis

Author: Hong-Fang Ma
Citation: Medicine (Baltimore). 2023 Nov 17; 102(46): e35928.

Background: This study aimed to conduct a comparative analysis of the efficacy and safety of neoadjuvant chemotherapy combined with endocrine therapy against the backdrop of single neoadjuvant chemotherapy or endocrine therapy, specifically in the context of hormone receptor-positive (HR+) breast cancer treatment.

Methods: We conducted a thorough literature search across several databases, including China National Knowledge Infrastructure, Wanfang, Weipu, Chinese Journal Full-text Database, PubMed, Web of Science, Cochrane Library, and EMBASE, adhering to the guidelines outlined in the PRISMA statement. Our specific focus was on identifying randomized controlled trials that directly compared the combined approach of neoadjuvant chemotherapy and endocrine therapy with single chemotherapy or endocrine therapy in the

context of treating HR+ breast cancer. Subsequently, we utilized statistical packages implemented in R software to perform comparative analyses of key clinical indicators, encompassing the complete response, objective response rate (ORR), disease control rate, pathological complete response (pCR), and adverse reactions.

Results: A total of 11 randomized controlled trials, involving 1359 patients, all of whom met our inclusion criteria and were thus included in our comprehensive analysis. Within this cohort, 688 patients (50.63%) administered neoadjuvant chemotherapy combined with endocrine therapy (NCET), 642 patients (47.24%) received neoadjuvant chemotherapy (NCT) alone, while 29 patients (2.13%) underwent neoadjuvant endocrine therapy (NET) alone. The results of our meta-analysis revealed that NCET exhibited a statistically significant enhancement in both ORR and pCR ($P < .05$). Nonetheless, when compared to NCT or NET, NCET did not yield a significant impact on complete response, disease control rate, and safety ($P > .05$). In addition, NCET demonstrated a significant improvement in ORR among patients with HR+, HER2-negative breast cancer ($P < .05$). However, it was also linked to a heightened incidence of serious adverse reactions within this particular patient subgroup ($P < .05$).

Conclusion: The combination of Neoadjuvant chemotherapy and endocrine therapy stands out as a significant contributor to enhancing the ORR and pCR for HR+ breast cancer patients. For breast cancer patients with HER2- status, NCET demonstrates a remarkable improvement in ORR but is also associated with the emergence of adverse reactions

Adding Ovarian Suppression to Tamoxifen for Premenopausal Women With Hormone Receptor-Positive Breast Cancer After Chemotherapy: An 8-Year Follow-Up of the ASTRRA Trial

Author: Soo Yeon Baek
Citation: J Clin Oncol. 2023 Nov 1;41(31):4864-4871.

Purpose: To determine the updated long-term outcomes of the Addition of Ovarian Suppression to Tamoxifen in Young Women With Hormone-Sensitive Breast Cancer Who Remain Premenopausal or Regain Vaginal Bleeding After Chemotherapy (ASTRRA) trial.

Patients and methods: This study is a post-trial follow-up of the ASTRRA trial, involving 1,483 premenopausal women younger than 45 years treated with definitive surgery after completing adjuvant or neoadjuvant chemotherapy for estrogen receptor-positive breast cancer. Patients were randomly assigned in a 1:1 ratio to complete 5 years of tamoxifen (TAM) alone (TAM-only) or 5 years of TAM with ovarian function suppression (OFS) for 2 years (TAM + OFS). The primary end point was disease-free survival (DFS), and the secondary end point was overall survival (OS).

Results: At 106.4 months of median follow-up, there was a continuous significant reduction in the DFS event rate in the TAM + OFS group. The 8-year DFS rate was 85.4% in the TAM + OFS group and 80.2% in the TAM-only group (hazard ratio [HR], 0.67; 95% CI, 0.51 to 0.87). There were no significant differences in OS between the two groups. The OS rate was 96.5% in the TAM + OFS group and 95.3% in the TAM-only group (HR, 0.78; 95% CI, 0.49 to 1.25).

Conclusion: Adding OFS for 2 years to adjuvant TAM with a longer follow-up resulted in consistent DFS benefits, suggesting that adding OFS to TAM should be considered for patients who remain in a premenopausal state or resume ovarian function after chemotherapy.

Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes

Author: N. Harbeckh
Citation: ESMO 2023:LBA17

Background: Two years (yrs) of adjuvant abemaciclib combined with endocrine therapy (ET) resulted in significant improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) that persisted beyond the 2-yr treatment (tx) period in patients (pts) with hormone receptor positive, human epidermal growth factor receptor 2 negative, node-positive, high-risk early breast cancer (EBC). Here, we report 5-yr efficacy results from a prespecified overall survival (OS) interim analysis.

Methods: Pts were randomized (1:1) to receive ET for at least 5 yrs +/- abemaciclib for 2 yrs (tx period). High-risk EBC was defined as either ≥4 positive axillary lymph nodes (ALN) or 1-3 ALN with Grade 3 disease and/or tumor ≥5 cm (Cohort 1). A smaller group of pts were enrolled with 1-3+ ALN and central Ki67 ≥20% (Cohort 2). The intent-to-treat (ITT) population consisted of Cohort 1 (5120 pts) and Cohort 2 (517 pts). OS in the ITT population was tested for statistical significance in the gated strategy. Hazard ratios (HR) were estimated using Cox proportional hazard model.

Results: In the ITT population, with a median follow-up of 54 months, the benefit of abemaciclib was sustained with a HR of 0.680 (95% CI: 0.599, 0.772) for IDFS and 0.675 (95% CI: 0.588, 0.774) for DRFS. This persistence of abemaciclib benefit translated to continued separation of the KM curves resulting in a 5-yr absolute improvement in IDFS and DRFS rates of 7.6% and 6.7%, respectively, compared with IDFS/DRFS rates of 6.0%/5.3% at 4 yrs and 4.8%/4.1% at 3 yrs. Tx benefit in Cohort 1 was consistent with ITT. No new safety signals were observed. There continued to be fewer deaths in the abemaciclib plus ET arm compared to the ET arm (208 vs 234; HR 0.903; p=0.284); significance was not met.

Conclusions: At the pivotal 5-yr mark for adjuvant EBC trials, abemaciclib plus ET continued to reduce the risk of developing invasive and distant disease recurrence well beyond the completion of tx. The increasing absolute improvement at 5 yrs is consistent with a carryover effect and further supports the use of abemaciclib in pts with high-risk EBC. OS data are evolving in favor of abemaciclib arm, and follow-up continues.

Imlunestrant with or without everolimus or alpelisib, in ER+, HER2- advanced breast cancer (aBC): Results from the phase Ia/b EMBER study

Author: K. Jhaveri
Citation: ESMO 2023: 383MO

Background: Imlunestrant is an investigational, next-generation, oral SERD designed to deliver continuous ER target inhibition, including in ESR1-mutant BC. In the first-in-human phase 1a/b EMBER study, imlunestrant demonstrated favorable safety, pharmacokinetics (PK), and clinical benefit rate when administered as monotherapy (Jhaveri ASCO 2022) or with abemaciclib (Jhaveri SABCS 2022). We present the first clinical data of imlunestrant with everolimus or alpelisib and updated imlunestrant monotherapy data from the EMBER study (NCT04188548).

Methods: Patients (pts) received imlunestrant alone as part of the phase 1a (escalation) or 1b (expansion), or with everolimus or alpelisib in 1b. Key phase 1b eligibility included ER+, HER2- aBC, prior endocrine therapy (ET) sensitivity, ≤2 prior therapies, and a PIK3CA mutation (alpelisib arm only). Assignment to phase 1b treatment arms was made by investigators. Men and premenopausal women received GnRH agonist. Key endpoints included RP2D, safety, PK, ORR (complete response [CR] plus partial response [PR]) and CBR (CR or PR, or stable disease ≥24 weeks) per RECIST v1.1.

Results: As of 6 Oct 2022, 114 pts received imlunestrant monotherapy, 42 pts received imlunestrant + everolimus, and 21 pts received imlunestrant + alpelisib. Baseline characteristics were similar across combination cohorts; 46% pts had visceral disease and 46% had an ESR1 mutation at baseline. Median number of prior aBC therapies in combination cohorts was: 1 (range 1-2); including prior ET (100%), CDK4/6i (100%), fulvestrant (35%) and chemo (17%). No cardiac or ocular toxicity was seen. Safety and preliminary efficacy are presented (Table)

Table: 383MO Safety and preliminary efficacy

Endpoint	Imlunestrant monotherapy (n = 114)	Imlunestrant + everolimus (n = 42)	Imlunestrant + alpelisib (n = 21)
All-grade treatment emergent AEs (TEAEs) - %	Nausea – 40 Fatigue – 32 Diarrhea – 31	Diarrhea – 55 Fatigue – 45 AST increase – 38	Diarrhea – 86 Rash – 67 Hyperglycaemia - 62
Grade ≥3 treatment related AEs (TRAEs) - %	5 Fatigue – 2 Neutropenia – 2	19 Hypertriglyceridemia – 5 AST increase – 5	62 Rash – 43 Hyperglycemia - 10
Dose reductions due to TRAEs - %			
Imlunestrant alone	2	0	0
Everolimus/alpelisib alone	N/A	12	24
Both	N/A	2	14
Discontinuations due to TRAEs - %			
Imlunestrant alone	0	0	0
Everolimus/ alpelisib alone	N/A	2	29
Both	N/A	0	0
ORR (%)	7/75 (9)	6/28 (21)	6/12 (50)
CBR (%)	48/114 (42)	26/42 (62)	13/21 (62)

AEs = adverse events.

PARSIFAL-LONG: Extended follow-up of hormone receptor-positive / HER2-negative advanced breast cancer patients treated with fulvestrant and palbociclib vs. letrozole and palbociclib in the PARSIFAL study

Author: A. Llombart-Cussac
Citation: SABCS 2023:RF01-03

Background: The Phase 2 PARSIFAL study assessed whether fulvestrant (FUL) or letrozole (LET) was the optimal endocrine partner for the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) palbociclib (PAL) in patients (pts) with untreated, endocrine-sensitive, hormone receptor positive (HR+)/HER2-negative (HER2-) advanced breast cancer (ABC) in the first-line setting.This trial failed to demonstrate an improvement in progression-free survival (PFS) of PAL+FUL over PAL+LET (Llombart-Cussac et al. Jama Oncol 2021). Following progression on CDK4/6ibased regimens in the metastatic setting, the EMERALD study (Bardia et al, SABCS 2022 GS3-01) identified early progressions (< 12 months [mo]) as a strong predictor of resistance to subsequent endocrine therapies. Here, we report updated PFS and overall survival (OS) from PARSIFAL, exploring a PFS <12 mo threshold as a prognostic factor for poor outcomes.

Methods: This was an observational, international, multicenter study that included pts from the prospective PARSIFAL study, in which pts were randomly assigned (1:1) to receive PAL (oral 125 mg/day, 28-day cycles; 3 weeks on, 1 week off) plus FUL or LET at conventional doses. The primary objective was to extend the assessment of OS of PARSIFAL study with a longer median follow-up. Secondary objectives included extended PFS, other post-progression efficacy data, and the identification of new prognostic and predictive markers. The design had a planned recruitment of at least 388 pts with 195 deaths. The 2-sided stratified log-rank test ($\alpha = 0.05$) had a 70% power to detect a hazard ratio ≤ 0.70 in favor of FUL + PAL arm.

Results: A total of 389 pts (80.5%) from the PARSIFAL study were included in this analysis, involving 32 of the 47 original sites. Pts signed a new informed consent form according to local regulations. Demographic and baseline disease characteristics were similar between the PARSIFAL-LONG and the overall PARISFAL intention-to-treat populations. At the time of analysis, after a median follow up of 5.0 years (range, 0.1-7.3), 241 and 213 events were reported for PFS and OS, respectively. No differences in efficacy were observed between treatment arms whether for PFS (hazard ratio, 1.0, p=0.985) or OS (hazard ratio, 0.94, p=0.635). In accordance with the protocol for PARSIFAL-LONG, both arms were combined for subsequent analysis. The median PFS (mPFS) for the first-line PAL-based regimen population was 33.2 mo (95%CI, 27.7-39.5), with a median OS (mOS) of 65.4 mo (95%CI, 57.8-72.0). A total of 86 pts (22.1% of the population) had a mPFS time <12 mo (early progressors). mOS and mPFS for this early progressor subgroup were 24.0 mo (95%CI, 17.3-30.1) and 7.0 mo (95%CI, 5.6-8.3), respectively, and only 11 pts (12.8%) were still alive at the time of analysis. The remaining 303 pts (77.9%) were progression-free on PAL-based regimens at 12 mo (PFS≥12). The number of events for PFS and OS at this time were 165 (54.5%) and 138 (45.5%), respectively. mOS from randomization for the PFS≥12 subgroup was 81.5 mo (95%CI, 70.2-not achieved) and the mPFS was 49.8 mo (95%CI, 40.9-59.8). Following progression on PAL-based regimens, the PFS≥12 criteria was a strong predictor for mOS, with 27.0 vs 18.0 mo (hazard ratio, 0.67, 95%CI, 0.51-0.90, p=0.007) for PFS≥12 and early progressors, respectively. These differences may increase in the future, as 54.5% of pts with PFS≥12 are still alive compared to 12.8% ofpts with an early progression.

Conclusions: Extended follow-up analysis from PARSIFAL study confirms no major differences between LET or FUL when combined with PAL. mPFS and mOS results are consistent with those reported in other first-line trials involving different CDK4/6i. Progression within the first year of first-line CDK4/6i-based regimen for HR+/HER2- ABC pts may be prognostic of less favorable outcomes.

Dynamics and type of ESR1 mutations under aromatase inhibitor or fulvestrant combined with palbociclib after randomization in the PADA-1 trial.

Author: Luc Cabel
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1002-1002.

Background: In PADA-1, ER+ HER2- metastatic breast cancer patients who displayed a rising ESR1 mutation in blood (bESR1mut) during a first-line therapy with aromatase inhibitor (AI) and palbociclib were randomized between keeping the same treatment or switching to fulvestrant (FUL) and palbociclib (PAL) (Bidard, Lancet Oncol 2022). In this analysis, we investigated the kinetics of bESR1mut after randomization, under AI+PAL or FUL+PAL.

Methods: Patients who had a rising bESR1mut detected and no synchronous disease progression underwent further serial ctDNA analyses at randomization and then every 2 months until disease progression. ctDNA analysis at randomization, i.e. before any change in endocrine therapy, was intended to study the impact of sampling fluctuations – since rising bESR1mut levels were often close to the limit of detection of the assay. bESR1mut detection was performed with droplet digital PCR (Jeannot, Oncogene 2020), while left over samples were subjected to next-generation sequencing, which allowed for bESR1mut typing and clonality assessment (Callens, Anal Chem 2022).

Results: 172 patients were randomized in PADA-1 after having a rising bESR1mut and no synchronous disease progression. In these patients, bESR1mut had a median mutant allelic frequency of 0.8 % (range 0.1-25.8%) and a median copy number of 14 copies/ml of plasma (4-1033) on the "rising" sample, with no imbalance between randomization arms. Among them, N=75 (46.6%) had no bESR1mut detected at the repeat blood sample at randomization. Of note, these patients had a lower level of bESR1mut at "rising" compared to those who remained bESR1mut+ at randomization (p=0.01). After treatment start, patients who were switched to FUL+PAL experienced a higher rate of bESR1mut

clearance at 2 months, compared to those remaining on AI (70.9% vs 32.8%, p<0.001). bESR1mut clearance at 2 months was associated with longer PFS (HR=0.36 95%CI=[0.25;0.52], p<0.001). The length of bESR1mut clearance was also longer in patients randomized to FUL (median: 7.3 mo 95%CI=[3.7;11.2] vs 1.9 mo 95%CI=[1.8;2.3]; p<0.001). At clinical disease progression, N=62 (83%) and N=49 (73%) patients tested positive for bESR1mut in the AI and FUL arms, respectively. Mutation typing in 95 patients with available material revealed that the Y537S mutation was the most prevalent (N=36, 37.9%), while N=25 (26.3%) and N=18 (69.2%) had polyclonal bESR1mut at time of rising bESR1mut and progression, respectively. The mutation type -including Y537S- and the presence of polyclonal bESR1mut at time of rising bESR1mut did not influence patients' survival and hazard ratio between arms.

Conclusions: bESR1mut ctDNA kinetics support the clinical benefit observed in the FUL+PAL arm over the AI+PAL arm. ESR1 mutation type and clonality did not impact the benefit of the treatment

Ten-year update: NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-42 randomized trial: extended letrozole therapy in early-stage breast cancer

Author: Eleftherios P Mamounas
Citation: J Natl Cancer Inst.2023 Nov 8;115(11):1302-1309.

Background: The National Surgical Adjuvant Breast and Bowel Project B-42 trial evaluated extended letrozole therapy (ELT) in postmenopausal breast cancer patients who were disease free after 5 years of aromatase inhibitor (AI)-based therapy. Seven-year results demonstrated a nonstatistically significant trend in disease-free survival (DFS) in favor of ELT. We present 10-year outcome results.

Methods: In this double-blind, phase III trial, patients with stage I-IIIA hormone receptor-positive breast cancer, disease free after 5 years of an AI or tamoxifen followed by an AI, were randomly assigned to 5 years of letrozole or placebo. Primary endpoint was DFS, defined as time from random assignment to breast cancer recurrence, second primary malignancy, or death. All statistical tests are 2-sided.

Results: Between September 2006 and January 2010, 3966 patients were randomly assigned (letrozole: 1983; placebo: 1983). Median follow-up time for 3923 patients included in efficacy analyses was 10.3 years. There was statistically significant improvement in DFS in favor of letrozole compared with placebo (hazard ratio [HR] = 0.85, 95% confidence interval [CI] = 0.74 to 0.96; P = .01; 10-year DFS: placebo = 72.6%, letrozole = 75.9%, absolute difference = 3.3%). There was no difference in the effect of letrozole on overall survival (HR = 0.97, 95% CI = 0.82 to 1.15; P = .74). Letrozole statistically significantly reduced breast cancer-free interval events (HR = 0.75, 95% CI = 0.62 to 0.91; P = .003; absolute difference in cumulative incidence = 2.7%) and distant recurrences (HR = 0.72, 95% CI = 0.55 to 0.92; P = .01; absolute difference = 1.8%). The rates of osteoporotic fractures and arterial thrombotic events did not differ between treatment groups.

Conclusions: The beneficial effect of ELT on DFS persisted at 10 years. Letrozole also improved breast cancer-free interval and distant recurrences without improving overall survival. Careful assessment of potential risks and benefits is necessary for selecting appropriate candidates for ELT.

HER 2 Positive Breast Cancer

A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in older patients with metastatic HER2-positive breast cancer. (JCOG1607 HERB TEA study)

Author: A. Shimomura
Citation: SABCS 2023:RF02-04

Background: A combination of trastuzumab, pertuzumab, and docetaxel (HPD) is recommended as first-line treatment for patients with HER2-positive metastatic breast cancer. For older patients, it is difficult to maintain a relative dose intensity, which often impairs their quality of life. A new standard treatment option for older patients is required with less toxicity and non-inferior efficacy compared to HPD.

Methods: The eligibility criteria were as follows: age 65 years and older, HER2-positive metastatic breast cancer, no previous systemic treatment with chemotherapy and anti-HER2 targeted drugs, ECOG PS 0–2 for 65–74 years or 0–1 for 75 years or older, and adequate organ function. Treatment consisted of trastuzumab emtansine (T-DM1) 3.6 mg/kg every 3 weeks or HPD (trastuzumab 8 mg/kg, then 6 mg/kg, pertuzumab 840 mg, then 420 mg/body, and docetaxel 60 mg/m^2, could be escalated to 75 mg/m^2 if there were no unmanageable toxicity) every 3 weeks after a 1:1 ratio randomization. The trial was designed to achieve 70% power to confirm the non-inferiority of T-DM1 to HPD at a one-sided alpha of 5% with a non-inferiority margin of 1.35 in terms of the hazard ratio (HR) for overall survival (OS) as the primary endpoint. With a median OS of 30 months in both arms, 6.5 years of accrual, and 5 years of follow-up, the planned sample size was 250. Secondary endpoints were progression-free survival (PFS), response rate (RR), adverse events, cumulative breast cancer-specific mortality (BCSM), safety, and deterioration of activities of daily living. (Clinical Trial Information: UMIN000030783).

Results: In total, 148 patients were enrolled between January 2018 and March 2023. A total of 135 patients were assessed in the preplanned first interim analysis. The median patient age was 72 years (range 65-88) in the T-DM1 arm and 71 (65-84) in the HPD arm. The proportion of estrogen receptor-positive (10%) patients was well balanced between both arms (49.3 and 55.6%, respectively). Of these patients, 64.8% had stage IV disease and 35.2% had recurrent disease. T-DM1 was not non-inferior to HPD (HR 1.487; 99.9% CI, 0.288 to 7.678) in terms of OS. The median PFS was 9.8 months in the TDM1 arm and 18.4 months in the HPD arm (HR 1.749; 95%CI, 1.124-2.723). Response rates were lower in the T-DM1 arm than that of the HPD arm (52.7% [95% CI, 38.8-66.4] and 76.8% [95% CI, 63.6-87.0], respectively) (p=0.099). BCSM was higher in the T-DM1 arm than that of the HPD arm (HR 1.617; 95% CI, 0.764-3.425). Grade 3 and higher neutropenia were less common in the T-DM1 arm than in the HPD arm (0 vs. 30.4%); however, thrombocytopenia was more common in the T-DM1 arm than in the HPD arm (16.9 vs. 0%). Grade 3 or more nonhematological adverse events were less common and lower in the T-DM1 arm (35.2%) than in the HPD arm (58.6%), including fatigue (5.6% vs. 22.9%), diarrhea (0% vs. 11.4%), appetite loss (8.5% vs. 11.4%), and febrile neutropenia (0% vs. 10.0%), which reduced the quality of life in older patients with HER2-positive metastatic breast cancer.

Conclusion: T-DM1 was not non-inferior to HPD in terms of OS. However, T-DM1 showed better tolerability in terms of frequency and severity of adverse events. HPD will continue to be the standard of care as the first-line treatment for older patients with HER2-positive metastatic breast cancer. Older patients with breast cancer have heterogeneous health conditions. A subset analysis according to age or geriatric assessment may identify the subpopulation of older patients with HER2- positive metastatic breast cancer for whom T-DM1 is an optional treatment.

A Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab in Hormone Receptor (HR)-Positive, HER2-Positive Metastatic Breast Cancer (ASPIRE)

Author: R. Patel
Citation: SABCS 2023:RF02-01

Background: Among patients (pts) with HR-positive and HER2-positive breast cancer, crosstalk between HER2 and estrogen receptor (ER) signaling pathways may contribute to endocrine resistance but anti-HER2 agents in combination with endocrine therapy can restore endocrine sensitivity. Mechanistically, HER2/HER3 signaling promotes survival by way of PI3K-AKT activation whereas ER-CDK4/6-Rb signaling promotes cell cycle progression. The combination of anti-HER2 therapy with an aromatase inhibitor (AI) and a CDK 4/6 inhibitor would allow for blockade of both pathways and provide a novel, all biologic, and chemotherapy-free approach to the treatment of HR-positive, HER2-positive metastatic breast cancer (MBC).

Methods: We conducted a phase I/II multi-institution trial in pts with previously untreated, HR-positive and HER2-positive MBC. In the Phase I portion, pts received escalating doses of palbociclib (100mg, 125mg) in conjunction with trastuzumab, pertuzumab and an AI anastrozole, using a 3+3 dose escalation trial design. In the phase II portion, pts received palbociclib at the maximum tolerated dose (MTD), anastrozole, trastuzumab, and pertuzumab. The primary endpoints of the Phase I and II portions were MTD and clinical benefit rate (CBR) defined as the sum of complete response, partial response, and stable disease for >/= 6 months, respectively. Secondary endpoints included progression free survival (PFS), objective response rate (ORR) and safety. The Phase II portion of this study was powered with 30 pts to show efficacy of palbociclib administered at the MTD in combination with anastrozole, trastuzumab and pertuzumab if the CBR achieved at 6 months exceeded 58%. The Clopper-Pearson method was used to calculate confidence intervals for ORR and CBR. The PFS distribution was estimated using the Kaplan-Meier method.

Results: In the Phase I portion, a total of 9 pts were enrolled. No DLTs were observed at the 100mg dose (N=3) or the 125mg dose (N=6) level, and thus, 125mg was established as the MTD. An additional 24 pts were enrolled to the Phase II portion at the MTD, with a total of 30 pts in the modified intention-to-treat population included in the efficacy analysis. The median age of the population was 57.6 years (range 50.5-63.8) and 27% of pts were premenopausal and received ovarian function suppression as part of treatment. As shown in Table 1, the primary endpoint, CBR, was 97% (95% CI: 0.83-1.0, p<0.0001). ORR was 70% (95% CI: 0.51-0.85). Median time to objective response was 2.8 months with earliest response at 3 months. Median duration of response was not reached with range of 5.1-42.2 months. Median PFS was also not reached with range of 8-44.8 months. Safety data were consistent with known toxicity profiles of agents. Most common adverse events included diarrhea (80%), neutropenia (77%), leukopenia (70%), anemia (67%), and fatigue (60%). Grade 3-4 events occurred in 63% (19/30) of pts and included neutropenia (68%), leukopenia (32%), decrease in absolute neutrophil count (21%), and anemia (21%).

Conclusions: The combination of anastrozole, palbociclib, trastuzumab, and pertuzumab was well tolerated and effective with a clinical benefit rate of 97% in pts with previously untreated HR-positive, HER2-positive MBC. The combination provides a chemotherapy-free alternative for pts with triple positive breast cancers. Further follow up will determine impact on PFS

Table 1. Results in Patients on Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab

Table 1. Results in Patients on Anastrozole, Palbociclib, Trastuzumab, and Pertuzumab

Outcome	Patient Population (N=30) % (N)
Clinical benefit rate, % [CI]	97% [83%, 100%]
Objective response rate, % [CI]	70% [51%, 85%]
Complete Response	7% (2)
Partial Response	63% (19)
Stable Disease	27% (8)
Progressive Disease	0% (0)
Unevaluable[1]	3% (1)

[1]Unevaluable patients treated as non-responders in CBR and ORR calculations.

HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer

Author: S. Hurvitz.
Citation: SABCS 2023:GS01-10

Background: Tucatinib is a highly selective HER2-directed tyrosine kinase inhibitor approved in combination with trastuzumab and capecitabine for previously treated HER2+ locally advanced or metastatic breast cancer (LA/MBC). Trastuzumab emtansine (T-DM1) is a HER2-directed antibody-drug conjugate approved to treat HER2+ LA/MBC previously treated with trastuzumab and a taxane. This is the first report of HER2CLIMB-02 (NCT03975647), a randomized, double-blind, placebo-controlled phase 3 study assessing the efficacy and safety of tucatinib combined with T-DM1 in patients with previously treated HER2+ LA/MBC.

Methods: Eligible patients had HER2+ LA/MBC previously treated with trastuzumab and a taxane in any setting with ECOG performance status ≤1 and adequate hepatic, renal, hematologic, and cardiac function. Patients with previously treated stable, progressing, or untreated brain metastases (BMs) not requiring immediate local therapy were also eligible. Patients were randomly assigned 1:1 to receive 21-day cycles of either tucatinib (300 mg orally twice a day [PO BID]) or placebo (PO BID), combined with T-DM1 (3.6 mg/kg intravenously every 3 weeks). The primary endpoint was progression-free survival (PFS) by investigator assessment per RECIST v1.1. Alpha-controlled secondary endpoints included overall survival (OS) and objective response rate (ORR) per RECIST v1.1 for the overall population, and PFS and OS for the subset of patients with BMs at baseline. Safety was analyzed as a secondary endpoint.

Results: From October 8, 2019, to June 16, 2022, 463 patients were randomly assigned, comprising 228 to the tucatinib arm (tucatinib + T-DM1) and 235 to the control arm (placebo + T-DM1). The median duration of follow-up (OS) was

24.4 months for the overall population. Patient demographics and baseline characteristics were balanced between the 2 arms. Almost half (44.1%) of the overall population had either active or stable BMs at baseline. As of the data cutoff (June 29, 2023), the study met its primary endpoint with a statistically significant improvement in PFS in the tucatinib arm vs control arm. The risk of progression or death decreased by 24.1% in the tucatinib arm (hazard ratio [HR]=0.759 [95% CI, 0.607-0.950]; P=0.0163). Median PFS was 9.5 months (95% CI, 7.4-10.9) vs 7.4 months (95% CI, 5.6-8.1) for the tucatinib and control arms, respectively. HRs for PFS across all prespecified subgroups were consistent with the HR of the overall population, including patients with BMs at baseline (HR=0.639 [95% CI, 0.459-0.891]). The interim OS results were immature with 134 of 253 total required events (53%) and did not meet the prespecified crossing boundary. The confirmed ORR was numerically higher in the tucatinib arm (42.0%) vs the control arm (36.1%). The most common treatment-emergent adverse events (TEAEs) included nausea (65.4% vs 49.4% for tucatinib and control arms, respectively), diarrhea (56.7% vs 26.6%), and fatigue (48.9% vs 37.3%). The most common grade ≥3 TEAEs in the tucatinib arm were alanine and aspartate aminotransferase elevations, each reported in 38 patients (16.5%) in the tucatinib arm and 6 patients (2.6%) in the control arm. TEAEs associated with any treatment discontinuation occurred in 51 patients (22.1%) in the tucatinib arm and 27 (11.6%) in the control arm. TEAEs leading to deaths occurred in 3 patients (1.3%) in the tucatinib arm and 2 patients (0.9%) in the control arm.

Conclusion: HER2CLIMB-02 demonstrated that the addition of tucatinib to T-DM1 significantly improved median PFS in patients with previously treated HER2+ LA/MBC, including those with BMs. Although discontinuations due to TEAEs were more common in the tucatinib arm, no new safety signals emerged for the combination therapy.

A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03

Author: Sara Hurvitz
Citation: Annals of Oncology (2023) 34 (suppl_2): S334-S390.

Background: T-DXd is approved for treatment of pts with HER2+ unresectable or mBC who have received ≥1 prior anti-HER2-based regimens. We report exploratory pooled efficacy and safety data of T-DXd vs comparator (comp) in pts from DB-01, DB-02, and DB-03 with treated/stable (treated) and untreated/active (untreated; from DB-02/-03) BMs at baseline, as defined by the US FDA (FDA 2020).

Methods: DB-01/-02 enrolled pts who were resistant/refractory to trastuzumab emtansine (T-DM1); DB-03 included pts previously treated with trastuzumab and taxane. T-DXd data and ad hoc exploratory intracranial analyses were pooled from DB-01/-02/-03. Comp data, physician's choice chemotherapy and T-DM1, were pooled from DB-02 and -03, respectively. Endpoints were intracranial (IC) objective response rate (ORR; complete [CR] or partial response [PR] in brain) per blinded independent central review (BICR) by RECIST, IC duration of response (DoR), central nervous system-progression-free survival (CNS-PFS) by BICR, and safety.

Results: Of the 148 pts with BMs at baseline who received T-DXd, 104 (70.3%) had treated and 44 (29.7%) had untreated BMs. Pts had a median of 3 (range, 1.0-14.0) prior regimens in the metastatic setting. Median treatment duration was 12.7 mo (range, 0.7-45.1) with T-DXd and 5.6 mo (range, 0.1-43.0) with comp. Efficacy data are in the Table. Any-grade drug-related treatment-emergent adverse events (TEAEs), drug-related grade ≥3 TEAEs, and serious drug-related AEs were observed in 94.5%, 43.2%, and 13.0% of pts with T-DXd, vs 94.0%, 36.1%, and 7.2% with comp, respectively.

Conclusions: T-DXd exhibited robust IC responses in pts with treated and, notably, untreated BMs vs comp. Although pt numbers were small and not statistically tested, numerically longer median IC-DoR and CNS-PFS were observed in pts with untreated BMs with T-DXd. Safety was acceptable and generally manageable with T-DXd. Table: 377O

IC efficacy summary

	T-DXd (N = 148)		Comp (N = 83)	
	Treated/stable BMs (n = 104)	Untreated/active BMs (n = 44)	Treated/stable BMs (n = 58)	Untreated/active BMs (n = 25)
Best overall IC response, n (%)				
CR	17 (16.3)	7 (15.9)	2 (3.4)	0
PR	30 (28.8)	13 (29.5)	14 (24.1)	3 (12.0)
Stable disease	48 (46.2)	15 (34.1)	28 (48.3)	15 (60.0)
Progressive disease	3 (2.9)	1 (2.3)	7 (12.1)	5 (20.0)
NE	4 (3.8)	5 (11.4)	1 (1.7)	2 (8.0)
Missing	2 (1.9)	3 (6.8)	6 (10.3)	0
IC-ORR (CR + PR in brain), n (%)	47 (45.2)	20 (45.5)	16 (27.6)	3 (12.0)
IC-DoR, median, mo (95% CI)	12.3 (9.1-17.9)	17.5 (13.6-31.6)	11.0 (5.6-16.0)	2.8 (2.7-NE)
CNS-PFS, median (95% CI)	12.3 (11.1-13.8)	18.5 (13.6-23.3)	8.7 (6.3-11.8)	4.0 (2.7-5.7)

NE, not evaluable.

Re-Evaluation of Pathologic Complete Response as a Surrogate for Event-Free and Overall Survival in Human Epidermal Growth Factor Receptor 2-Positive, Early Breast Cancer Treated With Neoadjuvant Therapy Including Anti-Human Epidermal Growth Factor Receptor 2 Therapy

Authors: Pierre Squifflet
Citation: J Clin Oncol.2023 Jun 1;41(16):2988-2997.

Purpose: Pathologic complete response (pCR) has prognostic importance and is frequently used as a primary end point, but doubts remain about its validity as a surrogate for event-free survival (EFS) and overall survival (OS) in human epidermal growth factor receptor 2 (HER2)-positive, early breast cancer.

Methods: We obtained individual-patient data from randomized trials of neoadjuvant anti-HER2 therapy that enrolled at least 100 patients, had data for pCR, EFS, and OS, and a median follow-up of at least 3 years. We quantified the patient-level association between pCR (defined as ypT0/Tis ypN0) and both EFS and OS using odds ratios (ORs, with ORs >1.00 indicating a benefit from achieving a pCR). We quantified the trial-level association between treatment effects on pCR and on EFS and OS using R2 (with values above 0.75 considered as indicating strong associations).

Results: Eleven of 15 eligible trials had data for analysis (3,980 patients, with a median follow-up of 62 months). Considering all trials, we found strong patient-level associations, with ORs of 2.64 (95% CI, 2.20 to 3.07) for EFS and 3.15 (95% CI, 2.38 to 3.91) for OS; however, trial-level associations were weak, with an unadjusted R2 of 0.23 (95% CI, 0 to 0.66) for EFS and 0.02 (95% CI, 0 to 0.17) for OS. We found qualitatively similar results when grouping trials according to different clinical questions, when analyzing only patients with hormone receptor-negative disease, and when using a more stringent definition of pCR (ypT0 ypN0).

Conclusion: Although pCR may be useful for patient management, it cannot be considered as a surrogate for EFS or OS in neoadjuvant trials of HER2-positive, operable breast cancer.

Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti-Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer

Author: Marion T van Mackelenbergh
Citation: J Clin Oncol. 2023 Jun 1;41(16):2998-3008.

Purpose: The achievement of pathologic complete response (pCR) is strongly prognostic for event-free survival (EFS) and overall survival (OS) in patients with early breast cancer (EBC), and adapting postneoadjuvant therapy improves

long-term outcomes for patients with HER2-positive disease not achieving pCR. We sought to investigate prognostic factors for EFS and OS among patients with and without pCR after neoadjuvant systemic treatment consisting of chemotherapy plus anti-HER2 therapy.

Materials and methods: We used individual data from 3,710 patients randomly assigned in 11 neoadjuvant trials for HER2-positive EBC with ≥100 patients enrolled, available data for pCR, EFS, and OS, and follow-up ≥3 years. We assessed baseline clinical tumor size (cT) and clinical nodal status (cN) as prognostic factors using stratified (by trial and treatment) Cox models separately for hormone receptor-positive versus hormone receptor-negative disease, and for patients who had pCR (pCR+; ypT0/is, ypN0) versus patients who did not achieve a pCR (pCR-).

Results: The median follow-up overall was 61.2 months. In pCR+ patients, cT and cN were significant independent prognostic factors for EFS, whereas only cT was a significant predictor for OS. In pCR- patients, cT, cN, and hormone receptor status were significant independent predictors for both EFS and OS. Regardless of hormone receptor status, cT, and cN, the 5-year EFS/OS rates were higher in pCR+ patients than in pCR- patients. In most subsets with regards to hormone receptor and pCR status, cT and cN were independent prognostic factors for both EFS and OS, including pCR+ patients.

Conclusion: These results confirm that patients achieving pCR have far better survival outcomes than patients who do not. The traditional poor prognostic features, namely tumor size and nodal status, remain important even after a pCR.

Pyrotinib versus placebo in combination with trastuzumab and docetaxel as first line treatment in patients with HER2 positive metastatic breast cancer (PHILA): randomised, double blind, multicentre, phase 3 trial

Author: Fei Ma
Citation: BMJ 2023;383:e076065

Objective: To assess the efficacy and safety of pyrotinib (an irreversible pan-HER (human epidermal growth factor receptor) inhibitor), trastuzumab, and docetaxel compared with placebo, trastuzumab, and docetaxel for untreated HER2 positive metastatic breast cancer.

Design: Randomised, double blind, placebo controlled, multicentre, phase 3 trial. Setting 40 centres in China between 6 May 2019 and 17 January 2022.

Participants: 590 female patients (median age 52 (interquartile range 46-58) years) with untreated HER2 positive metastatic breast cancer.

Interventions: Eligible patients were randomised 1:1 to receive either oral pyrotinib (400 mg once daily) or placebo, both combined with intravenous trastuzumab (8 mg/kg in cycle 1 and 6 mg/kg in subsequent cycles) and docetaxel (75 mg/m^2) on day 1 of each 21 day cycle. Randomisation was stratified by treatment history of trastuzumab in the (neo)adjuvant setting and hormone receptor status. Patients, investigators, and the sponsor's study team were masked to treatment assignment.

Main outcome measures: The primary endpoint was progression-free survival as assessed by the investigator.

Results: Of the 590 randomised patients, 297 received pyrotinib, trastuzumab, and docetaxel treatment (pyrotinib group), and 293 received placebo, trastuzumab, and docetaxel treatment (placebo group). At data cut-off on 25 May 2022, the median follow-up was 15.5 months. The median progression-free

survival according to the investigator was significantly longer in the pyrotinib group than in the placebo group (24.3 (95% confidence interval 19.1 to 33.0) months versus 10.4 (9.3 to 12.3) months; hazard ratio 0.41 (95% confidence interval 0.32 to 0.53); one sided P<0.001). Treatment related adverse events of grade 3 or higher were reported in 267 (90%) of the 297 patients in the pyrotinib group and 224 (76%) of the 293 patients in the placebo group. No treatment related deaths occurred in the pyrotinib group, and one (<1%; diabetic hyperosmolar coma) treatment related death occurred in the placebo group. Survival and toxicities are still under assessment with longer follow-up.

Conclusions: Pyrotinib, trastuzumab, and docetaxel showed superiority by significantly improving progression-free survival compared with placebo, trastuzumab, and docetaxel in patients with untreated HER2 positive metastatic breast cancer. The toxicity was manageable. The findings support this dual anti-HER2 regimen as an alternative first line treatment option in this patient population.

Type of adjuvant endocrine therapy and disease-free survival in patients with early HR-positive/HER2-positive BC: analysis from the phase III randomized ShortHER trial

Author: Maria Vittoria Dieci
Citation: NPJ Breast Cancer 9, 6 (2023).

The optimal adjuvant endocrine therapy for HR-positive/HER2-positive breast cancer patients is unknown. We included in this analysis 784 patients with HR-positive/HER2-positive BC from the randomized ShortHER trial of adjuvant trastuzumab (1 year vs 9 weeks) + chemotherapy. At a median follow-up of 8.7 years, patients who received AI had a significantly better DFS vs patients who received TAM or TAM-AI: 8-yr DFS 86.4 vs 79.7%, log-rank P = 0.013 (HR 1.52, 95% CI 1.09–2.11). In multivariate analysis, the type of endocrine therapy maintained a significant association with DFS (HR 1.64, 95% CI 1.07–2.52, p = 0.025 for TAM/TAM-AI vs AI). Among premenopausal patients aged ≤45

years, the use of GnRHa was associated with longer DFS: 8-yr DFS rate 85.2 vs 62.6% (log-rank p = 0.019, HR 0.41, 95% CI 0.19–0.88). In this post-hoc analysis of the ShortHER trial adjuvant treatment with AI was independently associated with improved DFS. Subgroup analysis in premenopausal patients suggests benefits with ovarian suppression.

Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial.

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Author: Pier Franco Conte
Citation: Journal of Clinical Oncology 41, no. 17_suppl (June 10, 2023) LBA637-LBA637.

Background: The ShortHER trial is a phase III non-inferiority, randomized trial comparing 9 weeks (short arm) versus 1 year (long arm) of adjuvant trastuzumab combined with chemotherapy in HER2+ eBC patients. The first primary end point of the study was the event-driven analysis of disease-free survival which was achieved in 2017, presented at ASCO 2017 and published in Annals of Oncology in 2018. The HR was 1.13 (90% CI 0.89-1.42) and the non-inferiority could not be claimed as the upper border of CI crossed the upper limit of 1.29 chosen as non-inferiority margin. According to a pre-planned Bayesian analysis, the probability that the short arm was not inferior to the standard one was 80%.

Methods: 1254 HER2+ early breast cancer patients were stratified according to nodal status and randomized. Median age was 55 years (range 25-78); 672 (54%) patients were node negative, 383 (30%) with 1-3 positive nodes, 198 (16%) 4 or more positive nodes. At the time of the event-driven analysis, median follow up was 6 years, 200 DFS events and 78 deaths were reported. Here we report the overall survival,+ which was the second co-primary end point, updated DFS and outcomes according to nodal status.

Results: Median follow-up is now 9 years, 248 DFS events and 116 deaths have been reported. The 10 year DFS is 77% in the long arm and 78% in the short

arm (HR 1.06; 90% CI 0.86-1.31). The 10-year OS is 89% in the long arm and 88% in the short arm (HR 1.15; 90% CI 0.85-1.56). The DFS and OS data overall and by nodal status are summarized in the table below.

Conclusions: At a median follow-up of 9 years, the ShortHER trial shows that 1 year trastuzumab is still the standard treatment for HER2+ eBC patients as non-inferiority cannot be claimed in terms of DFS or OS. Numerically however, the differences for the patients at low risk (N0) or intermediate risk (N 1-3) is negligible and patients with 4 or more positive lymph nodes have a clear benefit with 1 year trastuzumab. I. This long-term date can reassure clinicians if, for any reason a patient at low/intermediate risk has to stop trastuzumab and, more important, might facilitate access to a far less expensive treatment to the thousands of patients worldwide who cannot afford the cost of one year of trastuzumab

	10-y Disease-Free Survival			10-y Overall Survival		
Subgroups (n)	Long	Short	HR (90% CI)	Long	Short	HR (90% CI)
ITT (1,254)	77 %	78 %	1.06 (0.86-1.31)	89 %	88 %	1.15 (0.85-1.56)
N0 (672)	81 %	85 %	0.74 (0.54-1.04)	89 %	95 %	0.57 (0.33-0.99)
N 1-3 (383)	77 %	79 %	1.11 (0.76-1.64)	92 %	89 %	1.37 (0.77-2.44)
N > 4 (198)	63 %	53 %	1.84 (1.24-2.75)	84 %	64 %	1.87 (1.11-3.14)

Pertuzumab plus high-dose trastuzumab for HER2-positive breast cancer with brain metastases: PATRICIA final efficacy data

Author:Nancy U. Lin
Citation: NPJ Breast Cancer. 2023 Nov 17;9(1):94.

The PATRICIA study (NCT02536339) examined the efficacy and safety of pertuzumab plus high-dose trastuzumab in patients with HER2-positive metastatic breast cancer (MBC) with progressive central nervous system (CNS) metastases following radiotherapy. Primary analysis confirmed CNS objective response rate (ORR) was 11% (95% confidence interval [CI]: 3–25); clinical benefit rate (CBR) was 68% (4 months) and 51% (6 months). We report final efficacy data after a further 21-months of follow-up, updated safety, survival, and patient-reported outcomes (PROs). Patients received standard-dose pertuzumab plus high-dose trastuzumab (6 mg/kg weekly) until CNS or systemic disease progression or unacceptable toxicity. Primary endpoint: confirmed ORR (CNS) per Response Assessment in Neuro-Oncology Brain Metastases criteria. Secondary endpoints were response duration, CBR, progression-free survival (PFS), overall survival (OS), safety, and PROs. By clinical cut-off, 39 patients had completed or discontinued treatment. Confirmed ORR (CNS) was 11% (95% CI: 3.0–25.4). Median CNS-PFS was 4.6 months (95% CI: 4.0–8.9), as was median CNS-PFS or systemic PFS (95% CI: 4.0–8.9); median OS was 27.2 months (95% CI: 16.1–not reached). CBR in the CNS was 51% (19 patients, 95% CI: 34.4–68.1) at 6 months. Two patients remained on treatment until study closure, achieving stable disease for 4.1 and 4.8 years. Treatment-related grade 3/4 adverse events occurred in 7.7% of patients. Patients with confirmed partial response or stable disease (≥4 months) in the CNS had stable PROs over time. Pertuzumab plus high-dose trastuzumab represents a reasonable non-chemotherapeutic treatment option for selected patients with HER2-positive MBC with CNS metastases.

HER2-low status discordance between primary and recurrent/metastatic breast cancer in a large-scale cohort.

Author: Mingxi Lin
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1021-1021

Background: Trastuzumab deruxtecan (T-DXd) was recently approved to treat unresectable/metastatic HER2-low breast cancer. However, patients whose primary tumor is HER2-0 but recurrent/metastatic lesion is HER2-low will lose therapeutic opportunities for T-DXd if a rebiopsy is not performed. In this study, with the largest sample size to date, we aimed to investigate the prevalence of HER2 status conversion. Moreover, it remains debated whether HER2-0 and HER2-low tumors have different prognoses, probably because previous studies did not assess HER2 status entirely based on recurrent/metastatic lesions. Our study aimed to fill this gap.

Methods: We included 1299 patients with available HER2 status on both primary tumors and recurrent/metastatic lesions at Fudan University Shanghai Cancer Center and West China Hospital.

Results: A total of 370 (28.5%) patients experienced HER2 status conversion throughout disease recurrence. 144 (31.7%) HER2-0 tumors converted to HER2-low. Inter-metastases heterogeneity of HER2 status was also observed. Compared to HER2-low tumors, HER2-0 tumors showed a higher TP53 mutation rate in the ER-positive subgroup, and a lower PIK3CA mutation rate in the ER-negative subgroup. Patients with tumors converting from HER2-0 to HER2-low had a longer overall survival (HR = 0.59, adjusted P = 0.033) than those with consistent HER2-0 status in the ER-negative subgroup. By combining four risk factors (ER status, Ki67 index, biopsy site, and disease-free interval), we established the first prediction tool to estimate the probability of HER2 status conversion from HER2-0 to HER2-low/positive.

Conclusions: HER2 status was unstable during the disease course. Our prediction tool could help to screen out patients with a high probability of HER2 status conversion. Our results support that HER2-0 and HER2-low recurrent/metastatic tumors have different genomic features and prognoses

Efficacy of tucatinib+trastuzumab+capecitabine (TTC) after trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer: A French multicentre retrospective study.

Author: Jean-Sebastien Frenel
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1014-1014.

Background: Recent guidelines have positioned T-DXd as a preferred treatment in the second line setting for HER2+ metastatic breast cancer (MBC). TTC is the preferred treatment in third line, however little is known on the efficacy of this combination after T-DXd exposure.

Methods: We conducted a retrospective study in 12 French comprehensive cancer centers. All patients with HER2+ MBC treated with TTC after prior exposure to T-DXd were included. The primary end point was progression-free survival (PFS) in the whole population. Secondary end-points included overall survival (OS), PFS in subgroups and objective response rate.

Results: Between 08/2020 and 12/2022, 101 patients were included. Median age was 56.4 y.o. (range 30.8 - 84.8). Median number of prior line of treatment for metastatic disease at TTC start was 4 (2 - 15). 82% and 95% of patients had received previous pertuzumab and T-DM1 respectively. The median duration of previous exposure to T-DXd was 8.9 months (1.4 - 31.4) and 82/101 (81%) patients had progressed under T-DXd while 19 had stopped T-DXd for toxicity or other reasons. TTC regimen was given as a 3rd line or 4th line for metastatic disease in 37/101 (37%) and beyond for the remaining patients. TTC was the immediate subsequent therapy to T-DXd for 86/101 pts (85%). With a median follow-up of 8.5 m (95%CI [7.7; 9.4]), 68/101pts (67%) have stopped TTC for progressive disease. Median PFS was 4.7 m (95%CI [3.8; 5.6]) and median OS

not reached (95%CI [10.6; NA]) in the whole population. Patients treated with TTC as the immediate subsequent therapy to T-DXd, had a median PFS of 5.0 m (95%CI [4.0; 6.0]) and a median OS not reached (95%CI [11.9; NA]). Best response to TTC, evaluated by investigators in the 87/101 RECIST evaluable patients, was progressive disease, stable disease, partial response and complete response in 34%, 34%, 30% and 2% of patients respectively. At TTC initiation, 39 (39%) of patients had known brain metastases. Out of the 62 patients without known brain metastases at the initiation of TTC, 2 had brain metastases documented as a site of progression during TTC.

Conclusions: In this large retrospective cohort, TTC shows significant efficacy for patients with HER2+ MBC previously exposed to T-DXd. Data and subgroup analyses will be updated for the meeting.

Do tumor infiltrating lymphocytes (TILs) predict benefits from trastuzumab therapy for HER2 positive breast cancer? Meta-analysis of individual patient data from 4097 women in 5 trials.

Author: Robert Kerrin Hills
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 508-508

Background: High TIL counts are associated with a lower risk of breast cancer recurrence, especially in women with ER negative, HER2 negative tumors and, possibly, greater benefit from trastuzumab in women with HER2 positive cancer: the FinHER trial reported a differential effect of trastuzumab based upon TIL status. We performed a meta-analysis of randomized trials of trastuzumab in early breast cancer to attempt to validate this finding.

Methods: TILs were quantified in 4097 women in 5 randomized controlled trials (NSABP B-31, FinHER, HERA, Intergroup N9831, PACS-04). All trials contributed to the Early Breast Cancer Trialists' Collaborative Group individual patient data meta-analysis of trastuzumab for women with HER2 positive tumors which found a significant benefit for trastuzumab therapy. TILs were assessed using established International Guidelines, with HERA using digital

TIL-scores. The primary outcome was time to first recurrence. Cox regression analyses, adjusted for trial, treatment allocation, and nodal status, were used to quantify the prognostic value of TILs; and standard stratified logrank tests were used to assess the differential effect of trastuzumab therapy.

Results: The median percentage TILs was 13% (Interquartile Range 5-30), with fewer than 10% of patients exhibiting TILs >50%. The prognostic value of TILs was confirmed, with patients with higher TILs being at lower risk for recurrence (adjusted hazard ratio per 10% increase in TILs 0.87 (95% CI 0.84-0.90), p<.0001) with similar effects in both treatment groups. Outcomes improved steadily with increasing TILs, and unadjusted 10-year recurrence rates fell from 30% in women with TILs <10% to 15% in those with TILs 70% or greater. Consequently, analyses of the predictive effect of TILs were stratified into 5 groups (0-9, 10-19, 20-39, 40-59, 60+). Overall, there was a highly significant benefit of trastuzumab on recurrence (HR 0.62 (0.54-0.70) p<.0001), but there was no evidence of any interaction between TILs and the proportional reduction in recurrence (p=0.8 for heterogeneity and trend).

Conclusions: While higher TILs are associated with lower recurrence rates, there was no indication that the proportional reduction in recurrence with trastuzumab varied by TILs, although the number of patients with high levels was limited. Owing to a lower underlying recurrence rate, absolute benefits from trastuzumab were lower, but still substantial, in women with high TIL tumors.

Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis

Author: S. Loibl
Citation: SABCS 2023:GS03-12

Background: Patients with HER2-positive early breast cancer (EBC) who have residual invasive disease after neoadjuvant chemotherapy + HER2-targeted therapy have a high risk of recurrence and death. The standard of care when KATHERINE was designed was continuation of the same HER2-targeted therapy in the adjuvant setting for 1 year. The primary analysis of KATHERINE in 2018 showed that the risk of recurrence of invasive BC or death was 50% lower with adjuvant ado-trastuzumab emtansine (T-DM1) than with trastuzumab.

Methods: KATHERINE (NCT01772472/BO27938/NSABP B-50-I/GBG 77) is a phase III, open-label, global study of patients with centrally confirmed, HER2-positive (immunohistochemistry 3+ or in situ hybridization-positive) primary BC (T1–4, N0–3, M0) who received neoadjuvant chemotherapy + HER2-targeted therapy, which had to include a taxane and trastuzumab, followed by surgery, with pathologically documented residual invasive disease in the breast and/or axillary lymph nodes. Within 12 weeks of surgery, patients were randomized 1:1 to T-DM1 (3.6 mg/kg intravenously [IV] every 3 weeks [q3w]) or trastuzumab (6 mg/kg IV q3w) for 14 cycles. Randomization was stratified by clinical stage at presentation, hormone receptor status, single vs dual neoadjuvant HER2-targeted therapy, and pathologic nodal status after neoadjuvant therapy. Patients received radiotherapy and/or endocrine therapy per local standards. The primary endpoint was invasive disease-free survival (IDFS). We report the final IDFS analysis, which was to occur after ~384 events had been reported, and the preplanned second interim analysis of overall survival (OS); specified to occur at the same time.

Results: With a median follow-up of 8.4 years (101 months), T-DM1 sustained the improvement in IDFS over trastuzumab (unstratified hazard ratio [HR] 0.54; 95% confidence interval [CI] = 0.44, 0.66; $p < 0.0001$). Landmark 7-year IDFS rates were increased from 67.1% with trastuzumab to 80.8% with T-DM1; a difference of 13.7%.

At clinical cutoff for the final IDFS analysis, 215 deaths had been reported. T-DM1 significantly reduced the risk of death by 34% compared with trastuzumab (unstratified HR 0.66; 95% CI = 0.51, 0.87; $p = 0.0027$). Deaths had occurred in 89/743 patients (12.0%) in the T-DM1 arm and 126/743 (17.0%) in the trastuzumab arm. Landmark 7-year OS rates were increased from 84.4% with trastuzumab to 89.1% with T-DM1; a difference of 4.7%.

OS and IDFS benefits were seen across key subgroups.

A low incidence of adverse events (AEs) related to study treatment or to study procedures was observed during the post-treatment period: Grade ≥3 related AEs occurred in 3/740 patients (0.4%) in the T-DM1 arm and 3/720 (0.4%) in the trastuzumab arm; serious related AEs, in 2/740 (0.3%) and 4/720 (0.6%), respectively. Related AEs classed as "cardiac disorders" were rare in both arms with extended follow-up.

Conclusions: After 8.4 years (101 months) median follow-up, T-DM1 significantly improved OS in patients with HER2-positive EBC with residual invasive disease after neoadjuvant therapy. The IDFS benefit of T-DM1 was sustained in the intention-to-treat population with longer follow-up, and no new safety issues emerged. Cardiac toxicity was rare in both arms. T-DM1 is the first therapy to show improved survival post-surgery in patients with HER2-positive EBC with residual invasive disease after neoadjuvant therapy. Follow-up is ongoing for the final OS analysis.

HER2 amplification level by in situ hybridization predicts survival outcome in advanced HER2-positive breast cancer treated with pertuzumab, trastuzumab, and docetaxel regardless of HER2 IHC results

Author: Jeongmin Seo
Citation: Seo et al. Breast Cancer Research (2023) 25:154.

Background: The role of HER2 amplification level in predicting the effectiveness of HER2-directed therapies has been established. However, its association with survival outcomes in advanced HER2-positive breast cancer treated with dual HER2-blockade remains unexplored.

Methods: This is a single-center retrospective study of patients with advanced HER2-positive breast cancer treated with first-line pertuzumab, trastuzumab, and docetaxel. The primary objective was to ascertain the relationship between treatment outcomes and the level of HER2 amplification by in situ hybridization (ISH).

Results: A total of 152 patients were included with a median follow-up duration of 50.0 months. Among the 78 patients who received ISH, a higher HER2/CEP17 ratio correlated significantly with longer PFS (HR 0.50, $p = 0.022$) and OS (HR 0.28, $p = 0.014$) when dichotomized by the median. A higher HER2 copy number also correlated significantly with better PFS (HR 0.35, $p < 0.001$) and OS (HR 0.27, $p = 0.009$). In multivariate analysis, the HER2/CEP17 ratio was an independent predictive factor for PFS (HR 0.66, $p = 0.004$) and potentially for OS (HR 0.64, $p = 0.054$), along with HER2 copy number (PFS HR 0.85, $p = 0.004$; OS HR 0.84, $p = 0.049$). Furthermore, the correlation between HER2 amplification level by ISH with PFS and OS was consistent across the HER2 IHC 1+/2+ and 3+ categories.

Conclusions: This is the first study to report that a higher level of HER2 amplification by ISH is associated with improved PFS and OS in advanced HER2-positive breast cancer treated with dual HER2-blockade. Notably, HER2 amplification level had a predictive role regardless of IHC results. Even in patients with HER2 protein expression of 3+, treatment outcome to HER2-directed therapy was dependent on the level of HER2 gene amplification.

Antibody-Drug Conjugates (ADCs) in Breast Cancer: Real World Analysis of Outcomes

Author: A. Singareeka Raghavendra
Citation: SABC 2023:PS08-01

Methods: We estimated the distribution of progression-free survival (PFS), overall survival (OS), and time to treatment failure (TTF) using the Kaplan-Meier method. Differences in survival curves between groups categorized by initial ADC treatment and subsequent ADC treatments were assessed using the log-rank test. Cox proportional hazards regression models were employed to evaluate the association between each survival outcome and various measures of interest, such as age, gender, race, number of prior lines of treatment, hormone receptor status, and HER2 status.

Results: The analysis included a total of 469 breast cancer patients, with the distribution of clinical characteristics summarized in Table 1. The median age at the start of ADC treatment was 50 years (range: 20-85). Among the patients, 263 patients (56%) received SC as their initial ADC treatment, while 44% received T-DXd. Additionally, 29 patients received both ADCs during metastatic treatment. The median follow-up time for all patients was 7.9 months (range: 0.1- 39.1). Out of the total patient population, 29% died, while 71% were still alive at the last follow-up. The median OS for all patients was 21.6 months. Median OS of patients receiving SC or T-DXd as their initial ADC treatment, was 14 and 37.1 months, respectively. Patients who received both SC and T-DXd had a median OS of 26.1 months.

The median PFS for all patients was 6.0 months. Patients initially treated with SC had a median PFS of 4.7 months, whereas those treated with T-DXd had a median PFS of 9.0 months. In patients who received both, median of PFS was 4.9 months for T-DXd after SC, and 5.0 months for SC after T-DXd.

The median TTF for all patients was 6.1 months. Patients initially treated with SC had a median TTF of 4.7 months, while those treated with T-DXd had a median TTF of 9.0 months. In patients who received T-DXd after SC, TTF was 4.9 months and SC after T-DXd was 5.0 months. Clinician-judged responses were seen in 180 (74%)of patients with SC only, 80 (41%) with T-DXd only, 9 (100%) with SC as 2nd ADC and 20 (100%) with T-DXd as 2nd ADC. Furthermore, the analysis explored the association of OS, PFS, and TTF with various measures of interest, including age, gender, race, number of prior lines of treatment, type of treatment, hormone receptor status, HER2 status, Ki67, and best response to ADC. Some notable associations were observed, such as ER-positive status being associated with marginally longer OS compared to ER-negative status (median 24.7 vs. 16.4 months; p=0.06), and HER2-positive status being associated with longer PFS compared to HER2-negative status (median 14.2 vs. 5.4 months; p< 0.001). However, these associations should be interpreted cautiously as they were obtained from univariate analysis.

Conclusions: Overall, these results highlight the significant differences in survival outcomes between different ADC treatments in breast cancer patients, likely due to differing patient characteristics.

Distribution of clinical characteristics across ADCs

Variables	Level	T-DXd (N=206)	Sacituzumab (N=263)
No. of prior lines of treatment, n (%)	0	16 (8)	38 (14)
	1	38 (18)	81 (31)
	2	35 (17)	70 (27)
	>= 3	117 (57)	74 (28)
ER status, n (%)	0-9	61 (30)	178 (68)
	10-100	145 (70)	85 (32)
PR status, n (%)	0-9	100 (49)	207 (79)
	10-100	106 (51)	54 (21)
HER2 status, n (%)	0	20 (10)	111 (42)
	Low	26 (13)	50 (19)
	Pos	77 (38)	100 (38)
	HER2 FISH Neg (no IHC)	85 (18)	2 (1)

Efficacy of Sacituzumab-Govitecan (SG) post Trastuzumab-deruxtecan (T-DXd) and vice versa for HER2low advanced or metastatic breast cancer (MBC): a French multicentre retrospective study.

Author: François Poumeaud
Citation: SABCS 2023:PS08-02

Background: Based on ASCENT, TROPICS-02 and DESTINY-Breast04 trials, SG and T-DXd recently became approved for HER2low MBC. Since the payloads of both SG and T-DXd belong to the same cytotoxic class (topoisomerase-1 inhibitor), cross-resistance is a potential concern. However, no data is available on the efficacy of one antibody drug conjugate (ADC) after another and the best therapeutic sequence has not been evaluated yet.

Methods: We conducted a retrospective study in 19 French comprehensive cancer centres. All patients (pts) with HR+ or HR- and HER2low MBC treated with SG followed, immediately or not, by T-DXd (or vice versa) were included. HR expression was defined on the last available tumor sample. The study primary objective was to report the second ADC (ADC2) progression-free survival (PFS) in the whole population. Secondary objectives included first ADC (ADC1) progression-free interval (PFI) and overall survival (OS) in the whole population and subgroup analyses by HR status.

Results: The individual data of 126 eligible women were obtained from 19 participating centres. Median age was 54.5 years (range: 30-80y). N=110 (87.3%) pts had invasive carcinoma of not special type, N=12 (9.5%) invasive lobular carcinoma and 4 (3.2%) other histological subtype. N=87 (69%) and 39 (31%) had HR+/HER2low and HR-/HER2low MBC, respectively. N=16 patients were germline mutation carriers (BRCA1 N=7; BRCA2 N=6; other genes on HBOC panel N=3). ADC1 was given as a median of third (range: 1-10) line of chemotherapy and ADC2 as fifth (range: 2-12) line. A large majority (N=94, 74.6%) of pts received SG as ADC1 (N=82 with HR- and N=12 with HR+ MBC) while N=32 (25.4%) received T-DXd as ADC1 (N=27 with HR+ and n=5 with

HR- MBC). 53.2% (N=67) received ADC1 immediately followed by ADC2 while 46.8% (N=59) received ADC2 after 1 (N=40) or 2 (N=12) or ≥ 3 (N=6) other lines of chemotherapy. N=19 (15.07%) and N=26 (20.63%) had a meningeal and/or cerebral metastasis at the time of the initiation of ADC1 and ADC2 respectively. After a median follow-up of 3 months, ADC2 was discontinued in 63 pts of which 51 (82.3%) for progression disease and 4 (6.5%) for toxicity due to T-DXd. Importantly, 50% of pts (N=63) were still under ADC2 at the time of this first analysis. The observed median PFS for ADC2 and median PFI for ADC1 are presented in the Table below:

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
Whole population (N=126) SG → T-DXd (N=94) T-DXd→SG (N=32)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3]
HR-/HER2low (N=82) having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
HR+/HER2low (n=27) having received T-DXd as ADC1 then SG as ADC2	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

Median OS was not reached independently of the sub-populations of pts.

Conclusion: To the best of our knowledge, this is the largest cohort evaluating the efficacy of subsequent ADCs administration in HER2low MBC. In these heavily pre-treated pts, subsequent use of ADCs seem to be associated with shortened PFS in both HR+/HR- subgroups, independently of their administration order. Data will be updated and completed for the meeting. Moreover, the number of eligible pts will be increased.

Table 1: median TPP and PFS2 in whole population and HR subgroups

Population and sequential regimen	Median (mo) PFI ADC1	Median (mo) PFS ADC2
Whole population (N=126) SG → T-DXd (N=94) T-DXd→SG (N=32)	4.5 (95%CI [3.4-5.1])	2.7 (95%CI [2.1-3.3]
HR-/HER2low (N=82) having received SG as ADC1 then T-DXd as ADC2	4.8 (95%CI [3.8-5.1])	3.3 (95%CI [2.5-3.7])
HR+/HER2low (n=27) having received T-DXd as ADC1 then SG as ADC2	2.7 (95%CI [2.0-3.2])	2.0 (95%CI [1.6-NR])

Sequencing Antibody-Drug Conjugate after Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 study): Multi-Institution Experience and Biomarker Analysis

Author: Rachel Occhiogrosso Abelman
Citation: SABCS 2023:PS08-03

Background: Antibody-drug conjugates (ADCs) improve survival in patients with metastatic breast cancer (MBC) and offer the potential for targeted delivery of highly potent therapy. Many patients are now candidates for multiple ADCs, but optimal strategies for sequencing are unknown. We previously reported on a single institution experience of patients receiving multiple ADCs for MBC (Abelman, ASCO 2023). Here we report a multi-institution update with biomarker analysis.

Methods: We included all patients treated at three academic medical institutions who received multiple ADCs for MBC. Patients were included if they had hormone receptor positive, HER2-negative (HR+/HER2-) breast cancer or triple-negative breast cancer (TNBC); patients with HER2+ metastatic breast cancer were excluded. Clinical information was determined by chart review. The metric of "cross-resistance" to the second ADC was defined as patients with progressive disease on first restaging assessment or progression within 60 days of treatment initiation. Every subsequent ADC beyond the first was compared against the prior ADC for presence of identical "antibody target" and "payload". Comparisons across ADCs were performed using Fisher's exact test. Significance was determined to be a type I error less than 0.05. A subset of patients had available whole exome tissue sequencing through commercially available sequencing platforms (BostonGene and Caris) performed around the time of receipt of ADC. All sequencing reports were examined for presence of pathogenic variants, variants of uncertain significance, and currently undefined variants and fusions as defined by each sequencing platform.

Results: 68 patients were identified who received two or more ADCs for metastatic HR+/HER2- breast cancer or TNBC from August 2014-June 2023. 30 patients (44.1%) had HR+/HER2- disease and 38 patients (55.9%) had TNBC; 50 patients (73.5%) had HER2-low disease. Median age at time of second ADC was 59.6 (range 29.9-88.6). Patients had received a median of 4 lines of treatment in the metastatic setting prior to initiation of the second ADC. At time of first restaging, cross-resistance was present in 38/64 evaluable cases (59.4%). When the antibody target of the latter ADC was the same as the prior, cross-resistance was present in 11/14 cases (78.5%) compared to 26/49 cases (53.1%) when the later ADC targeted a different tumor-associated antigen. Relatively similar patterns of cross-resistance were observed regardless of whether the later ADC contained an identical payload to prior (6/10 cases, 60%) versus a different payload (22/42, 52.4%). Sequencing information was available for 20 patients who received multiple ADCs with 15 unique reports performed at the time of resistance to ADC1, prior to initiation of ADC2, or after ADC2 if presence of cross-resistance. Variants in topoisomerase-I associated genes (TOP1, TOP2A, TOP3A, TOP3B) were identified in a subset of patients mediating cross-resistance to the second ADC with a topoisomerase-I inhibitor payload.

Conclusions: In this multi-institution study, cross-resistance to the second ADC appears to be driven by the antibody target in some patients versus the payload in others, highlighting the heterogeneity of mechanisms related to ADC resistance. Tumor sequencing revealed candidate resistance mutations that may guide optimal sequencing for patients with MBC.

Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

Author: Laura Huppert
Citation: SABCS 2023:PS08-04

Introduction: T-DXd is FDA-approved for patients (pts) with hormone receptor positive (HR+) or HR- HER2-low (IHC 1+ or 2+, ISH-) MBC and SG is FDA-approved for pts with HR+/HER2- and triple negative MBC. However, several outstanding questions impact the use of these drugs in clinic, including: 1) what is the efficacy and safety of these agents in real-world populations with diverse pt characteristics not well represented in the pivotal phase III trials, and 2) what is the impact of sequential treatment with ADCs on the efficacy and safety of these agents.

Methods: In this multicenter retrospective cohort study, we identified pts with HR+/HER2-low and HR-/HER2-low MBC who had received both T-DXd and SG monotherapy (in either order, with or without intervening therapies) treated at 5 academic centers between 2020-2023. Pts received treatment per standard of care or on a clinical trial with ADC monotherapy. We describe pt demographic and clinical characteristics, treatment history, key safety parameters, and response and survival data by HR+ status and ADC sequence order.

Results: Sixty pts with MBC treated sequentially with T-DXd and SG were included in this analysis, including 45 pts with HR+/HER2-low MBC (75.0%) and 15 pts with HR-/HER2-low MBC (25.0%). Most pts were female (n=59; 98.3%), non-Hispanic (n=49, 81.7%), and white (n=43, 71.7%). Median age at start of ADC #1 was 56.6 years (range 23-82). Prior to treatment with ADC #1, most pts had visceral disease (n=45, 75.0%) and 16 (26.7%) had central nervous system metastases.

Among pts with HR+/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 49.0 months, with 4 median lines of prior therapy in the metastatic setting (2 endocrine, 2 chemo). Approximately half of the HR+ pts received T-DXd prior to SG (n=22, 48.9%; median 3.0 prior lines of therapy for MBC, range 1-9) while the other half received SG prior to T-DXd (n=23, 51.1%; median 4.5 prior lines of therapy for MBC, range 1-10). 44% (n=20) received an intervening therapy between ADCs. For HR+ pts who received T-DXd prior to SG, response and survival data is as follows for T-DXd and SG respectively: Overall response rate (ORR) [54.5% and 21.1%], time to next treatment (TTNT) [4.3 mo and 1.6 mo], and real-world overall survival (rwOS) [19.8 mo and 4.9 mo]. For HR+ pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [78.3% and 42.9%], TTNT [8.6 mo and 2.8 mo], and rwOS [22.3 mo and 7.3 mo].

Among pts with HR-/HER2-low MBC, median time from MBC diagnosis to treatment with ADC #1 was 8.2 months with 2 median lines of prior therapy in the metastatic setting (2 chemotherapy); 66.7% (n=10) received prior immunotherapy. Most HR- pts received SG prior to T-DXD (n=14, 93.3%) and 40.0% (n=6) received an intervening therapy between ADCs. For HR- pts who received SG prior to T-DXd, response and survival data is as follows for SG and T-DXd respectively: ORR [64.3% and 38.5%], TTNT [6.2 mo and 2.7 mo, and rwOS [15.7 mo and 6.5 mo].

In terms of key safety parameters during treatment with T-DXd, 13.3% of pts (8/60) required a dose reduction. 16.7% (10/60) were diagnosed with interstitial lung disease (ILD)/pneumonitis of any grade including 3 pts with grade 3-4 ILD (5.0%) and 3 pts with grade 5 ILD (5.0%). During treatment with SG, 40.0% of pts (24/60) required a dose reduction. 83.3% (50/60) received growth factor support (24 pts primary prophylaxis; 26 pts secondary prophylaxis); 9 pts (15%) required treatment delay due to neutropenia.

Conclusion: This study represents the largest multicenter series to date of pts treated with sequential ADCs for HR+/HER2-low or HR-/HER2-low. ORR was higher and TTNT was longer for ADC #1 than ADC #2 in all subgroups, regardless of HR+ status and ADC sequence order. An additional ~30 pts will be reported at time of final analysis. Future prospective studies are planned to further clarify the efficacy and safety of sequential ADC use and to identify biomarkers of response and resistance.

Key demographic, clinical and treatment characteristics in pts with HR+ and HR- HER2-low MBC treated sequentially with T-DXd and SG (in either order, with or without intervening therapies)

	HR+/HER2-low MBC (n=41)	HR-/HER2-low MBC (n=15)
Demographic data		
Median age at time of ADC #1, yrs (range)	56.4 (23.0-81.7)	56.9 (37.7-70.3)
Sex, n (%)		
Female	44 (97.8%)	15 (100.0%)
Male	1 (2.2%)	0 (0%)
Ethnicity, n (%)		
Non-Hispanic	36 (80.0%)	12 (80.0%)
Hispanic	9 (20.0%)	3 (20.0%)
Race, n (%)		
White	33 (73.3%)	9 (60.0%)
Black	3 (6.7%)	3 (20.0%)
Asian	5 (11.1%)	3 (20.0%)
Other/unknown	4 (8.9%)	0 (0%)
Histology, n (%)		
Ductal	34 (75.6%)	12 (80.0%)
Lobular	4 (8.9%)	1 (6.7%)
Mixed ductal/lobular	3 (6.7%)	1 (6.7%)
Other/unknown	4 (8.9%)	1 (6.7%)
De novo metastatic disease, n (%)	7 (15.6%)	3 (17.6%)
Sites of metastatic disease prior to ADC #1		
Bone	35 (77.8%)	10 (66.7%)
Liver	29 (64.4%)	6 (40.0%)
Lung	14 (31.1%)	9 (60.0%)
CNS	9 (20.0%)	4 (26.7%)
Prior and intervening treatment		
Median time from MBC diagnosis to ADC #1, months (range)	49.0 (1.2-140.6)	8.2 (0.5-58.4)
Median lines of therapy prior to ADC #1 by type of therapy		
Median lines ET, number (range)	2 (0-5)	0 (0)
Median lines chemotherapy, number (range)	2 (0-6)	2 (0-4)
Median total lines of therapy, number (range)	4 (0-10)	2 (0-5)
Median time on ET for MBC, months (range)	36.0 (0-111.1)	n/a
Receipt of prior immunotherapy, n (%)	12 (29.8%)	10 (66.7%)
Receipt of intervening therapy between ADCs, n (%)	20 (44.4%)	6 (40.0%)
Median lines intervening therapy, number (range)	0 (0-1)	0 (0-6)
ADC use and efficacy data		
T-DXd → SG, n (%)	**22 (48.9%)**	**1 (6.7%)**
Median prior lines of therapy, range	4.5 (1-9)	3.0 (n/a)
ORR by investigator assessment ADC #1 (T-DXd), %	54.5% (12/22)	0% (0/1)
ORR by investigator assessment ADC #2 (SG), %	21.1% (4/19)*	0% (0/1)
TTNT ADC #1 (T-DXd), months (95% CI)	4.3 (2.7-6.3)	2.3 (n/a)
TTNT ADC #2 (SG), months (95% CI)	1.6 (0.9-2.9)	0.3 (n/a)
rwOS ADC #1 (T-DXd), months (95% CI)	19.8 (13.2-25.0)	5.1 (n/a)
rwOS ADC #2 (SG), months (95% CI)	4.9 (2.2-7.1)	0.1 (n/a)
SG → T-DXd, n (%)	**23 (51.1%)**	**14 (93.3%)**
Median prior lines of therapy, range	3.0 (1-10)	2.0 (1-5)
ORR by investigator assessment ADC #1 (SG), %	78.3% (18/23)	64.3% (9/14)
ORR by investigator assessment ADC #2 (T-DXd), %	42.9% (9/21)*	38.5% (5/13)*
TTNT ADC #1 (SG), months (95% CI)	8.8 (4.9-11.0)	6.2 (1.9-11.3)
TTNT ADC #2 (T-DXd), months (95% CI)	2.8 (1.5-5.1)	2.7 (1.4-6.8)
rwOS ADC #1 (SG), months (95% CI)	22.3 (18.9-27.1)	15.7 (10.3-21.6)
rwOS ADC #2 (T-DXd), months (95% CI)	7.3 (5.5-9.8)	6.5 (4.2-11.1)

Abbreviations: T-DXd (trastuzumab deruxtecan), SG (sacituzumab govitecan), MBC (metastatic breast cancer), ADC (antibody drug conjugate), HR (hormone receptor), HER2 (human epidermal growth factor receptor 2), CNS (central nervous system), ET (endocrine therapy), ORR (overall response rate), TTNT (time to next treatment), rwOS (real world overall survival), CI (confidence interval)

* Several pts on ADC #2 with ongoing treatment and first scan pending, hence smaller denominator for response assessment

BL-B01D1, a first-in-class EGFRxHER3 bispecific antibody-drug conjugate, in patients with Locally Advanced or Metastatic Breast Cancer and other Solid Tumor: Results from a phase 1 study.

Author: Jiong Wu
Citation: SABCS 2023:PS08-07

Background: BL-B01D1 is a first-in-class novel antibody drug conjugate (ADC) consisting of an EGFRxHER3 bispecific antibody bounded to a novel TOP-I inhibitor payload via a cleavable linker. We now present safety/efficacy data from a phase I study of BL-B01D1 in breast cancer.

Methods: This study included patients (pts) with locally advanced or metastatic breast cancer (BC) and other solid tumors. BL-B01D1 was administered intravenously at doses of 2.5mg/kg Day 1 & Day 8 every 3 weeks (D1D8Q3W) or 5.0mg/kg Day 1 every 3 weeks (D1Q3W) during dose escalation (D-ESC, i3+3) based on the information obtained during the first-in-human study in solid tumors. A subset of pts will be enrolled in the dose-expansion (D-EXP) phase.

Results: As of June 26, 2023, 42 pts were enrolled and received at least one dose (D-ESC, n=8; D-EXP, n=34) of BL-B01D1. Only one DLT of febrile neutropenia was observed at 5.0mg/kg D1 Q3W, maximum tolerated dose (MTD) has not been reached. D-EXP was conducted at 2.5mg/kg D1D8 Q3W. Forty-one pts with BC and 1 pt with non-small cell lung cancer (NSCLC) were enrolled in this study. The most common TRAEs (>10%, all grade / ≥ G3) were leukopenia (67%/24%), neutropenia (55%/33%), anemia (55%/26%), thrombocytopenia (60%/24%), nausea (38%/0%), vomiting (38%/0%), stomatitis (31%/2%), asthenia (29%/0%), hypokalemia (21%/5%), aspartate aminotransferase increased (19%/0), alanine aminotransferase increased (19%/0%), decreased appetite (19%/0%), hypertriglyceridemia (19%/0%), hyperglycemia (19%/0%), hyperglycemia (17%/0%), weight decreased (14%/0%), diarrhea (12%/0%), epistaxis (12%/0%), hypercholesterolemia (12%/0%). No ILD was observed. Twenty-four pts. were evaluable for efficacy (at least 1 tumor assessment). Updated information will be provided during the meeting.

Conclusions: BL-B01D1 demonstrated encouraging efficacy in metastatic/ locally advanced breast cancer that have failed standard of care, especially in pts with TNBC. The safety profile showed adequate safety and tolerability.

Clinical trial information: NCT05470348.

Efficacy in Patients with Breast Cancer

	TNBC (n=11)	HR+ HER2 Low/Zero (n=9)	HER2 positive (n=8)
Median Prior treatment line (range)	2(1-9)	4(3-13)	5(2-6)
Best Response, n[1]			
PR	5	3	2
SD	6	5	5
PD	0	1	1
ORR, % (95% CI)	45.5% (16.8-76.6)	33.3% (7.5-70.1)	25.0% (3.2-65.1)
DCR, % (95% CI)	100%	88.9% (51.8-99.7)	87.5% (47.4-99.7)

1 Including pts whose PRs were not yet confirmed but still under treatment.

Updated efficacy and safety of SKB264 (MK-2870) for previously treated metastatic triple negative breast cancer (mTNBC) in Phase 2 study

Author: Yongmei Yin
Citation: SABCS 2023:PS08-08

Background: Patients (pts) with mTNBC have limited treatment options and poor prognosis. The estimated median overall survival (OS) of pts with mTNBC is 12 to 18 months (mo) after diagnosis. SKB264, an antibody drug conjugate (ADC) composed of an anti-TROP2 antibody coupled to a cytotoxic belotecan-derivative via a novel linker with an average Drug to Antibody Ratio (DAR) of 7.4, has shown promising anti-tumor activity and tolerable safety profile in pts with mTNBC (Yin, Y. et al. SABCS 2022). Here, we report the updated data from a Phase 2 expansion cohort for pts with mTNBC (NCT04152499).

Methods: Pts with previously treated mTNBC were enrolled to receive SKB264 at 4 mg/kg Q2W or 5 mg/kg Q2W in a non-randomized manner until disease progression or unacceptable toxicity. Tumor assessment was performed every 8 weeks per RECIST v1.1 assessed by investigator. The primary objective was to assess objective response rate (ORR). Secondary objectives included DoR, PFS, and OS. The TROP2 expression was scored using the semi-quantitative H-score method, and a preliminary cutoff was set as 200. TROP2 expression and its association with anti-tumor activity were retrospectively analyzed.

Results: At data cut-off date (May 05, 2023), 59 pts were enrolled (23 in 4 mg/kg, 36 in 5 mg/kg), and 88% (52 pts) had received ≥3 prior lines of therapy for metastatic disease. The median follow-up was 22.8 months (mo; 95% CI, 21.3-25.2). The ORR was 42.4% (25/59, 22 confirmed and 3 unconfirmed) and disease control rate (DCR) was 76.3% (45/59). The median duration of response (DoR) was 11.5 mo (range, 3.7 to 22.1+). Median PFS (mPFS) was 5.7 mo (95% CI: 3.8, 9.1). Median OS (mOS) was 16.8 mo (95% CI: 12.7, NE), while 12-mo and 24-mo OS rates were 65.0% and 39.5%, respectively. In the subset of pts with high TROP2 expression (H-score>200, N=32), ORR was 53.1% (including 3 complete

response), mDoR was 11.1 mo (range, 3.7 to 22.1+), mPFS was 5.8 mo (95% CI: 3.7, 13.3), mOS was not reached (95% CI: 9.7, NE), while 12-mo and 24-mo OS rates were 65.3% and 57.3%, respectively. Treatment-related adverse events (TRAEs) of ≥ Grade 3 severity were reported in 57.6% (34/59) of pts. The most common ≥ Grade 3 TRAEs (≥ 10%) were neutrophil count decreased (25.4%), white blood cell count decreased (23.7%), anemia (22.0%) and platelet count decreased (16.9%). TRAEs leading to dose reduction and dose delay occurred in 13.6% (8/59) and 47.5% (28/59) of pts, respectively. Three pts discontinued treatment due to TRAEs (platelet count decreased, dry eye, anaphylactic shock). No cases of interstitial lung disease (ILD), neuropathy or grade ≥3 diarrhea were observed. Serious TRAEs were reported in 28.8% (17/59) of pts; no deaths associated with TRAEs were observed.

Conclusions: The updated data continues to demonstrate that pts with heavily pretreated mTNBC could achieve durable response and a trend of long-term OS benefit from SKB264 treatment, along with a manageable safety profile. Higher response rate was seen in mTNBC pts with high TROP2 expression. A Phase 3 study of SKB264 vs. investigator's choice of chemotherapy in 3L+ mTNBC (NCT05347134) and a Phase 2 study evaluating SKB264 as monotherapy or combination with anti-PD-L1 antibody in first-line setting (NCT05445908) are ongoing in China.

First-in-human/phase I trial of HS-20089, a B7-H4 ADC, in patients with advanced solid tumors

Author: J. Wu
Citation: ESMO 2023:Abstract 3810

Background: B7-H4, a transmembrane glycoprotein in the B7 superfamily, has limited expression in normal tissues but is highly expressed in various cancers. HS-20089 is a novel B7-H4 directed antibody-drug conjugate (ADC) with a drug to antibody ratio of 6. We conducted a first-in-human phase I trial to evaluate the dose-limiting toxicity (DLT), safety, tolerability, pharmacokinetics, and

efficacy of HS-20089 in patients (pts) with advanced solid tumors refractory to standard therapy.

Methods: Eligible pts were enrolled in sequentially escalating dose cohorts (0.7 to 7.2 mg/kg) of HS-20089 administered intravenously every 3 weeks. The accelerated titration combined with Bayesian optimal interval (BOIN) was used as the dose escalation schedule in this phase I dose escalation trial.

Results: As of Apr. 11th, 2023, 44 pts with advanced solid tumors (41 breast cancers, 2 ovarian cancers, and 1 endometrial cancer) received HS-20089 treatment. Three DLTs were observed in 2 pts (both in 7.2 mg/kg). The most common treatment-emergent adverse events (≥20%) were leukopenia, neutropenia, nausea, anemia, thrombocytopenia, vomiting, fatigue, increased alanine aminotransferase, anorexia, increased aspartate aminotransferase and hyponatremia. No interstitial lung disease and infusion reaction were reported. Of 33 response-evaluable pts, 8 partial responses (PRs) were observed in pts treated with HS-20089 (response rate: 24.2%), including 3 confirmed PRs and 5 PRs awaiting confirmation. The disease control rate was 63.6%. In the subset of 16 triple-negative breast cancer (TNBC) pts, 6 PRs were observed (response rate: 37.5%), including 2 confirmed PRs and 4 PRs awaiting confirmation. At potential target therapeutic dose (4.8 and 5.8 mg/kg), 5 PRs of 12 pts were observed (response rate: 41.7%) in TNBC. The patient achieving PR with the longest treatment duration of 403 days remains on treatment in 0.7 mg/kg cohort.

Conclusions: Based on data from the ongoing study, HS-20089 was well tolerated and showed antitumor activities in advanced solid tumors, with encouraging clinical efficacy in TNBC.

Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial

Author: Hope S Rugo
Citation: Lancet. 2023 Oct 21;402(10411):1423-1433.

Background: Sacituzumab govitecan demonstrated significant progression-free survival benefit over chemotherapy in the phase 3 TROPiCS-02 trial in patients with pretreated, endocrine-resistant hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+ and HER2-) metastatic breast cancer with limited treatment options. Here, we report the protocol-specified final analysis of overall survival and endpoints by trophoblast cell-surface antigen 2 (Trop-2) expression and other variables.

Methods: In this randomised, open-label, multicentre, phase 3 trial, which took place in 91 centres across North America (the USA and Canada) and Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, and the UK), patients were randomly assigned (1:1) to receive sacituzumab govitecan or chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine). Patients had confirmed HR+ and HER2- locally recurrent inoperable or metastatic breast cancer and had received at least one previous endocrine therapy, a taxane, and a CDK4/6 inhibitor in any setting and two to four previous chemotherapy regimens for metastatic disease. The primary endpoint was progression-free survival (previously reported and not included in this analysis), and secondary endpoints included overall survival, objective response rate (ORR), and patient-reported outcomes. Overall survival was assessed using stratified log-rank tests and Cox regression. Trop-2 expression was assessed in tumour tissue by immunohistochemistry. In the statistical testing hierarchy, ORR and patient-reported outcomes were tested sequentially if overall survival was significant. This study is registered with ClinicalTrials.gov, NCT03901339.

Findings: At the data cutoff date of July 1, 2022, 543 of 776 screened patients were randomly assigned between May 30, 2019, and April 5, 2021, with 272 patients in the sacituzumab govitecan group and 271 patients in the chemotherapy group. With a 12·5-month (IQR 6·4-18·8) median follow-up, 390 deaths occurred among 543 patients. Overall survival was significantly improved with sacituzumab govitecan versus chemotherapy (median 14·4 months [95% CI 13·0-15·7] vs 11·2 months [10·1-12·7]; hazard ratio [HR] 0·79, 95% CI 0·65-0·96; p=0·020); survival benefit was consistent across Trop-2 expression-level subgroups. ORR was significantly improved with sacituzumab govitecan compared with chemotherapy (57 [21%] patients vs 38 [14%]; odds ratio 1·63 [95% CI 1·03-2·56]; p=0·035), as was time to deterioration of global health status and quality of life (median 4·3 months vs 3·0 months; HR 0·75 [0·61-0·92]; p=0·0059) and fatigue (median 2·2 months vs 1·4 months; HR 0·73 [0·60-0·89]; p=0·0021). The safety profile of sacituzumab govitecan was consistent with previous studies (including the TROPiCS-02 primary analysis and the ASCENT trial). One fatal adverse event (septic shock caused by neutropenic colitis) was determined to be related to sacituzumab govitecan treatment.

Interpretation: Sacituzumab govitecan demonstrated statistically significant and clinically meaningful benefit over chemotherapy, with a 3·2-month median overall survival improvement and a manageable safety profile. These data support sacituzumab govitecan as a new treatment option for patients with pretreated, endocrine-resistant HR+ and HER2- metastatic breast cancer.

A phase 2 study of HER3-DXd in patients (pts) with metastatic breast cancer (MBC).

Author: Erika P. Hamilton
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1004-1004.

Background: HER3-DXd is an antibody drug conjugate (ADC) comprised of a fully human anti-HER3 IgG1 monoclonal antibody (patritumab), attached to a topoisomerase 1 inhibitor via a tetrapeptide-based cleavable linker that has

shown promising efficacy in pts with HER3-expressing MBC (Krop, 2022). This 3-part Phase 2 study examines efficacy of HER3-DXd across MBC subsets and defines the pt population likely to derive greater benefit (NCT04699630).

Methods: Part A is reported here (Data cutoff 6Sep2022). Pts had HER2 negative MBC with measurable disease per RECIST v1.1, 0-2 prior chemo and prior endocrine therapy (ET) + CDK4/6 inhibitor for hormone receptor (HR)+ BC, or 1-3 prior chemo for triple negative BC (TNBC). Prior treatment (tx) with anti-HER3 agents and ADCs with exatecan derivatives were prohibited. Pts provided pre-tx tissue to evaluate the association of biomarker expression with progression free survival at 6 months (PFS6months). Primary endpoints for Part A are objective response rate (ORR) and PFS6months. Secondary endpoints are safety/tolerability, duration of response (DOR), and clinical benefit rate (CBR) (CR, PR or SD ≥180 days).

Results: 60 pts were treated in Part A: median age 57.5 y, 98.3% female; median 5 prior lines of therapy (range 1-15). 32% had TNBC. 48% were HR+. 48% had liver and 32% had lung metastases. HER3 membrane expression was evaluated by overall % membrane positivity at 10X. 47/60 (78%) pts provided evaluable samples at baseline. Among evaluable pts, 64% (30/47) had HER3 expression ≥75%, 28% (13/47) had 25-74% expression and 8% (4/47) had <25% expression. The median tx duration was 5.2 mos and 21 pts remained on tx at data cut-off. All pts experienced a tx emergent adverse event and 93% of pts experienced a tx related AE (TRAE) with Gr ≥3 TRAE in 19 pts (32%). The most common (≥ 25%) any grade TRAEs were nausea (50%), fatigue (45%), diarrhea (37%), vomiting (32%), alopecia and anemia (30% each). 7 pts (12%) experienced a serious AE (SAE), including 4 pts (7%) with a related SAE (interstitial lung disease, nausea/vomiting, pneumonitis, thrombocytopenia). 15% of pts experienced a dose reduction and 23% experienced a dose interruption due to an AE. 3 pts died while on tx, 2 unrelated to tx 1 cause unknown. ORR was 35% (95% CIs 23.1, 48.1) for all pts, and the CBR was 48% (95% CIs 35.2, 61.6). Pts with ≥75% HER3 expression had an ORR of 33% and CBR of 50%, pts with HER3 25-74%

expression had an ORR of 46% and CBR of 54%. There were 4 pts with HER3 < 25% expression, limiting efficacy assessment. The median DOR was 10.0 mos (95% CIs 5.5, NA). The PFS6months was 60% for all pts, 50% for pts with HER3 ≥75%, and 70% for pts with HER3 25-74%.

Conclusions: HER3-DXd had an acceptable safety profile, and the data further confirm the clinical activity in MBC in heavy pre-tx MBC across the broad range of HER3 expression levels. Parts B and Z are ongoing and data from this report support the potential entry of HER3-DXd into the therapeutic paradigm in MBC

Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial

Author: Fabrice André
Citation: Lancet. 2023 May 27;401(10390):1773-1785.

Background: In the single-arm, phase 2 DESTINY-Breast01 trial, trastuzumab deruxtecan showed robust activity in patients with HER2-positive metastatic breast cancer who were refractory or resistant to trastuzumab emtansine; a population with scarce effective treatments. In DESTINY-Breast02, we aimed to compare the efficacy and safety of trastuzumab deruxtecan with treatment of physician's choice in this patient population.

Methods: This randomised, open-label, multicentre, phase 3 trial was conducted at 227 sites (hospitals, university hospitals, clinics, community centres, and private oncology centres) in North America, Europe, Asia, Australia, Brazil, Israel, and Türkiye. Eligible patients were aged 18 years or older, had unresectable or HER2-positive metastatic breast cancer, previously received trastuzumab emtansine, disease progression, an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate renal and hepatic function. Patients were randomly assigned (2:1) to receive trastuzumab deruxtecan (intravenously at 5·4 mg/kg once every 3 weeks) or treatment of physician's choice using block randomisation. Treatment of physician's choice was either

capecitabine (1250 mg/m^2; orally twice per day on days 1-14) plus trastuzumab (8 mg/kg intravenously on day 1 then 6 mg/kg once per day) or capecitabine (1000 mg/m^2) plus lapatinib (1250 mg orally once per day on days 1-21), with a 21-day schedule. The primary endpoint was progression-free survival based on blinded independent central review in the full analysis set. This study is registered with ClinicalTrials.gov, NCT03523585.

Findings: Between Sept 6, 2018, and Dec 31, 2020, 608 patients were randomly assigned to receive trastuzumab deruxtecan (n=406; two did not receive treatment) or treatment of physician's choice (n=202; seven did not receive treatment). 608 (100%) patients were included in the full analysis set. The median age was 54·2 years (IQR 45·5-63·4) in the trastuzumab deruxtecan group and 54·7 years (48·0-63·0) in the treatment of physician's choice group. 384 (63%) patients were White, 603 (99%) were female, and five (<1%) were male. The median follow-up was 21·5 months (IQR 15·2-28·4) in the trastuzumab deruxtecan group and 18·6 months (8·8-26·0) in the treatment of physician's choice group. Median progression-free survival by blinded independent central review was 17·8 months (95% CI 14·3-20·8) in the trastuzumab deruxtecan group versus 6·9 months (5·5-8·4) in the treatment of physician's choice group (HR 0·36 [0·28-0·45]; p<0·0001). The most common treatment-emergent adverse events were nausea (293 [73%] of 404 with trastuzumab deruxtecan vs 73 [37%] of 195 with treatment of physician's choice), vomiting (152 [38%] vs 25 [13%]), alopecia (150 [37%] vs eight [4%]), fatigue (147 [36%] vs 52 [27%]), diarrhoea (109 [27%] vs 105 [54%]), and palmar-plantar erythrodysaesthesia (seven [2%] vs 100 [51%]). Grade 3 or higher treatment-emergent adverse events occurred in 213 (53%) patients receiving trastuzumab deruxtecan versus 86 (44%) receiving treatment of physician's choice; whereas drug-related interstitial lung disease occurred in 42 (10%; including two grade 5 death events) versus one (<1%).

Interpretation: DESTINY-Breast02 shows the favourable benefit-risk profile of trastuzumab deruxtecan in patients with HER2 positive metastatic breast cancer, as previously reported in DESTINY-Breast01, and is the first randomised study to show that one antibody-drug conjugate can overcome resistance to a previous one.

Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

Author: Sara A Hurvitz
Citation: Lancet. 2023 Jan 14;401(10371):105-117.

Background: An improvement in progression-free survival was shown with trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer in the progression-free survival interim analysis of the DESTINY-Breast03 trial. The aim of DESTINY-Breast03 was to compare the efficacy and safety of trastuzumab deruxtecan versus trastuzumab emtansine.

Methods: This open-label, randomised, multicentre, phase 3 trial was done in 169 study centres in North America, Asia, Europe, Australia, and South America. Eligible patients were aged 18 or older, had HER2-positive unresectable or metastatic breast cancer previously treated with trastuzumab and a taxane, had an Eastern Cooperative Oncology Group performance status 0-1, and at least one measurable lesion per Response Evaluation Criteria in Solid Tumours version 1.1. Patients were randomly assigned (1:1) to receive trastuzumab deruxtecan 5·4 mg/kg or trastuzumab emtansine 3·6 mg/kg, both administered by intravenous infusion every 3 weeks. Randomisation was stratified by hormone receptor status, previous treatment with pertuzumab, and history of visceral disease, and was managed through an interactive web-based system. Within each stratum, balanced block randomisation was used with a block size of four. Patients and investigators were not masked to the treatment received. The primary endpoint was progression-free survival by blinded independent

central review. The key secondary endpoint was overall survival and this prespecified second overall survival interim analysis reports updated overall survival, efficacy, and safety results. Efficacy analyses were performed using the full analysis set. Safety analyses included all randomly assigned patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT03529110.

Findings: Between July 20, 2018, and June 23, 2020, 699 patients were screened for eligibility, 524 of whom were enrolled and randomly assigned to receive trastuzumab deruxtecan (n=261) or trastuzumab emtansine (n=263). Median duration of study follow-up was 28·4 months (IQR 22·1-32·9) with trastuzumab deruxtecan and 26·5 months (14·5-31·3) with trastuzumab emtansine. Median progression-free survival by blinded independent central review was 28·8 months (95% CI 22·4-37·9) with trastuzumab deruxtecan and 6·8 months (5·6-8·2) with trastuzumab emtansine (hazard ratio [HR] 0·33 [95% CI 0·26-0·43]; nominal p<0·0001). Median overall survival was not reached (95% CI 40·5 months-not estimable), with 72 (28%) overall survival events, in the trastuzumab deruxtecan group and was not reached (34·0 months-not estimable), with 97 (37%) overall survival events, in the trastuzumab emtansine group (HR 0·64; 95% CI 0·47-0·87]; p=0·0037). The number of grade 3 or worse treatment-emergent adverse events was similar in patients who received trastuzumab deruxtecan versus trastuzumab emtansine (145 [56%] patients versus 135 [52%] patients). Adjudicated drug-related interstitial lung disease or pneumonitis occurred in 39 (15%) patients treated with trastuzumab deruxtecan and eight (3%) patients treated with trastuzumab emtansine, with no grade 4 or 5 events in either group.

Interpretation: Trastuzumab deruxtecan showed a significant improvement in overall survival versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer, as well as the longest reported median progression-free survival, reaffirming trastuzumab deruxtecan as the standard of care in the second-line setting. A manageable safety profile of trastuzumab deruxtecan was confirmed with longer treatment duration.

Trastuzumab deruxtecan (T-DXd) in combination with anastrozole or fulvestrant in patients with HER2-low HR+ advanced/metastatic breast cancer: a Phase 1b, open-label, multicenter, dose-expansion study (DESTINY-Breast08)

Author: Komal Jhaveri
Citation: SABCS 2023:RF02-03

Background: Trastuzumab deruxtecan (T-DXd) is approved in over 40 countries for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low (a score of 1+ on immunohistochemistry [IHC] analysis or an IHC score of 2+ and negative results on in-situ hybridization) breast cancer who have received prior chemotherapy in the metastatic setting or who developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. DESTINY-Breast08 (DB-08) was designed to establish the safety, tolerability, and preliminary activity of T-DXd in combination with widely used standard of care therapies in HER2-low hormone receptor (HR)+ metastatic breast cancer (mBC). Results reported here are from the dose-expansion stage of the Phase 1b, multicenter, open-label, parallel-assignment DB-08 study arms investigating T-DXd–endocrine therapy (ET) combinations [NCT04556773].

Methods: Eligible patients had centrally confirmed HER2-low advanced/mBC with measurable disease per RECIST 1.1 and were documented as HR+. Among patients with mBC, ≤1 prior line of ET ± a targeted therapy was allowed, and prior chemotherapy in the mBC setting was exclusionary. Patients received T-DXd 5.4 mg/kg intravenously (IV) every three weeks (Q3W) + anastrozole 1 mg orally daily (T-DXd + ANA) or T-DXd 5.4 mg/kg IV Q3W + fulvestrant 500 mg intramuscularly Q4W, with a 500 mg loading dose on Cycle 1 Day 15 (T-DXd + FUL). Primary endpoints were safety and tolerability; secondary endpoints included objective response rate (ORR), progression-free survival, duration of response (all evaluated by investigator per RECIST 1.1), and overall survival (OS). Data cutoff (DCO) was ~24 weeks after the last patient in each arm had received study treatment.

Results: As of February 20, 2023, 21 patients in the T-DXd + ANA arm and 20 patients in the T-DXd + FUL arm had received study treatment. Median age was 55 and 66 years, 67% and 75% of patients received a prior line of ET ± a targeted therapy for mBC, 33% and 25% had no prior line of treatment for mBC, and median follow up in censored patients was 12.1 months (range 4.0, 17.3) and 8.5 months (range 1.3, 15.1) in the T-DXd + ANA and T-DXd + FUL arms, respectively. Adverse events (AEs) occurred in 95.2% (20/21) of patients in the T-DXd + ANA arm and 100% (20/20) of patients in the T-DXd + FUL arm, with AEs ≥Grade 3 occurring in 47.6% (10/21) and 55.0% (11/20) of patients in each arm, respectively. The most common any-grade AEs, occurring in ≥30% of patients in either arm, are reported in the Table. Three (15%) adjudicated drug-related interstitial lung disease / pneumonitis events were reported in the T-DXd + FUL arm (all Grade 2; at DCO, one case had resolved, one was resolving, and one was not resolved); none were reported in the T-DXd + ANA arm. AEs were manageable by drug interruption and dose reduction. Confirmed ORR was 71.4% (15/21; 95% confidence interval [CI] 47.8, 88.7) in the T-DXd + ANA arm, and 40.0% (8/20; 95% CI 19.1, 64.0) in the T-DXd + FUL arm (Table). OS data were not mature at this DCO.

Conclusions: Safety profiles for T-DXd-ET combinations were generally comparable to T-DXd monotherapy and manageable with dose modification and routine clinical practice. T-DXd in combination with anastrozole or fulvestrant was active in first- or second-line treatment of patients with HER2-low HR+ mBC.

Table. Summary of safety and efficacy data for T-DXd plus anastrozole and T-DXd plus fulvestrant in the total population

	T-DXd + anastrozole (T-DXd + ANA)	T-DXd + fulvestrant (T-DXd + FUL)
	All (N=21)	All (N=20)
Safety data		
Any-grade AEs, n (%)	20 (95.2)	20 (100)
Any-grade AEs occurring in ≥30% of patients in either arm, n (%)		
Nausea	14 (66.7)	17 (85.0)
Alopecia	9 (42.9)	9 (45.0)
Fatigue	9 (42.9)	3 (15.0)
Anemia	7 (33.3)	5 (25.0)
Decreased appetite	7 (33.3)	10 (50.0)
Neutropenia*	7 (33.3)	7 (35.0)
Vomiting	6 (28.6)	6 (30.0)
Any AEs ≥Grade 3, n (%)	10 (47.6)	11 (55.0)
AEs leading to dose interruptions / delays of T-DXd, n (%)	12 (57.1)	8 (40.0)
AEs leading to dose reduction of T-DXd, n (%)	7 (33.3)	6 (30.0)
AEs leading to discontinuation of T-DXd, n (%)	2 (9.5)	3 (15.0)
Median actual treatment duration, months (range)†	10.4 (2.8, 16.9)	6.2 (1.4, 16.1)
Efficacy data		
cORR, % (95% CI)	71.4 (47.8, 88.7)	40.0 (19.1, 64.0)
uORR, % (95% CI)	76.2 (52.8, 91.8)	50.0 (27.2, 72.8)
Median PFS, months (95% CI)‡	13.4 (8.5, 15.1)	NE (5.6, NE)
Median DOR, months (95% CI)‡	9.7 (6.7, NE)	NE (4.1, NE)
Median follow up in censored patients, months (range)	12.1 (4.0, 17.3)	8.5 (1.3, 15.1)

*Grouped term including patients with neutropenia and patients with decreased neutrophil count. †Actual treatment duration was reported as total treatment duration, excluding duration of drug interruptions and delays. ‡NE signifies that DOR/PFS was not reached for these patients at the time of DCO

AE, adverse event; ANA, anastrozole; CI, confidence interval; cORR, confirmed overall response rate; DCO, data cutoff; DOR, duration of response; FUL, fulvestrant; NE, not evaluable; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; uORR, unconfirmed overall response rate

Trastuzumab deruxtecan (T-DXd) versus treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): Results of DESTINY-Breast04, a randomized, phase 3 study.

Author: Shanu Modi
Citation: Journal of Clinical Oncology 40, no. 17_suppl (June 10, 2022) LBA3-LBA3.

Background: About 55% of mBC typically categorized as HER2 negative, express low levels of HER2 (IHC 1+ or IHC 2+/ISH– by ASCO/CAP 2018 guidelines) with poor outcomes in later lines (Tarantino 2020). T-DXd has shown promising efficacy in HER2-low mBC in a phase 1 study (NCT02564900; Modi2020). This is the primary report from DESTINY-Breast04 (NCT03734029), the first randomized, multicenter, open-label, phase 3 study comparing efficacy and safety of T-DXd vs TPC in pts with HER2-low mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting.

Methods: 557 pts with centrally confirmed HER2-low mBC were randomly assigned 2:1 to T-DXd 5.4 mg/kg or TPC (capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel). The primary endpoint was progression-free survival (PFS) determined by blinded independent central review (BICR) in pts with hormone receptor–positive (HR+) mBC. Key secondary endpoints (hierarchically tested after the primary endpoint) include PFS by BICR in the full analysis set (FAS; HR+/–) and overall survival (OS) in pts with HR+ mBC and in FAS. Other endpoints were objective response rate, duration of response, safety, and an exploratory analysis of pts with HR– mBC.

Results: As of Jan 11, 2022, 373 and 184 pts (88.7% and 88.6% HR+ mBC) were assigned to T-DXd and TPC, respectively. Median follow-up was 18.4 months (mo; 95% CI, 17.9-19.1). Median treatment duration was 8.2 mo (range, 0.2-33.3) with T-DXd and 3.5 mo (range, 0.3-17.6) with TPC. Efficacy results are in the Table. 52.6% of pts with T-DXd vs. 67.4% of pts with TPC had grade (G) ≥ 3 treatment-emergent adverse events (TEAEs). With T-DXd, 45 pts (12.1%; 10.0% G1/2, 1.3%

G3/4, 0.8% G5) had independently adjudicated drug-related interstitial lung disease [ILD]/pneumonitis vs. 1 pt (0.6% G1) with TPC.

Conclusions: DESTINY-Breast04 is the first phase 3 trial of a HER2-directed therapy in pts with HER2-low mBC to show a statistically significant and clinically meaningful benefit in PFS and OS compared to standard-of-care treatment, regardless of HR status, with a generally manageable safety profile.

Efficacy results.

	T-DXd (HR+) n = 331	TPC (HR+) n = 163	T-DXd (FAS) n = 373	TPC (FAS) n = 184	T-DXd (HR-)[a] n = 40	TPC (HR-)[a] n = 18
mPFS[b] mo (95% CI)	10.1 (9.5-11.5)	5.4 (4.4-7.1)	9.9 (9.0-11.3)	5.1 (4.2-6.8)	8.5 (4.3-11.7)	2.9 (1.4-5.1)
Hazard ratio[c] (95% CI)	0.51 (0.40-0.64)		0.50 (0.40-0.63)		0.46 (0.24-0.89)	
P value[d]	< 0.0001		< 0.0001		-	
mOS, mo (95% CI)	23.9 (20.8-24.8)	17.5 (15.2-22.4)	23.4 (20.0-24.8)	16.8 (14.5-20.0)	18.2 (13.6-NE)	8.3 (5.6-20.6)
Hazard ratio[c] (95% CI)	0.64 (0.48-0.86)		0.64 (0.49-0.84)		0.48 (0.24-0.95)	
P value[d]	0.0028		0.0010		-	

[a]Based on electronic data capture corrected for mis-stratification. [b]PFS by BICR. [c]T-DXd vs. TPC. [d]*P* values were determined by 2-sided log-rank test.m, median; NE, non-estimable.

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): a detailed safety analysis of the randomized, phase 3 DESTINY-Breast04 trial

Author: Hope Rugo
Citation: Annals of Oncology (2023) 8 (1suppl_4): 101223-101223.

Background: DESTINY-Breast04 (NCT03734029) demonstrated significantly improved overall and progression-free survival (PFS) with T-DXd vs TPC in pts with HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization-negative) mBC, with manageable safety. Here, we report additional safety data.

Methods: Pts with centrally confirmed HER2-low mBC, treated with 1-2 prior lines of chemotherapy, were randomly assigned 2:1 to receive T-DXd or TPC. An analysis of selected treatment-emergent adverse events (TEAEs) and age (<65 vs ≥65 years [y]) was done; endpoints included time to first onset (TTO), duration of first event (DUR), and resolution.

Results: At data cutoff (January 11, 2022), median (m) treatment duration was 8.2 months (mo; range [r], 0.2-33.3) for T-DXd vs 3.5 mo (r, 0.3-17.6) for TPC. Exposure-adjusted incidence rates (EAIRs; per pt-y) for any-grade TEAEs were lower for T-DXd vs TPC (1.30 vs 2.66). mTTO and mDUR of any-grade interstitial lung disease (ILD) in pts treated with T-DXd were 129 days (d; r, 26-710 d) and 47 d (r, 13-365 d). 13 pts had adjudicated drug-related grade 1 ILD; of those pts, 6 were rechallenged with T-DXd after resolution (details to be presented). Incidence of any-grade drug-related neutropenia (NP) and febrile NP was lower for T-DXd vs TPC; subsequent granulocyte colony-stimulating factor use was 6.7% vs 19.8%. Nausea/vomiting (N/V) events in T-DXd vs TPC were 79.5% vs 35.5%. T-DXd-treated pts received more antiemetic prophylaxis (AP; 50.9%) vs TPC-treated pts (37.2%); 92.3% of T-DXd and 68.8% of TPC N/V events in AP-treated pts resolved. Incidence of any-grade drug-related TEAE was consistent between pts aged <65 y and ≥65 y. For T-DXd, incidence of grade ≥3 TEAEs and

TEAEs associated with drug discontinuations (DD) was higher in pts aged ≥65 y compared to those aged <65 y; the most common TEAE associated with DD was ILD/pneumonitis. However, mPFS favored T-DXd over TPC in all patients, regardless of age. EAIR, TTO, and DUR data for selected TEAEs will be presented.

Conclusions: T-DXd demonstrated a manageable safety profile to support its use as the new standard of care in pts with HER2-low mBC

Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study.

Author: Rachel Occhiogrosso Abelman
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1022-1022.

Background: Optimizing sequential use of Antibody Drug Conjugates (ADCs) is an area of unmet need and of rising clinical importance. With the recent approvals of sacituzumab govitecan (SG) for HR+/HER2- and triple negative metastatic breast cancer (MBC) as well as trastuzumab deruxtecan (T-DXd) for HER2-low MBC, many patients are now candidates for multiple ADCs. However, given potential cross-resistance based on antibody target vs payload (Coates et al, Cancer Discov. 2021), optimal sequencing remains uncertain. We evaluated the safety and efficacy of ADC after ADC for patients with HER2 negative MBC.

Methods: We included all patients at an academic institution treated with more than one ADC for MBC. Each line of ADC beyond the first was evaluated for presence of the same "antibody target" or "payload" compared to prior ADC. Clinicopathological information was gathered by chart review. We defined "cross-resistance" as progressive disease (PD) at time of first restaging on second ADC. Progression-free survival (PFS) was evaluated as time from start of treatment to disease progression or death from any cause. All PFS estimation was done using the KM method. All pairwise comparisons across ADC were done using a Wilcoxon Rank Sum test to allow for divergences from normality in progression times. Significance was declared as a type I error less than 0.05.

Results: A total of 193 patients with MBC were treated with ADCs between August 2014-February 2023. Among these,32 patients were identified as having received more than one ADC (HR+/HER2- = 13, TNBC = 19, HER2 low = 22). Median age at time of second ADC was 57.1 years (range 31.3-88.6) and patients had received a median of 4 lines (range 2-12) of prior treatment before initiation of second ADC. The median PFS on the first ADC used (ADC1) was significantly longer at 7.55 months (95% CI 3.22-10.25) compared to a median of 2.53 months on the second ADC (ADC2) (95% CI 1.38-4.14) (p=0.006). PFS for ADC2 with antibody target change was 3.25 months (95% CI 1.38 months, n/a) compared to 2.30 months with no target change (95% CI 1.38 months, n/a) (p=0.16). At time of first imaging, cross-resistance was present in 17 cases (53.1%), absent in 12 (37.5%), and not evaluable in 3 cases. When the second ADC contained the same antibody target as the first, cross-resistance was present in 9/13 cases (69.2%), compared to 8/16 cases (50.0%) when the second ADC targeted a different tumor antigen. Similarly, differences were noted based on payload switch vs not.

This study highlights a subset that had cross-resistance to ADC after ADC, while others had durable responses on latter lines of therapy, particularly if a different antibody target was utilized. Further research is needed to validate these findings and discern mechanisms of clinical resistance to guide optimal sequencing of ADC-based treatment options

Triple Negative Breast Cancer

Long-term outcomes of neoadjuvant immunotherapy plus chemotherapy in patients with early-stage triple-negative breast cancer: an extracted individual patient data and trial-level meta-analysis

Author: Mateus Trinconi Cunha
Citation: Br J Cancer.2023 Nov 27.

Background: Neoadjuvant immunotherapy (nIO) has emerged as a treatment option for stage II-III triple-negative breast cancer (TNBC). While randomised clinical trials (RCTs) demonstrated pathological complete response rate benefit to nIO added to chemotherapy, additional data on long-term outcomes is warranted. We performed this analysis to evaluate long-term efficacy outcomes of nIO in TNBC.

Methods: We searched databases for RCTs evaluating nIO in early-stage TNBC. A meta-analysis of extracted individual patient data (EIPD) was performed to evaluate EFS and OS, with data from reported Kaplan-Meier plots. Additionally, we conducted a trial-level meta-analysis using fixed and random effects models.

Results: The literature search resulted in four included RCTs with available EFS or OS (KEYNOTE-522, IMpassion031, I-SPY2 and GeparNuevo). EIPD showed that the addition of nIO to chemotherapy provides statistically significant benefits in EFS (HR 0.62, 0.50-0.76; $p < 0.001$) and OS (HR 0.62, 0.46-0.82, $p < 0.001$). Number needed to treat to avoid one EFS or OS event in 4 years was 9 and 14, respectively. Trial-level meta-analysis yielded similar results (EFS: HR 0.64, 0.51-0.79; OS: 0.57, 0.37-0.89).

Conclusions: Results show that nIO combined with chemotherapy can provide significant EFS and OS benefits, supporting its use as standard treatment for early-stage TNBC.

Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)
Citation: Lancet. 2023 Apr 15;401(10384):1277-1292.

Background: Anthracycline–taxane chemotherapy for early - stage breast cancer substantially improves survival compared with no chemotherapy. However, concerns about short-term and long-term side-effects of anthracyclines have led to increased use of taxane chemotherapy without anthracycline, which could compromise efficacy. We aimed to better characterise the benefits and risks of including anthracycline, and the comparative benefits of different anthracycline–taxane regimens.

Methods: We did an individual patient-level meta-analysis of randomised trials comparing taxane regimens with versus without anthracycline, and updated our previous meta-analysis of anthracycline regimens with versus without taxane, as well as analysing 44 trials in six related comparisons. We searched databases, including MEDLINE, Embase, the Cochrane Library, and meeting abstracts to identify trials assessing anthracycline and taxane chemotherapy. Adjuvant or neoadjuvant trials were eligible if they began before Jan 1, 2012. Primary outcomes were breast cancer recurrence and cause-specific mortality. Log-rank analyses yielded first-event rate ratios (RRs) and CIs.

Findings: 28 trials of taxane regimens with or without anthracycline were identified, of which 23 were deemed eligible, and 15 provided data on 18 103 women. Across all 15 trials that provided individual data, recurrence rates were 14% lower on average (RR 0·86, 95% CI 0·79–0·93; p=0·0004) with taxane regimens including anthracycline than those without. Non-breast cancer deaths were not increased but there was one additional acute myeloid leukaemia case per 700 women treated. The clearest reductions in recurrence were found when anthracycline was added concurrently to docetaxel plus

cyclophosphamide versus the same dose of docetaxel plus cyclophosphamide (10-year recurrence risk 12·3% vs 21·0%; risk difference 8·7%, 95% CI 4·5–12·9; RR 0·58, 0·47–0·73; p<0·0001). 10-year breast cancer mortality in this group was reduced by 4·2% (0·4–8·1; p=0·0034). No significant reduction in recurrence risk was found for sequential schedules of taxane plus anthracycline when compared with docetaxel plus cyclophosphamide (RR 0·94, 0·83–1·06; p=0·30). For the analysis of anthracycline regimens with versus without taxane, 35 trials (n=52 976) provided individual patient data. Larger recurrence reductions were seen from adding taxane to anthracycline regimens when the cumulative dose of anthracycline was the same in each group (RR 0·87, 0·82–0·93; p<0·0001; n=11 167) than in trials with two-fold higher cumulative doses of non-taxane (mostly anthracycline) in the control group than in the taxane group (RR 0·96, 0·90–1·03; p=0·27; n=14 620). Direct comparisons between anthracycline and taxane regimens showed that a higher cumulative dose and more dose-intense schedules were more efficacious. The proportional reductions in recurrence for taxane plus anthracycline were similar in oestrogen receptor-positive and oestrogen receptor-negative disease, and did not differ by age, nodal status, or tumour size or grade.

Interpretation: Anthracycline plus taxane regimens are most efficacious at reducing breast cancer recurrence and death. Regimens with higher cumulative doses of anthracycline plus taxane provide the greatest benefits, challenging the current trend in clinical practice and guidelines towards non-anthracycline chemotherapy, particularly shorter regimens, such as four cycles of docetaxel–cyclophosphamide. By bringing together data from almost all relevant trials, this meta-analysis provides a reliable evidence base to inform individual treatment decisions, clinical guidelines, and the design of future clinical trials.

Randomized trial of fixed-dose capecitabine compared to standard dose capecitabine in metastatic breast cancer: The X-7/7 trial.

Author: Qamar J. Khan
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1007-1007.

Background: In metastatic breast cancer (MBC), oral capecitabine prescribed at the FDA approved dose of 1250 mg/m^2 twice daily, 14 days on followed by 7 days off, is associated with poor tolerance and high discontinuation rates. Mathematical models suggest a fixed dose, dose dense (7 days on, 7 days off) schedule may be optimal for capecitabine efficacy. We conducted a randomized trial to compare the efficacy and tolerability of fixed-dose capecitabine, 1500 mg twice daily, 7 days on, 7 days off (FD) to the FDA approved dose and schedule (SD).

Methods: Females with MBC and any prior lines of endocrine therapy or chemotherapy were included. HER-2 positive patients were allowed with concurrent trastuzumab. Patients were stratified by line of chemotherapy (first or subsequent), measurable disease, and ER status, and randomized 1:1 to either FD or SD. The primary endpoint was 3-month progression free survival (PFS). Additional endpoints included PFS and overall survival (OS). Capecitabine related toxicities were solicited and graded at each visit.

Results: Between October 2015 and April 2021, 153 patients were enrolled (N=80 FD, N=73 SD). 78% were hormone receptor positive/HER-2 negative, 11% each were HER-2 positive and triple negative. The 3-month PFS was 76% in the FD arm and 76% in the SD arm (HR=1.01; 95% CI, 0.52 to 1.94; p=0.99). Landmark analysis of PFS at 12, 24 and 36 months is reported. Non-proportional hazards were detected, so restricted mean survival time (RMST) was used to report estimates of effect.PFS (restricted mean) at 36 months was 13.9 months in the FD arm versus 14.6 months in the SD arm (hazard ratio for progression or death, 1.31; 95% CI, 0.56 to 1.15; p=0.24). OS (restricted mean) at 36 months was 21.2 months in the FD arm versus 19.6 months in the SD arm (hazard ratio for death,

0.80; 95% CI, 0.55 to 1.81; p=0.27). Toxicity related treatment discontinuation occurred in 21 patients (28.8%) in the SD arm compared to 6 patients (7.5%) in the FD arm (p<0.0006). Grade 2-4 toxicities (Table) occurred more frequently in patients receiving SD capecitabine (49.3%) as compared to FD capecitabine (25.0%) (p=0.0018).

Conclusions: Fixed dose capecitabine (1500 mg twice daily) on a 7/7 schedule has less toxicity and similar survival when compared to standard BSA-based dosing on a 14/7 schedule in MBC.

Progression free survival by time; adverse events.

Time	FD, N=80 (%)	SD, N=73 (%)	P-value (HR; 95% CI)
12-month	39	50	0.23 (1.31; 0.84-2.02)
24-month	25	23	0.77 (1.06; 0.73-1.53)
36-month	11	0	0.24 (0.81; 0.56-1.15)
Adverse Event			
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	2 (2.5)	15 (20.5)	0.0008
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	3 (3.8)	11 (15.1)	0.0019
Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	0	4 (5.48)	<0.0001
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	17 (21.25)	20 (27.4)	0.68

BRCA-CRisk: A Contralateral Breast Cancer Risk Prediction Model for BRCA Carriers

Author: Jie Sun
Citation: J Clin Oncol. 2023 Feb 10;41(5):991-999.

Purpose: The absolute cumulative risk of contralateral breast cancer (CBC) for patients with BRCA1/2 variants is unknown. The purpose of this study was to develop a CBC risk prediction model for assessing CBC risk for BRCA1/2 carriers.

Methods: The primary cohort of 491 patients with BRCA1/2 variants was derived from a large series of unselected patients with breast cancer. A nomogram was established on the basis of the results of a multivariate Cox regression analysis from this cohort. This model, named BRCA-CRisk, was further validated by an independent cohort of 205 patients with BRCA1/2 variants. Discrimination and calibration of the model were assessed.

Results: In the primary cohort of 491 patients, 66 developed contralateral breast cancer after a median follow-up of 7.0 years. Four variables were significantly associated with risk of CBC and were incorporated in the establishment of the BRCA-CRisk prediction model: younger age at first breast cancer (with continuous variable, P = .002), positive first-degree family history of breast and/or ovarian cancer (hazard ratio [HR], 1.89; 95% CI, 1.16 to 3.08; P = .011), variant located near the 3' region of BRCA (HR, 2.01; 95% CI, 1.23 to 3.30; P = .006), and endocrine therapy (HR, 0.54; 95% CI, 0.33 to 0.88; P = .013). The area under the time-dependent curves for the 5- and 10-year cumulative risks of CBC were 0.775 and 0.702, respectively. The model was well validated in the independent cohort of 205 BRCA1/2 carriers, with area under the curves of 0.750 and 0.691 for 5 and 10 years, respectively.

Conclusion: BRCA-CRisk model provides a useful tool for assessing the absolute cumulative risk of CBC for BRCA1/2 carriers and may help carriers and clinicians optimally select risk-reducing strategies on the basis of individual CBC risk.

Patient characteristics and real-world outcomes in HER2 negative/ ER zero and ER low patients treated as triple-negative breast cancer in Sweden 2008-2020

Author: Irma Fredriksson
Citation: Annals of Oncology (2023) 34 (suppl_2): S278-S324.

Background: Estrogen receptor-low (ER-low) Her2-negative breast cancer has similar pathological and molecular characteristics as triple-negative breast cancer (TNBC), and it is questionable whether it should be considered a separate entity. When the international guidelines lowered the cutoffs for ER to ≥1% in 2010, the ≥10% threshold was kept in Sweden. ER-low breast cancer (ER 1-9%) has thus in Sweden been treated as TNBC, which is interesting now that the international community recognize limited data for benefit of endocrine therapy in the ER-low group The benefit of endocrine therapy in these tumors is under debate and discussion. We aimed to describe real-world patient and tumor characteristics, treatment patterns and overall survival in a Swedish population-based cohort of patients with HER2 negative/ ER zero and ER low breast cancer treated as TNBC.

Methods: TNBC cases diagnosed in Sweden 2008-2020 were included in a population-based cohort study. Patient, tumour and treatment characteristics were analysed by ER status (ER-negative 0% vs ER-low 1-9%), and associations between subgroups compared using $\chi 2$ test. Endpoints were overall survival (OS) and distant disease-free survival (DDFS). Kaplan-Meier curves were used to describe time-to-event endpoints and Cox proportional hazards models to estimate adjusted hazard ratios.

Results: Of the 5657 tumors, 90.1% were ER-negative and 9.9% ER-low. In the unadjusted analysis of OS, ER-low disease was associated with a borderline significantly better OS than ER-negative disease (n=3893, HR 0.83 (0.70-1.001), p=0.051), but this was restricted to patients not given chemotherapy (n=1764, HR 0.65 (0.50-0.88), p=0.002). ER-status 0% vs 1-9% did not affect OS in the

multivariable analysis (HR 1.09, 95% CI 0.89-1.34). DDFS did not differ by ER-status 0% vs 1-9% (n=1299, HR 0.97 for ER-negative vs ER-low (0.62-1.53)). After preoperative treatment, the importance of pCR for OS did not significantly differ between ER-negative or ER-low disease.

Conclusions: ER-low breast cancer has characteristics and prognosis similar to ER-negative breast cancer when treated as TNBC. The use of ≥10% as threshold for ER positivity is supported by this study.

Risk factors for the development of triple-negative breast cancer versus non-triple-negative breast cancer: a case-control study

Author: Shona Nag
Citation: Sci Rep.2023 Aug 20;13(1):13551.

The risk factors for breast cancer have been defined in several studies but there is deficient data for specific subtypes. We report here the pathological characteristics of a breast cancer cohort and risk factors for patients with triple-negative disease. In this case-control study, a prospective breast cancer cohort was evaluated for demographic, reproductive, obesity-related and other risk factors using a validated questionnaire. Tumors were characterized for routine pathological characteristics and immunohistochemical markers of basal-like breast cancer. Patients with triple-negative breast cancer (TNBC) constituted cases and those with non-TNBC were controls. Odds ratios (OR) were calculated for each risk factor and independent associations were tested in an unconditional logistic regression analysis. Between 2011 and 2014, 1146 patients were recruited, of whom 912 [TNBC 266 (29.1%), non-TNBC 646 (70.9%)] with sufficient pathology material were analysed. Reproductive factors of parity, breastfeeding, age-at-menarche, age at first full-term pregnancy and oral contraceptive use were not significantly associated with TNBC. Higher body mass index (BMI > 24.9 vs ≤ 24.9, OR 0.89, 95%CI 0.63-1.24, p = 0.49) was not significantly associated while lesser waist circumference (> 80 cm vs ≤ 80 cm, OR 0.64, 95%CI 0.45-0.9, p = 0.012) and lower waist-to-hip

ratio were significantly associated (> 0.85 vs ≤ 0.85, OR 0.72, 95%CI 0.51-1.0, p = 0.056), with TNBC. History of tobacco use was not significantly associated while lower socio-economic status was borderline associated with TNBC (socio-economic category > 5 versus ≤ 5, OR 0.73, 95%CI 0.50-1.06, p = 0.106). No factor was significant after adjustment for covariates. Central obesity seems to be preferentially associated with non-TNBC, and lower socio-economic status with TNBC in India, while most other conventional risk factors of breast cancer show no significant association with TNBC versus non-TNBC.

Contralateral breast cancer risk in patients with breast cancer and a germline-BRCA1/2 pathogenic variant undergoing radiation

Author: Mark van Barele
Citation: J Natl Cancer Inst. 2023 Nov 8;115(11):1318-1328.

Background: Radiation-induced secondary breast cancer (BC) may be a concern after radiation therapy (RT) for primary breast cancer (PBC), especially in young patients with germline (g)BRCA-associated BC who already have high contralateral BC (CBC) risk and potentially increased genetic susceptibility to radiation. We sought to investigate whether adjuvant RT for PBC increases the risk of CBC in patients with gBRCA1/2-associated BC.

Methods: The gBRCA1/2 pathogenic variant carriers diagnosed with PBC were selected from the prospective International BRCA1/2 Carrier Cohort Study. We used multivariable Cox proportional hazards models to investigate the association between RT (yes vs no) and CBC risk. We further stratified for BRCA status and age at PBC diagnosis (<40 and >40 years). Statistical significance tests were 2-sided.

Results: Of 3602 eligible patients, 2297 (64%) received adjuvant RT. Median follow-up was 9.6 years. The RT group had more patients with stage III PBC than the non-RT group (15% vs 3%, P < .001), received chemotherapy more often (81% vs 70%, P < .001), and received endocrine therapy more often (50% vs 35%, P < .001). The RT group had an increased CBC risk compared with the

non-RT group (adjusted hazard ratio [HR] = 1.44; 95% confidence interval [CI] = 1.12 to 1.86). Statistical significance was observed in gBRCA2 (HR = 1.77; 95% CI = 1.13 to 2.77) but not in gBRCA1 pathogenic variant carriers (HR = 1.29; 95% CI = 0.93 to 1.77; P = .39 for interaction). In the combined gBRCA1/2 group, patients irradiated when they were younger than or older than 40 years of age at PBC diagnosis showed similar risks (HR = 1.38; 95% CI = 0.93 to 2.04 and HR = 1.56; 95% CI = 1.11 to 2.19, respectively).

Conclusions: RT regimens minimizing contralateral breast dose should be considered in gBRCA1/2 pathogenic variant carriers.

Homologous recombination (HR) status of platinum responsive advanced triple negative breast cancers (aTNBC) treated with olaparib as maintenance therapy

Author: Tira Tan
Citation: Annals of Oncology (2023) 8 (1suppl_4): 101218-101218.

Background: HR deficiency (HRD) may be exploited through use of DNA-damaging chemotherapy and/or PARP inhibitors (PARPi). The current biomarker to infer HRD in breast cancer (BC) is a germline pathogenic variant (PV) in BRCA1/2 (gBRCAm). This biomarker strategy misses a significant proportion of HRD BC. We analysed the HR status of an enriched cohort of platinum-responsive aTNBC on the DORA study.

Methods: Between Feb 2019, and Dec 2020, 45 patients (pts) were enrolled to receive maintenance olaparib (O) +/- durvalumab (D). HRD testing using Pillar Biosciences oncoReveal™ HRD Panel was performed on archival tissue. This panel detects SNVs and indels in 33 HR related genes. Quantitation of BRCA1 and RAD51C promoter methylation assessed using oncoReveal™ BRCA1 & RAD51C Methylation Panel. Median progression free survival (mPFS) by HR status was compared using log-rank test.

Results: Of the 45 pts, 40 had available samples for HRD testing. gBRCAm were reported from medical history: 15 (37.5%) gBRCA unknown, 17 (42.5%) gBRCA wildtype, 8 (20%) gBRCAm. 21 (52.5%), harbored any HR alterations (HRD). OncoReveal™ panel identified 8 BRCA1 (1 FANCA co-mutation), 1 BRCA2, 2 PALB2, 1 BRIP1, 1 RAD51D PV. Mutually exclusive to BRCA PV, 9 were identified to have BRCA1 promoter hypermethylation, 5 classified as highly methylated. 1 tumor with partial BRCA1 hypermethylation had concurrent highly methylated RAD51C. 1 BRCA1 highly methylated tumor had a co-mutation with BRIP1. The mPFS of pts with HRD vs. no HRD was 7.8 months (m) (3.9 - not estimable) vs. 2.1 m (1.9 - 3.4), p=0.002. The association between mPFS and HRD did not vary by maintenance therapy. The mPFS of O pts (HRD n=9 vs. no HRD n=10) is 7.8 vs 1.9 m HR 0.3; 0.11-0.8 and of O+D pts (HRD n=12 vs. no HRD n=9) is 7.4 vs 3.3 m HR 0.34; 0.12-1.0. 11 of the 21 pts with HRD were on maintenance therapy for >6 months vs. 3 of the 19 pts without HRD.

Conclusions: BRCA1/RAD51C promoter hypermethylation and mutations are mutually exclusive with similar proportions identified in this enriched cohort of aTNBC. Current companion diagnostic for PARPi therapy underestimates the proportion of BC with HRD. Testing for BRCA1/RAD51C hypermethylation to guide therapies is worthy of further exploration.

Translational Science

Predicting early breast cancer recurrence from histopathological images in the Carolina Breast Cancer Study

Author: Yifeng Shi
Citation: NPJ Breast Cancer. 2023 Nov 11;9(1):92.

Approaches for rapidly identifying patients at high risk of early breast cancer recurrence are needed. Image-based methods for prescreening hematoxylin and eosin (H&E) stained tumor slides could offer temporal and financial efficiency. We evaluated a data set of 704 1-mm tumor core H&E images (2-4 cores per case), corresponding to 202 participants (101 who recurred; 101 non-recurrent matched on age and follow-up time) from breast cancers diagnosed between 2008-2012 in the Carolina Breast Cancer Study. We leveraged deep learning to extract image information and trained a model to identify recurrence. Cross-validation accuracy for predicting recurrence was 62.4% [95% CI: 55.7, 69.1], similar to grade (65.8% [95% CI: 59.3, 72.3]) and ER status (66.3% [95% CI: 59.8, 72.8]). Interestingly, 70% (19/27) of early-recurrent low-intermediate grade tumors were identified by our image model. Relative to existing markers, image-based analyses provide complementary information for predicting early recurrence.

Prognostic value of plasma circulating tumor DNA fraction across four common cancer types: a real-world outcomes study

Author: Z R Reichert
Citation: Ann Oncol. 2023 Jan;34(1):111-120.

Background: Genomic analysis of circulating tumor DNA (ctDNA) is increasingly incorporated into the clinical management of patients with advanced cancer. Beyond tumor profiling, ctDNA analysis also can enable calculation of circulating tumor fraction (TF), which has previously been found to be prognostic. While most prognostic models in metastatic cancer are tumor type specific and require

significant patient-level data, quantification of TF in ctDNA has the potential to serve as a pragmatic, tumor-agnostic prognostic tool.

Patients and methods: This study utilized a cohort of patients in a nationwide de-identified clinico-genomic database with metastatic castration-resistant prostate cancer (mCRPC), metastatic breast cancer (mBC), advanced non-small-cell lung cancer (aNSCLC), or metastatic colorectal cancer (mCRC) undergoing liquid biopsy testing as part of routine care. TF was calculated based on single-nucleotide polymorphism aneuploidy across the genome. Clinical, disease, laboratory, and treatment data were captured from the electronic health record. Overall survival (OS) was evaluated by TF level while controlling for relevant covariables.

Results: A total of 1725 patients were included: 198 mCRPC, 402 mBC, 902 aNSCLC, and 223 mCRC. TF ≥10% was highly correlated with OS in univariable analyses for all cancer types: mCRPC [hazard ratio (HR) 3.3, 95% confidence interval (CI) 2.04-5.34, $P < 0.001$], mBC (HR 2.4, 95% CI 1.71-3.37, $P < 0.001$), aNSCLC (HR 1.68, 95% CI 1.34-2.1, $P < 0.001$), and mCRC (HR 2.11, 95% CI 1.39-3.2, $P < 0.001$). Multivariable assessments of TF had similar point estimates and CIs, suggesting a consistent and independent association with survival. Exploratory analysis showed that TF remained consistently prognostic across a wide range of cutpoints.

Conclusions: Plasma ctDNA TF is a pragmatic, independent prognostic biomarker across four advanced cancers with potential to guide clinical conversations around expected treatment outcomes. With further prospective validation, ctDNA TF could be incorporated into care paradigms to enable precision escalation and de-escalation of cancer therapy based on patient-level tumor biology.

Molecular classification of hormone receptor-positive HER2-negative breast cancer

Author: Xi Jin
Citation: Nat Genet. 2023 Oct;55(10):1696-1708.

Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer is the most prevalent type of breast cancer, in which endocrine therapy resistance and distant relapse remain unmet challenges. Accurate molecular classification is urgently required for guiding precision treatment. We established a large-scale multi-omics cohort of 579 patients with HR+/HER2- breast cancer and identified the following four molecular subtypes: canonical luminal, immunogenic, proliferative and receptor tyrosine kinase (RTK)-driven. Tumors of these four subtypes showed distinct biological and clinical features, suggesting subtype-specific therapeutic strategies. The RTK-driven subtype was characterized by the activation of the RTK pathways and associated with poor outcomes. The immunogenic subtype had enriched immune cells and could benefit from immune checkpoint therapy. In addition, we developed convolutional neural network models to discriminate these subtypes based on digital pathology for potential clinical translation. The molecular classification provides insights into molecular heterogeneity and highlights the potential for precision treatment of HR+/HER2- breast cancer.

Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival

Author: Josephine M N Lopes Cardozo
Citation: J Clin Oncol. 2023 Apr 1;41(10):1849-1863.

Purpose: A polygenic risk score (PRS) consisting of 313 common genetic variants (PRS313) is associated with risk of breast cancer and contralateral breast cancer. This study aimed to evaluate the association of the PRS313 with clinicopathologic characteristics of, and survival following, breast cancer.

Methods: Women with invasive breast cancer were included, 98,397 of European ancestry and 12,920 of Asian ancestry, from the Breast Cancer Association Consortium (BCAC), and 683 women from the European MINDACT trial. Associations between PRS313 and clinicopathologic characteristics, including the 70-gene signature for MINDACT, were evaluated using logistic regression analyses. Associations of PRS313 (continuous, per standard deviation) with overall survival (OS) and breast cancer-specific survival (BCSS) were evaluated with Cox regression, adjusted for clinicopathologic characteristics and treatment.

Results: The PRS313 was associated with more favorable tumor characteristics. In BCAC, increasing PRS313 was associated with lower grade, hormone receptor-positive status, and smaller tumor size. In MINDACT, PRS313 was associated with a low risk 70-gene signature. In European women from BCAC, higher PRS313 was associated with better OS and BCSS: hazard ratio (HR) 0.96 (95% CI, 0.94 to 0.97) and 0.96 (95% CI, 0.94 to 0.98), but the association disappeared after adjustment for clinicopathologic characteristics (and treatment): OS HR, 1.01 (95% CI, 0.98 to 1.05) and BCSS HR, 1.02 (95% CI, 0.98 to 1.07). The results in MINDACT and Asian women from BCAC were consistent.

Conclusion: An increased PRS313 is associated with favorable tumor characteristics, but is not independently associated with prognosis. Thus, PRS313 has no role in the clinical management of primary breast cancer at the time of diagnosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS313 as increasing PRS313 is associated with an increased risk of disease. This information is crucial for modeling effective stratified screening programs.

Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2

Author: Siddhartha Yadav
Citation: J Clin Oncol. 2023 Mar 20;41(9):1703-1713.

Purpose: To estimate the risk of contralateral breast cancer (CBC) among women with germline pathogenic variants (PVs) in ATM, BRCA1, BRCA2, CHEK2, and PALB2.

Methods: The study population included 15,104 prospectively followed women within the CARRIERS study treated with ipsilateral surgery for invasive breast cancer. The risk of CBC was estimated for PV carriers in each gene compared with women without PVs in a multivariate proportional hazard regression analysis accounting for the competing risk of death and adjusting for patient and tumor characteristics. The primary analyses focused on the overall cohort and on women from the general population. Secondary analyses examined associations by race/ethnicity, age at primary breast cancer diagnosis, menopausal status, and tumor estrogen receptor (ER) status.

Results: Germline BRCA1, BRCA2, and CHEK2 PV carriers with breast cancer were at significantly elevated risk (hazard ratio > 1.9) of CBC, whereas only the PALB2 PV carriers with ER-negative breast cancer had elevated risks (hazard ratio, 2.9). By contrast, ATM PV carriers did not have significantly increased CBC risks. African American PV carriers had similarly elevated risks of CBC as non-Hispanic White PV carriers. Among premenopausal women, the 10-year cumulative incidence of CBC was estimated to be 33% for BRCA1, 27% for BRCA2, and 13% for CHEK2 PV carriers with breast cancer and 35% for PALB2 PV carriers with ER-negative breast cancer. The 10-year cumulative incidence of CBC among postmenopausal PV carriers was 12% for BRCA1, 9% for BRCA2, and 4% for CHEK2.

Conclusion: Women diagnosed with breast cancer and known to carry germline PVs in BRCA1, BRCA2, CHEK2, or PALB2 are at substantially increased risk of CBC and may benefit from enhanced surveillance and risk reduction strategies.

Overall Survival With Circulating Tumor Cell Count-Driven Choice of Therapy in Advanced Breast Cancer: A Randomized Trial

Author: François-Clément Bidard
Citation: J Clin Oncol. 2023 Nov 6:JCO2300456.

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.In patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer, the STIC CTC trial established that, for choosing between endocrine therapy (ET) or chemotherapy, the use of circulating tumor cell (CTC) count is noninferior to the investigator's choice in terms of progression-free survival. Here, we report overall survival (OS) results, a secondary end point. Patients were randomly assigned in a 1:1 ratio to have their first-line treatment (ET or chemotherapy) determined by investigators or CTC count (chemotherapy if ≥ 5 CTCs/7.5 mL; ET if low CTC count; CellSearch). OS was assessed at the discontinuation of follow-up. After a median follow-up of 4.7 years, 382 deaths (50.6%) had occurred among 755 patients. Median OS was 51.3 months (95% CI, 46.8 to 55.1) in the CTC arm and 45.5 months (95% CI, 40.9 to 51.1) in the standard arm (hazard ratio [HR] for death, 0.85; 95% CI, 0.69 to 1.03; P = .11). Among 189 patients (25.0%) with ET recommended by clinicians and high CTC count, chemotherapy was superior to ET (HR for death, 0.53; 95% CI, 0.36 to 0.78; P = .001). In case of a discordant estimate, OS data demonstrate the clinical utility of CTC count.

Detection of circulating tumor DNA following neoadjuvant chemotherapy and surgery to anticipate early relapse in ER positive and HER2 negative breast cancer: Analysis from the PENELOPE-B trial.

Author: Nicholas C. Turner
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 502-502.

Background: The PENELOPE-B phase III trial investigated the addition of one year of palbociclib to endocrine therapy (ET), in patients with hormone receptor positive HER2 negative breast cancer with residual invasive disease after neoadjuvant chemotherapy. Prior research has demonstrated that detection of circulating tumor DNA (ctDNA) in the adjuvant setting is associated with a high risk of disease relapse. We assessed the potential of ctDNA analysis to predict future clinical relapse for patients enrolled in the PENELOPE-B trial.

Methods: Patients who were endocrine naïve at the time of study entry were selected for ctDNA analysis. Plasma samples were collected at baseline (after completion of neoadjuvant chemotherapy and surgery), prior to cycle 7 (approximately 6 months into ET +- palbociclib), end of treatment (EOT), and progressive disease. A tumor sample was subjected to exome sequencing, and up to 50 tumor somatic mutations were tracked in plasma using error-corrected sequencing combined with a proprietary algorithm for ctDNA detection (RaDaR assay). Detection of ctDNA was associated with invasive disease-free survival (iDFS) and distant metastasis-free survival using Cox proportional hazard models.

Results: Of 1250 patients enrolled in PENELOPE-B, 129 were endocrine naïve at trial entry, and 78 had a baseline ctDNA sample analyzed. The ctDNA analysis group was representative of the overall endocrine naïve group, with median follow-up of 42.9 months. Seven patients had baseline ctDNA detected, with detection strongly associated with iDFS (HR 8.8, 95% CI 3.3-23.4, $p < 0.0001$). Detection of ctDNA at cycle 7 (4 patients) was also strongly associated with iDFS (HR 25.5, 95% CI 6.5-99.6, $p < 0.0001$). Of the 7 patients with baseline ctDNA

detection, 2 had undetectable ctDNA at cycle 7 and remained progression free at 30 months, although one later relapsed; the 3 patients with detectable ctDNA at cycle 7 all relapsed within 25 months. Of the 12 patients with a distant relapse within 24 months, only 4 had ctDNA detected at baseline and 3 first at cycle 7/EOT. Of the 8 patients with distant relapse after 24 months, 2 had ctDNA detected at baseline and none first at cycle 7/EOT.

Conclusions: Detection of ctDNA following neoadjuvant chemotherapy, and surgery, is associated with a very high risk of early relapse suggesting limited efficacy of adjuvant ET. Clinical imaging and studies of experimental therapy are warranted in this patient population. Testing ctDNA after recent neoadjuvant chemotherapy in luminal-A like breast cancer has relatively low 'sensitivity' for predicting future relapse, in particular for later relapses, in part suggesting that response to neoadjuvant chemotherapy may reduce ctDNA detection

Inflammatory profiling of individuals with germline TP53 mutations (gTP53m) and its relationship to subsequent cancer development

Author: Tarek BEN AHMED
Citation: Annals of Oncology (2023) 8 (1suppl_4): 101222-101222.

Background: Individuals with gTP53m have nearly 24 times higher incidence of any cancer than the general population, of which breast cancer (BC) comes first. Beside prophylactic mastectomy, no preventative measures are currently available. Nothing or very little is known regarding the role of immune and inflammatory factors. We aimed to search for predictors of the development of new subsequent cancers (NSC) among inflammatory and immune cytokines, in patients (pts) with gTP53m from the prospective LIFSCREEN MRI screening trial (NCT01464086).

Methods: All pts with gTP53m who entered the LIFSCREEN trial at Gustave Roussy 11/2011 - 12/2014, with frozen serum samples available were eligible. We analysed inflammatory cytokines and chemokines on samples collected sequentially at accrual month (M) 0 and at M12 using multiplex immunoassay

of serum analytes (Bio-Plex Pro™ 40-plex, Bio-Rad). Primary objective was potential associations between M0 and M12 biomarkers and the incidence of any NSC. We used Wilcoxon-Mann Whitney tests and logistic regressions.

Results: Among 107 pts, 42 had serum stored and were eligible. Median age 35.5 (7-67), 67% females. Median follow-up 100 months (95% CI 83-117). 24 pts (57%) had already had cancer before entering the study, of which 7 BC. 11 NSC were diagnosed. At M0, a Th1-like profile (high serum IL-2 (>2 pg/ml) (p=0.03; overall) and CXCL9 levels (>50 pg/ml) (p=0.01; without history of cancers)) was associated with the incidence of NSC. In logistic regression, the Th1 CXCL9 and CXCL10 chemokines were associated with a higher probability of NSC (p=0.03 and 0.04, respectively). At M12, high levels of the follicular T helper cell CXCL13 (>25 pg/ml) chemokine were protective against NSC (p=0.04). Individuals with a significant drop between M0 and M12 of neutrophil and T cell-chemoattracting factors (such as CXCL1 and IFNg/CXCL16 respectively) did not develop cancer.

Conclusions: This exploratory study identifies a disbalance between Th1 and TFH soluble markers in Li Fraumeni deemed to experience additional neoplasia among pts carrying gTP53m. These findings warrant further validation and could be actionable for cancer interception.

First results of the SOLTI-1903 HOPE's patient-centric molecular screening program in advanced breast cancer

Author: Tomás Pascual
Citation: Annals of Oncology (2023) 34 (suppl_2): S334-S390.

Background: The SOLTI-1903 HOPE study aims to assess the feasibility of a molecular screening program promoting active participation of patients with Advanced Breast Cancer (ABC) in the management of their disease to better characterize the genomic landscape of ABC and to facilitate pt access to matched-targeted therapies in Spain.

Methods: HOPE (NCT04497285) is a patient-centric study where pts diagnosed with ABC lead their inclusion, participation, and follow-up through a digital tool (DT). They report clinical information and provide archival tumor samples to be analyzed by FoundationOne CDx. At progression disease, patients undergo a liquid biopsy with the Guardant360 panel. Clinical and genomic information is discussed by a Molecular Advisory Board (MAB) that issues a report explaining the alterations and enumerating potentially useful targeted treatments. Then, participants record disease evolution in the DT for 2y. The primary objective is to assess the real-world clinical practice of integrating molecular profiling into the Standard of Care management of pts with ABC.

Results: Between Oct 2020 and Feb 2022, 604 patients were included in the study, and the median age was 51 ys (range 27-82y). The most common reported IHC subtype was ER+/HER2- (74%), followed by HER2+ (14%) and triple negative (12%). 512 tumor samples were received from 423 patients, and DNA-seq results with positive results were obtained in 298 (58%) cases. Common alterations were PIK3CA mut (34%), CCND1 amp (27%), and TP53 mut (26%). Blood extractions were obtained from 378 patients, and ctDNA detection was observed in 303 (80%) cases. Frequently mutated genes were PIK3CA (38%), TP53 (38%), and ESR1 (29%). As of April 2023, the MAB reviewed 306 cases, observing at least one ESCAT I-III alteration in 75% of cases. Of these, only 15% were already known before HOPE. After a mean follow-up of 1.3ys, 20% of ABC cases discussed received a targeted treatment.

Conclusions: Patient-centric molecular screening programs implemented on a nationwide level are viable, have the potential to impact treatment decisions in a subgroup of patients and seems more efficient to bring patients to receive treatments targeted to the identified alterations

Association of tumor-infiltrating lymphocytes (TILs) with recurrence score (RS) in patients with hormone receptor-positive (HR+)/HER2-negative (HER2-) early breast cancer (BC): A translational analysis of four prospective multicentric studies

Author: Federica Miglietta
Citation: Annals of Oncology (2023) 34 (suppl_2): S278-S324.

Background: Oncotype DX represents one of the genomic assays associated with the highest quality of evidence driving a strong recommendation for its use to guide decisions on adjuvant therapy for HR+/HER2- early BC patients. The clinical value of TILs in HR+/HER2- BC may be unearthed by focusing on patients whose tumors exhibit features of higher biological aggressiveness. Here we deepen and describe the correlation between RS and TILs, proposing an immuno-genomic model for HR+/HER2- BC.

Methods: We enrolled T1-T3, N0-N1 BC patients with available RS and TILs in the context of four multicenter, prospective studies primarily aimed at assessing the impact of the Oncotype DX® test on adjuvant treatment decisions in a clinical practice scenario. RS was categorized into: 0-10 (low risk), 11-25 (intermediate risk) and 26-100 (high risk); TILs were categorized into: low (0-10%), intermediate (11-59%) and high (60-100%).

Results: 811 patients were included. RS distribution was (n=810): low risk 22.0%, intermediate risk 61.2%, high risk 16.8%. TIL distribution was (n=455): low TILs 84.6%, intermediate TILs 13.6% and high TILs 1.8%. A significant, weak positive, linear correlation was found between continuous TILs and RS (Pearson coefficient=0.223, $p<0.001$). When considering RS and TILs categories, tumors with intermediate/high TIL levels significantly enriched the high RS subgroup ($p=0.006$). This was confirmed both within Luminal A (Ki67<20% and PgR ≥20%) and Luminal B cohorts (ki67≥20% and/or PgR <20%). Among high-RS patients, 16.7% of Luminal A and 26.7% of Luminal B tumors had intermediate/high TILs.

Conclusions: We observed that RS and TILs capture only slightly overlapping information on the biology of HR+/HER2- tumor microenvironment. We demonstrated the feasibility of combining RS and TILs into a composite immuno-genomic model, which may identify patients simultaneously showing features of high biological/clinical risk and enhanced immunogenicity and may serve the purpose of guiding and focalizing patient selection in the further development of immunotherapy strategies for Luminal-like disease.

Multiparametric prognostic score in early HR+/HER2- breast cancer: Impact of recurrence score, clinical-pathological factors, gene mutations and histology

Author: Oleg Gluz
Citation: Annals of Oncology (2023) 34 (suppl_2): S1254-S1335.

Background: Several analyses have shown prognostic impact of clinical and IHC markers in addition to genomic signatures in HR+/HER2 EBC. However, it remains unclear whether histology (e.g. invasive lobular BC (ILC) or further factors provide additional information. We present outcome from the prospective WSG-ADAPT HR+/HER- trial combining both static and dynamic biomarkers to optimize adjuvant therapy in luminal EBC.

Methods: pN0-1 with clinically high-risk HR+/HER2- EBC pts with RS0-11 OR RS12-25/Ki67postendocrine≤10% after 3 +/- of preoperative ET received ET alone; the remaining high-risk cohort was randomized to the CT trial. Prognostic scores containing clinical factors with and w/out mutational/copy number data were derived retrospectively after splitting the data into training- and validation sets. LASSO and cross validation methods were used to predict iDFS in therapy subgroups. Additionally, multivariate Cox models were adapted using a forward-backward selection approach to identify prognostic markers.

Results: 4491 pts were included (n=2246 ET- and n=2245 CT-treated). In the whole set, tumor and nodal (T/N) stage, RS and PR expression were prognostic for iDFS (Cox model). In ET-treated pts, only T-stage, RS and ER expression by RT-pCR

were significant by Cox analysis, but prognostic score could not be determined. In CT-treated patients, T/N stage, G2-3 vs. G1, RS, ILC, and PR expression, but not IHC4 entered the model. In the CT cohort, a prognostic score consisting of T/N stage, age (≤50, >50), RS, ILC, PR expression and baseline and post-ET Ki67 yields a ROC AUC of 66% in the validation set. ILC was associated with lower RS than IDC (RS>25: 5.62% vs. 19.37%).High-risk CT-treated ILC had more frequently ERBB2 (11.6% vs. 2.5%) and a lower frequency of CDH1 mutations (60.5% vs 70.7%). Only CCND1 amplification was associated with worse iDFS in the NGS sub-cohort (n=584).

Conclusions: Use of RS in combination with further clinical and genetic factors improves prognostic ability; however, there is no treatment-independent prognostic model for HR+ HER2- EBC pts. For the first time, we have shown worse prognosis of the ILC high-risk subgroup, associated with distinct biological features.

A phase II trial targeting disseminated dormant tumor cells with hydroxychloroquine, everolimus or the combination to prevent recurrent breast cancer ("CLEVER")

Author: Angela DeMichele
Citation: Annals of Oncology (2023) 34 (suppl_2): S278-S324.

Background: Breast cancer (BC) recurrence may follow a dormant phase in which quiescent cells reside in niches such as bone marrow (BM). Dormant BM disseminated tumor cells (DTCs) are independently associated with BC recurrence/death. We investigated whether targeting dormancy through autophagy inhibition (hydroxychloroquine (HCQ), and/or mTOR signaling (everolimus (EVE) in DTC+ BC survivors was feasible, reduced DTCs and/or prevented recurrence.

Methods: The CLEVER trial (NCT03032406) is a randomized, phase II trial in patients (pts) diagnosed within 5 years, with positive nodes, triple-negative disease, high-risk Oncotype/Mammaprint, and/or residual disease

post-neoadjuvant therapy who completed all treatment except endocrine therapy. DTCs were detected in BM aspirate (BMA) by IHC with pan-CK antibody AE1/AE3. DTC+ pts were randomized to six 28-day cycles (C) of HCQ (600 mg BID), EVE (10 mg daily) or both (+/- 3-month (m0) observation period). If DTC+ persisted after C6, pts received another 6C HCQ+EVE. DTC assessment was done after C3, C6, C12 (if applicable) and 6-mo after end of treatment. Adverse events (AE) were assessed by CTCAEv4. Primary endpoint was feasibility, defined as >75% completion of C6C without G3/G4 AE. Secondary endpoints were safety, DTC response rate (RR) and 3-year RFS. DTC RR was analyzed with Bayesian Poisson regression models.

Results: 184/197 eligible pts had baseline BMA, 55 (30%) were DTC+, 53 were randomized: HCQ (n=15), EVE (n=15), and HCQ+EVE (n=23). 13 patients had repeat after 3-mo observation. Feasibility endpoint was met. There were no G4/5 toxicities. At a median follow up of 42 mo (range 7-60), 1 pt recurred in lung (after 2 cycles EVE), 1 pt developed new contralateral breast cancer. The posterior probabilities that HCQ, EVE, and HCQ+EVE reduced DTCs by at least 80% after C3 vs observation alone are 99.1%, 98.2%, and 99.9%, respectively.

Conclusions: The CLEVER trial provides proof-of-principle that therapeutic targeting of dormant BC is feasible and active in eliminating DTCs by targeting dormancy-specific mechanisms. Follow up for recurrence and survival is ongoing.

CDK4/6 inhibition is a potential vulnerability in NF1-depleted ER+ breast cancer

Author: Ze-Yi Zheng
Citation: SABCS 2023:GS01-08

CDK4/6 control a key checkpoint by phosphorylating Rb, leading to Rb degradation and subsequent S-phase entry. CDK4/6 inhibition, together with endocrine therapy, is standard of care for advanced ER+ breast cancer; however, CDK4/6 inhibition typically is cytostatic. This study aims to identify breast

cancer patients who may better respond to treatments targeting CDK4/6. NF1/neurofibromin is a key tumor suppressor that we have shown can represses not only RAS as a GAP but also ER as a transcriptional co-repressor. Dual activation of RAS and ER promotes endocrine therapy resistance. We computed kinase activity scores from phosphor-proteomic data in the CPTAC breast cancer cohort and found that both CDK4/6 activity scores and Rb-pS780 levels negatively correlated with NF1 protein levels. Furthermore, NF1 mutations co-occur with mutations in CDK4/6 and CCND1-3 in breast tumors. These results suggest a functional dependency between NF1 loss and activation of the CDK4/6-Rb pathway.

To delineate how NF1 and CDK4 interact molecularly, we depleted NF1 in ER+ breast cancer cells and found an increase in Rb-pS780 and in phosphorylation in CDK4's activation loop (CDK4-pT172). Cyclin-D binding is required for CDK4 activation. CCND1 expression is under the direct control by ER, and upon NF1-depletion, Cyclin D1 expression was increased, partly due to enhanced ER recruitment to an ERE in CCND1. Cyclin-D-bound CDK4 must be phosphorylated at T172 to be fully active; however, what kinase is responsible for this is largely unknown. We have evidence that CDK4-T172 phosphorylation is RAF, but not ERK, dependent. When the NF1-depleted ER+ cells were seeded in the presence of fulvestrant together with either palbociclib or abemaciclib, apoptosis readily occurred. Remarkably, fulvestrant plus palbociclib efficiently caused durable tumor regression in two ER+ PDX models, in which NF1 is undetectable by IHC. In contrast, no tumor regression was seen in a PDX model with detectable NF1. Finally, greater growth inhibition and apoptosis were detected in NF1-low tumors in the neoadjuvant NeoPalAna trial when palbociclib was added after anastrozole.

These data support a model whereby ER and RAS signaling converge upon CDK4/6, and CDK4/6 activation is a key survival mechanism when ER signaling is attenuated by treatment in NF1-depleted ER+ breast cancer cells. This apparent addiction for CDK4/6 activity makes NF1-depleted ER+ breast tumors vulnerable

to CDK4/6 inhibition, thus creating a potential therapeutic opportunity to match CDK4/6 inhibition with patients who can benefit the most.

Novel Mechanisms of CDH1 Inactivation in Breast Invasive Lobular Carcinoma Unveiled by the Integration of Artificial Intelligence and Genomics

Author: Fresia Pareja
Citation: SABCS 2023:GS03-04

Background: Invasive lobular carcinoma (ILC) of the breast is the second most common histologic subtype of breast cancer (BC), following invasive ductal carcinoma of no special type (IDC-NST). The hallmark histologic feature of ILC is cellular discohesiveness, the result of bi-allelic inactivation of CDH1, and represents an important genotypic-phenotypic correlation in BC. Although most ILCs harbor CDH1 loss-of function mutations associated to loss-of-heterozygosity (LOH) of the wild type-allele, a subset of ILCs lack these alterations despite displaying a typical lobular phenotype. Here, we sought to identify alternative molecular mechanisms converging on CDH1 inactivation by employing an integrative artificial intelligence (AI) and genomics approach.

Materials and Methods: A genomics-driven AI-based algorithm using hematoxylin and eosin (H&E) whole slide images (WSIs) as input, previously developed to detect bi-allelic CDH1 mutations (inactivating mutation associated to LOH) in BC was employed. WSIs of 1,057 BCs including ILCs (n=187) and non-lobular BCs (n=870) previously subjected to FDA-cleared tumor/normal targeted sequencing were subjected to analysis with the AI-based algorithm. Cases predicted to harbor CDH1 bi-allelic mutations by the AI-model but lacking CDH1 bi-allelic mutations by targeted sequencing were assessed through targeted sequencing data re-analysis, CDH1 gene promoter methylation evaluation and/or whole genome sequencing analysis.

Results: AI-based analysis WSIs corresponding to 1,057 BCs resulted in the identification of 34 cases found to lack CDH1 bi-allelic mutations by targeted

sequencing but predicted to harbor these genetic alterations by the AI-based model. CDH1 gene promoter methylation assessment revealed CDH1 promoter methylation in 18 cases. Targeted sequencing data reanalysis revealed other genetic mechanisms of CDH1 inactivation including CDH1 homozygous deletions (n=3), intragenic deletion with LOH (n=1), and likely pathogenic non-coding CDH1 alterations associated with LOH (n=2). WGS analysis of an ILC revealed a novel deleterious CDH1 fusion stemming from translocation t(13;16), resulting in loss of the 5'UTR, transcription start site and exons 1 and 2 of CDH1, associated with complete loss of E-cadherin protein expression. Taken together, we identified alternative/novel mechanisms of bi-allelic CDH1inactivation in 74% (25/34) cases analyzed.

Conclusions: By applying an AI-based algorithm trained to detect a genetic alteration (i.e., CDH1 bi-allelic mutations), we were able to identify alternative epigenetic and genetic molecular mechanisms of CDH1 inactivation in ILCs, including novel non-coding CDH1 genetic alterations and a new inactivating CDH1 fusion gene. These findings indicate that molecular mechanisms affecting a single gene or process converging on the same phenotype can be unveiled by the integration of AI and genomics, highlighting the robustness of this approach for the discovery of novel biology.

Genomic and transcriptomic profiling of primary tumors from patients with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial

Author: Nicholas Turner
Citation: SABCS 2023:GS03-06

Background: Two years of adjuvant abemaciclib combined with endocrine therapy (ET) resulted in significant and clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in patients (pts) with HR+, HER2-, node-positive, high-risk early breast cancer in the monarchE trial (NCT03155997). Abemaciclib benefit was sustained beyond the

completion of treatment (tx) with deepening magnitude of absolute benefit in IDFS and DRFS at 5 years. Here, we evaluate comprehensive molecular profiling of archived primary tumor tissue and association with clinical outcomes.

Methods: For biomarker analysis, a proportionally stratified random sampling case-cohort design was utilized to include all patients who experienced an IDFS event at a pre-specified interim analysis with a median follow up of 54 months. A cohort of 895 pts (189 with IDFS event) in the abemaciclib + ET arm was matched 1:1 with 903 pts (270 with IDFS event) in the ET arm. Baseline primary tumor samples underwent exome-capture RNA sequencing (RNAseq; n=1324, 23% intent-to-treat (ITT) population) and paired tumor-normal (germline blood samples) whole-exome sequencing (WES; n=1234, 22% ITT population). Expression-based intrinsic subtypes (i.e., luminal A (LumA), luminal B (LumB), HER2-enriched (HER2E), basal- and normal-like) were characterized using the Absolute Intrinsic Molecular Subtyping model. The 21-gene expression signature score (Oncotype DX test) was inferred from RNAseq; samples were categorized into lower (0-25) and high (26-100) risk groups. To investigate associations of biomarkers with abemaciclib benefit, WES genomic events including oncogenic and hotspot mutations by OncoKB, and copy number events, of incidence >9% were pre-selected.

Results: The biomarker subset of monarchE was reflective of the ITT population. A total of 1190 tumors (abemaciclib+ET n= 605; ET alone n=585) yielded adequate RNAseq results. Intrinsic subtype distribution was consistent across tx arms (Table A). Low tumor purity limited assessment of the normal-like subtype. The 4-year IDFS benefit of abemaciclib was consistent across all subtypes. LumA cancers had the lowest risk of recurrence while HER2E and basal-like subtypes had the highest. Inferred 21-gene expression signature score showed similar benefits from abemaciclib in both lower and high-risk groups (Table B). A total of 1173 tumors yielded adequate WES results (abemaciclib+ET n=580; ET alone n=593). Consistent abemaciclib benefit was observed across the most frequently altered genes (Table C). In exploratory analysis, lower benefit from

abemaciclib was seen in the subset of focal-high level MYC amplified tumors (n=176, HR 1.30, 95% CI, 0.77, 2.20) compared to MYC non-amplified tumors (n=997, HR 0.62, 95% CI, 0.47, 0.80, nominal interaction p=0.014). The treatment benefit of abemaciclib was observed across all subpopulations of altered genes based on gene expression data.

Conclusions: Adjuvant abemaciclib+ET maintained IDFS benefit compared to ET alone across all molecular subtypes as measured by RNAseq. Benefit was consistent across most altered genes assessed by WES, except for the subset of tumors with MYC amplification. Additional research is necessary to confirm these findings.

Table. RNA signatures, most frequent genomic alterations and IDFS.

	Abemaciclib + ET			ET			HR (95% CI)	Interaction p-value
	Event/ N	4-year IDFS rate (95% CI)	Incidence (%)	Event/ N	4-year IDFS rate (95% CI)	Incidence (%)		
A. RNA Molecular subtypes								
All pts	138/ 605	77.4 (74.1-80.9)	NA	182/ 585	69.8 (66.1-73.7)	NA	0.703 (0.563, 0.877)	NA
Luminal A	28/230	87.4 (83.1-92.0)	38%	45/228	81.4 (76.3-86.8)	39%	0.594 (0.371, 0.952)	0.602
Luminal B	65/265	76.0 (70.9-81.5)	44%	88/262	66.6 (61.1-72.7)	45%	0.701 (0.509, 0.966)	
HER2E	32/69	53.4 (42.5-67.2)*	11%	34/59	42.5 (31.4-57.5)*	10%	0.74 (0.456, 1.20)*	
Basal-like	9/21	59.1 (41.7-83.7)*	4%	8/15	46.7 (27.2-80.2)*	3%	0.748 (0.288, 1.94)*	NE
Normal-like (Low purity)	4/20	85 (70.7-100)*	3%	7/21	79.2 (62.9-99.6)*	4%	0.492 (0.144, 1.68)*	
B. Inferred 21-gene expression signature score								
All pts	138/ 605	77.4 (74.1-80.9)	NA	182/ 585	69.8 (66.1-73.7)	NA	0.7 (0.56, 0.88)	NA
Lower risk (0-25)	18/ 173	90.2 (85.8-94.9)	26%	28/ 165	84.2 (78.7-90.1)	27%	0.59 (0.33, 1.1)	0.532
High-risk (26-100)	120/ 432	72.3 (68.1-76.8)	74%	154/ 420	64.1 (59.6-69.0)	73%	0.73 (0.57, 0.92)	
C. Genomic alterations								
PIK3CA mutation	55/ 217	76 (70.5-82.1)	37%	73/ 229	68.5 (62.6-75)	39%	0.75 (0.528, 1.06)	0.758
TP53 mutation/deep deletion	55/ 189	72.1 (65.8-78.9)	33%	82/ 184	55.6 (48.8-63.4)	31%	0.597 (0.424, 0.841)	0.184
CCND1 amplification	36/ 113	72.9 (65.1-81.7)	19%	42/ 129	67.6 (59.9-76.2)	22%	0.938 (0.601, 1.46)	0.177
ZNF703 amplification	28/ 96	72.5 (63.9-82.3)	17%	37/ 100	64.8 (55.9-75.1)	17%	0.768 (0.47, 1.26)	0.776*
MYC amplification	34/ 92	66.7 (57.6-77.2)	16%	25/ 84	69.4 (60-80.1)	14%	1.29 (0.767, 2.16)	0.014*
FGFR1 mutation/ amplification	26/ 88	72.4 (63.4-82.7)	15%	35/ 98	66.4 (57.6-76.6)	17%	0.803 (0.483, 1.33)	0.641*
GATA3 mutation	13/ 73	84.3 (76.1-93.3)	13%	17/88	81.1 (73.2-89.9)	15%	0.861 (0.417, 1.78)	0.513*

NA, not applicable; NE, not estimated due to low numbers. *Limited sample size

Protocol-defined biomarker analysis in the PALLAS (AFT-05) adjuvant trial: Genomic subtype derived from RNA sequencing of HR+/HER2- early breast cancer.

Author: Daniel Stover
Citation: SABCS 2023:GS03-07

Background: The phase 3 PALLAS trial (NCT02513394) compared two years of the CDK4/6 inhibitor palbociclib with endocrine therapy of provider choice, versus endocrine therapy alone, as adjuvant treatment for patients with Stage II-III hormone receptor-positive HER2-negative (HR+/HER2-) breast cancer. Genomic subtype (PAM50 intrinsic subtype) measured from whole-transcriptome RNA sequencing data was defined in the protocol of the PALLAS trial as the primary biomarker for analysis of prediction and prognosis. Clinical data have been previously presented (Gnant et al, JCO 2022), and the trial now has 5-year median follow-up.

Methods: As part of trial eligibility, all participants in PALLAS provided a tumor tissue block prior to randomization (surgical if primary resection, core biopsy if neoadjuvant treatment) for translational analyses (TRANS-PALLAS). The biorepository and laboratory were blinded to identity and processed samples in random order, to minimize bias. Nucleic acids were extracted from samples with sufficient tumor tissue and cellularity (>25 mm^2 with ≥20% cancer nuclei). The Genome Sequencing Center at Washington University St. Louis performed whole-transcriptome RNA sequencing. Libraries were prepared from 1 µg DNase-1 treated total RNA, if total RNA DV200 >28 (Agilent Bioanalyzer), using an unbiased library protocol of RNA HyperPrep kit with RiboErase (HMR) (Kapa Biosystems, Wilmington, MA). 100 bp paired-end sequencing was performed on NovaSeq 6000 using S4 Reagent Kit (Illumina, San Diego, CA), with 48 libraries pooled per lane. Intrinsic subtype was determined using Bioclassifier package (Research PAM50 script, Parker et al.) only for the analysis population of primary breast cancer samples that had not been exposed to prior neoadjuvant therapy. Invasive disease-free survival (IDFS) will be visualized using Kaplan-Meier plots,

with log-rank test between groups. Cox models of proportional hazards will be developed to evaluate prognosis adjusted for known clinical covariates, or for predictive interactions. The pre-defined level of significance is a two-sided 0.05.

Results: From the total study population of 5796 enrolled patients, 4655 tissue blocks had sufficient tumor content to process for RNA, with 3931 yielding sufficient RNA for sequencing, and 2669/4655 (57.3%) submitted tissue blocks had DV200 ≥28 and were successfully sequenced. Clinical unblinding revealed 2370 unique patients (1182 in the palbociclib treatment arm and 1188 in the control arm) with intrinsic subtype defined from their untreated primary tumor: 1555 (65.6%) luminal A, 287 (12.1%) luminal B, 167 (7.0%) HER2-enriched, 310 (13.1%) basal-like, 51 (2.2%) normal-like. We will report the results for association of molecular subtype, proliferation score, and Risk of Recurrence (ROR) scores with invasive disease-free survival (IDFS) by treatment arm at the meeting.

Conclusions: The TRANS-PALLAS cohort represents one of the largest biorepositories of HR+/HER2- early breast cancer reflecting contemporary systemic management in the framework of a prospectively randomized global trial. Required tumor block submission in this phase 3 trial yielded data from unbiased whole-transcriptome RNA sequencing of the primary tumor prior to treatment from 41% of the PALLAS participants. The proportion of luminal A cancers was unexpectedly high (66%), indicating a lower-risk distribution of cancers in this population. The planned analyses of prediction and prognosis are ongoing and those results will be presented at the time of the meeting.

Characterization and proposed therapeutic exploitation of fusion RNAs in metastatic breast cancers

Author: Nolan Priedigkeit
Citation: SABCS 2023:GS03-09

Background: Large-scale genomic studies such as The Cancer Genome Atlas (TCGA) and Pan-Cancer Analysis of Whole Genomes (PCAWG) show that the breast cancer (BrCa) genome is dominated by structural variation (SV) rather

than single base pair mutations, producing a fertile environment for gene fusions. In this study, we implement a rigorous, expression-based approach to create a comprehensive landscape of fusion RNAs in metastatic breast cancer (MBC). We find fusion RNAs—many of which are novel involving known oncogenes—are surprisingly common in the advanced setting and credential their use as base-editing therapeutic targets.

Methods: Two retrospective cohorts of MBC RNA-sequencing data were analyzed— Dana-Farber Cancer Institute CCPM (n = 252 cases, 276 specimens), MichiganCSER (n = 171 cases, 190 specimens)—with a Fusion MetaCaller that integrates 5 unsupervised fusion-finding algorithms. Fusion RNAs identified in at least 2 callers (High-Confidence) and absent in RNA-seq from normal tissue (Cancer-Specific) were classified as HCCS-Fusions. Further removal of common artifactual fusions was performed using public databases. Expression of each HCCS-Fusion was quantified using a supervised method (FusionInspector)—expressed HCCS-Fusions were defined as having a Fusion Fragment Per Million (FFPM) value > 0.1 and at least 10% of read counts mapping to the fusion breakpoint versus the flanking 5' or 3' partners' exons. Normalized gene-level expression abundances were calculated to correlate transcriptomic features (gene expression, PAM50) with fusion RNAs. Recurrent, potentially pathogenic fusion RNAs were annotated using OncoKB and outlier expressed fusions (Q3 FFPM + [1.5 X IQR]) were interrogated.

Results: The frequency of HCCS-Fusions differed between subtypes with basal BrCa harboring the most per tumor followed by Her2, LumB and LumA—with a median HCCS-Fusion count of 13, 12, 7, 4 respectively. 64.5% of cases harbored a HCCS-Fusion in an OncoKB cancer-related gene. The most recurrent fusions involving a cancer-related gene were 5' ESR1 fusions (14 cases)—all with in-frame breakpoints near exon6/7, disrupting ESR1's ligand binding domain. 13 of 14 ESR1 fusions were called in Luminal B (LumB) metastases (Fisher's exact enrichment $p < 0.005$ vs other subtypes)—defining an ESR1 fusion frequency of 6.5% in LumB disease. Beyond ESR1, we identify recurrent, low-frequency (2-4

cases) in-frame kinase fusions involving FGFR2, ADK, TLK2, PRKCA, BRAF, CHKA, CSNK1D, NEK11, TNIK—some potentially targetable with FDA-approved small molecule inhibitors—as well as recurrent, predicted loss-of-function fusion RNAs in NF1, MSI2, USP32, PTEN, and CDH1. Lastly, 33.6% of cases harbored at least one outlier expressed fusion RNA; including highly expressed in-frame fusions involving known BrCa mediators such as ERBB2, BRCA1, ARID1B, RPS6KB1/2, PIK3R3, AXIN1, TGFB1/2, FOXP1, PAK1, and CREBBP.

Conclusions: Taken together, these results demonstrate that fusion RNAs in MBC—some recurrent, many highly expressed and unique to individual tumors—are common. We create the most comprehensive catalog of ESR1 fusions in MBC, better define their frequency, discover their enrichment in LumB-like tumors, and will discuss clinicopathologic and transcriptomic features associated with ESR1 fusion positive disease. We identify druggable fusions that would likely be missed by current testing standards, find recurrent loss-of-function fusion RNAs, and show that over one-third of metastatic cases harbor at least one outlier expressed fusion—many of which involve BrCa-related genes. In summary, we propose that fusion RNAs are a driving and perhaps overlooked mechanism of tumor evolution in therapy-resistant disease and postulate fusion transcripts present a compelling therapeutic opportunity in MBC. Preliminary data targeting fusion RNA breakpoints using a novel RNA base-editing approach will be discussed.

Allosteric PI3K-alpha inhibition overcomes on-target resistance to orthosteric inhibitors mediated by secondary PIK3CA mutations

Author: Andreas Varkaris
Citation: SABCS 2023:GS03-10

Background: PIK3CA mutations occur in ~40% of HR-positive breast cancers, where alpelisib, an orthosteric PI3Kα inhibitor, is FDA-approved in combination with fulvestrant. Although prior studies have identified potential resistance mechanisms, such as PTEN loss, clinical acquired resistance to orthosteric PI3Kα

inhibitors and the role of next-generation allosteric PI3Kα inhibitors remain poorly understood.

Methods: To identify on-target and off-target alterations potentially mediating resistance to PI3Kα inhibitors, we used a targeted next-generation sequencing assay (Guardant360; Guardant Health) to analyze ctDNA in serially collected plasma samples from 32 patients with PIK3CA-mutated advanced HR-positive, HER2-negative breast cancer treated with alpelisib and inavolisib. In addition, we performed whole exome sequencing (WES) of 100 tissue samples collected from 8 autopsy series from patients with metastatic, PIK3CA-mutant HR-positive, HER2-negative breast cancer previously treated with PI3Kα inhibitors. Acquired alterations were prioritized through a combination of structural modeling and free-energy perturbation simulation and validated in genomically engineered PIK3CA mutant breast cancer cell lines T47D (PIK3CA H1047R-mutant) or MCF7 (PIK3CA E545K-mutant).

Results: We observed that 50% of patients acquire genomic alterations within the PI3K-pathway, including PTEN loss and activating AKT1 mutations. Notably, while secondary PIK3CA mutations were previously reported to increase sensitivity to PI3Ka-inhibitors, we identified emergent secondary resistance mutations in PIK3CA that alter the inhibitor binding pocket including PIK3CA Q859K and PIK3CA W780R. Some mutations had differential effects on PI3Ka-selective vs. pan-PI3K inhibitors, but resistance induced by all mutations could be overcome by the novel allosteric pan-mutant-selective PI3Ka-inhibitor RLY-2608.

Conclusion: In one of the largest patient cohorts analyzed to date, this study defines the clinical landscape of acquired resistance to PI3Ka inhibitors. Genomic alterations within the PI3K pathway represent a major mode of resistance and identify a novel class of secondary PIK3CA resistance mutations that can be overcome by an allosteric PI3Ka inhibitor. Together, these findings provide insights to guide strategies to overcome resistance in PIK3CA-mutated cancers.

Germline-mediated immunoediting sculpts breast cancer subtypes and metastatic proclivity

Author: Kathleen Houlahan
Citation: SABCS 2023:GS03-11

Background: Somatic genomic aberrations are acquired within the context of germline genomes which differ across individuals at millions of polymorphic sites. However, the role of germline variation in somatic evolution remains poorly understood. The most compelling example is that deleterious germline variants in BRCA1 and, to a lesser extent, BRCA2 are preferentially associated with the development of triple-negative breast cancer (BC). The variable frequency of BC subtypes across ancestral populations further suggests a role for germline contributions. On the other hand, various lines of evidence indicate that avoidance of the adaptive immune system is a strong determinant of which somatic mutations persist within a tumor. Whether and how germline differences influence immunoediting has not been studied. Building on these observations, we sought to investigate whether germline variation mediates somatic evolution through immunoediting.

Specifically, we hypothesize inherited variation in oncogenes would be subject to varied immunoediting pressures during malignant transformation and progression. A high burden of germline-derived epitopes in recurrently amplified oncogenes is predicted to select against amplification of the cognate gene during malignant transformation because this would increase epitope availability, the likelihood of epitope presentation, and immune-mediated cell death. Instead, immune pressures may select for amplification of an alternate driver gene with a lower germline-mediated epitope burden. We evaluated this hypothesis in a collection of 3,855 BC, spanning ductal carcinoma in situ (DCIS) to invasive BC, and metastatic lesions.

Methods: We analyzed paired tumor and normal sequencing data from 1,087 primary and 702 metastatic breast cancer patients as well as somatic genomic profiles from 341 patients with DCIS using a novel algorithm to estimate germline-derived epitope burden (GEB) based on an individual's genotype and class 1 HLA alleles. The relationship between GEB and subtype commitment, defined by the acquisition of focal oncogenic amplifications in five prognostic subgroups of BC: HER2+ disease and four high-risk of relapse ER+/HER2 integrative subgroups/clusters (ICs) which we previously described (IC1: 17q23, IC2: 11q13, IC6: 8p12, and IC9: 8q24) was evaluated. Specifically, we evaluated the association between the GEB per gene and whether an individual developed the corresponding subtype via logistic regression, correcting for the first six genetic principal components and somatic mutation burden. Outcome associations were evaluated via Cox Proportional Hazards Models.

Results: Interrogating 3,855 breast cancer lesions, we demonstrate that germline-derived epitopes in recurrently amplified genes influence somatic evolution by mediating immunoediting. Individuals with a high GEB in ERBB2/HER2 are significantly less likely to develop HER2-positive breast cancer compared to other subtypes. The same holds true for recurrent amplicons that define four aggressive, high-risk of relapse, ER-positive integrative subgroups. Thus, GEB selects against cognate oncogene amplification. Tumors that overcome such immune-mediated negative selection are more aggressive and exhibited microenvironments depleted of lymphocytes, consistent with "immune cold" tumors.

Conclusions: We demonstrate that inherited variation sculpts breast cancer subtypes, aggressivity, and immune landscapes by mediating anti-tumor immune responses. The implications of these findings are severalfold. First, GEB is prognostic, complementing other molecular measurements. Second, immunoediting pressures differ across the disease course, with implications for the timing of therapeutic interventions. Third, these data illuminate a broad source of currently under-appreciated immunogenic antigens.

Functional assessment of RAD51 foci and replication fork dynamics in PARPi resistant BRCA1/2 mutated breast cancer

Author: Elizabeth Harvey-Jones
Citation: SABCS 2023:RF01-05

Background: Although platinum salts (Pt) or Poly (ADP-Ribose) Polymerase inhibitors (PARPi) are effective in treating homologous recombination defective (HRD) breast cancer, resistance often emerges, especially in advanced disease. Predicting response and relapse is complex, even in patients with germline BRCA1/2 mutations (gBRCA1/2m). Clinically approved HRD detection methods are limited to identification of pathogenic mutations in HR genes or mutational signatures in the genome of tumors caused by HRD. In PDX models derived from HRD breast cancer, the restoration of nuclear RAD51 foci formation, a key feature of functional HR, can predict resistance to HRD-targeted treatment.1 In addition, the restoration of replication fork stability, despite PARPi or induction of Pt adducts that induce replication fork arrest and collapse, confers resistance in pre-clinical models2; to date this resistance mechanism has not been clinically validated. Here we analyse RAD51 foci in FFPE samples and DNA replication fork dynamics, using DNA fibre combing assays, in patient derived organoids (PDO) relating these to clinical response to illustrate how such assays might predict clinical HRD-targeted therapy resistance in metastatic breast cancer (MBC).

Patients and Methods: We used immunofluorescent detection of RAD51 foci as a marker for HR proficiency (HRP) in tumors from 29 patients with gBRCA1/2m with MBC treated with HRD-targeted treatment (n=6 PARPi, n=2 Pt and n=21 both agents in sequence). All patients developed resistance that was either de novo or acquired. RAD51 and BRCA1 foci were scored in a minimum of 50 geminin (a marker of S/G2 phase) positive tumor cells; cells with ≥5 foci were classified as positive, and tumours where ≤10% or >10% of cells were positive were considered HRD or HRP, respectively. DNA replication fork dynamics were assessed in with or without PARPi using thymidine analogue labelling. DNA fibre analysis was performed in PDOs developed from fresh tumor sampling

of HRD-targeted treatment sensitive or resistant tumors, to determine the relationship between replication fork dynamics, stability and PARPi sensitivity.

Results: RAD51 analysis was performed on 9 treatment naïve samples (n=9 patients), 8 samples obtained after HRD-targeted treatment resistance (n=8 patients) and 27 samples obtained pre and post HRD-targeted treatment resistance (n=12 patients). Functional HRD by RAD51 in treatment naive samples was seen in 100% (n=17) of patients with acquired resistance and 66% of patients with de novo resistance. All patients, whether with de novo or acquired resistance, exhibited high RAD51 scores in post-resistance tumour samples, suggesting restoration of HR function is the dominant mechanism of PARPi resistance. As such, RAD51 analysis shows potential as a biomarker of clinical PARPi resistance. Replication fork stability fibre was analysed after exposure to potent PARP1 trapping inhibitors or an ATRi control in 3 PDOs (2 gBRCA1m, 1 BRCAwt). As controls we used an isogenic 2D cell line with and without a CRISPR engineered BRCA1 reversion mutation (SUM149 parental BRCA1m and SUM149BS*1 revertant) or with a PARP1 mutation (SUM149 TR2 clone) that prevents PARP1 being trapped on DNA. These experiments indicate that replication fork dynamics can be assessed in "patient derived" models of breast cancer and that PARPi sensitivity was associated with PARPi induced replication fork instability (median ratio IdU:CldU in resistant lines: 0.98, sensitive lines: 0.60).

Conclusion: We show that HRP restoration and RAD51 foci in advanced BRCA1/2m breast cancers is the dominant form resistance to HRD-targeted treatment. We also demonstrate for the first time that analysis of DNA replication fork dynamics can be carried out in breast cancer PDOs and could be further explored as a functional predictive biomarker of PARPi resistance.

Characterization of the immune microenvironment in matched primary and metastatic breast cancer lesions from the AURORA study: BIG 14-01.

Author: Florentine Hilbers
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1009-1009.

Background: Immunotherapy benefit in patients with metastatic breast cancer (MBC) is limited to patients with triple negative breast cancer and PD-L1 expression in the tumor sample. Multi-omics characterization of the anti-cancer immune response in MBC could provide novel insights into the mechanisms behind immune response failure.

Methods: The AURORA program (NCT02102165) enrolled patients with MBC who received at most one line of treatment in the metastatic setting. RNA sequencing was performed on primary and metastatic lesions. Stromal tumor infiltrating lymphocytes (sTIL) were scored in line with the International Immuno-Oncology Biomarker Working Group for Breast Cancer recommendations. T cell and B cell receptor (TCR and BCR) analysis was performed with MiXCR. Deconvolution of bulk RNA sequencing data was performed using xCell. ImmuneScore-normalized Relative Abundance metastasis/primary Ratios (RAR) of immune cell types were calculated. All comparisons between primary and metastatic lesions were performed on matched samples. Wilcoxon signed-rank tests were used.

Results: As expected, sTILs decreased from primary to metastatic lesion. However, 9% of metastatic lesions still had ≥20% sTILs. Matched RNA expression data was available for 204 patients. Relative abundance of macrophages (RAR 3.3, $p<0.001$) and Th1 cells (RAR 1.5, $p<0.001$) was increased in the metastases, while Treg cells (RAR 0.12, $p<0.001$), CD8+ T cells (RAR 0.32, $p<0.001$) and B cells (RAR 0.32, $p<0.001$) decreased the strongest. Metastases with ≥20% sTILs had higher Treg cells ($p<0.001$) and B cells ($p<0.001$) compared to metastases with low sTILs, which had more Th1 cells ($p<0.001$), mast cells

(p<0.001) and NKT cells (p<0.001). De novo metastatic and synchronous primary samples had more BCR (p<0.001) and TCR (p<0.001) clones in common as compared to non-de novo metastatic cancers.

Conclusions: sTIL percentage decreased from primary tumor to metastatic lesion. Metastatic lesions with many sTILs (≥20%) were enriched for immune response suppressing regulatory T cells.

		matched samples	Primary mean sTIL % (IQR)	Metastatic mean sTIL % (IQR)	p-value	Metastatic samples with ≥20% sTILs
Total		716	13 (1-10)	6 (1-1)	<0.001	9%
Subtype	ER+, HER2-	491	11 (1-10)	5 (1-1)	<0.001	6%
	ER+, HER2+	66	12 (1-5)	8 (1-5)	0.39	15%
	ER-, HER2+	31	16 (1-13)	11 (1-5)	0.27	19%
	ER-, HER2-	128	23 (1-40)	10 (1-5)	<0.001	15%
Metastasis	Liver	313	13 (1-10)	2 (1-1)	<0.001	3%
	Lymph node	169	15 (1-15)	12 (1-10)	0.04	19%
	Skin	58	12 (1-7)	4 (1-1)	0.002	3%
	Lung	38	12 (1-10)	20 (1-35)	0.19	32%

Cyclin E cytoplasmatic isoform to predict outcome and benefit to capecitabine treatment in patients with HR+/HER2- metastatic breast cancer from the GEICAM/2013-02 PEARL study.

Author: Angel Guerrero
Citation: Journal of Clinical Oncology 41, no. 16_suppl (June 01, 2023) 1023-1023.

Background: Cytoplasmic cyclin E protein expression, serving as a surrogate for the low molecular weight cyclin E isoform (LMW-E), is a biomarker associated with aggressive breast cancer and predicts resistance to aromatase inhibitors in luminal breast cancer. We investigated the prognostic and predictive value of cytoplasmic and nuclear isoforms of cyclin E in HR+/HER2- metastatic breast cancer (MBC) patients receiving palbociclib CDK4/6 inhibitor and endocrine therapy (PALBO+ET) versus capecitabine (CAPE) in the GEICAM/2013-02 PEARL trial (NCT02028507).

Methods: Expression of Cytoplasmic and Nuclear isoforms of cyclin E were assessed by immunohistochemistry (IHC). An H-score based on the proportion and intensity of stained cells was explored using median value to categorize in Low / High expression the Nuclear and Cytoplasmic scores (N and C, respectively). In addition, N and C were independently assigned according to staining intensity (1 = no staining, 2 = weak, 3 = intermediate and 4 = strong staining) and then, combined in 4 phenotypes (Ph): Ph1 (N-/C-); Ph2 (N+/C-); Ph3 (N+/C+); and Ph4 (N-/C+), where negative=1-2, and positive=3-4. Cox regression models' analysis were assessed to predict outcome and benefit to treatment, in terms of PFS and OS. Multivariate models were adjusted for confounders: age, site of disease, sites of metastasis, prior chemotherapy for MBC and treatment. Interaction analysis with treatment arm were performed.

Results: Cyclin E protein was obtained from 344 tumors, with 73% being primary tumors and 27% metastatic. High expression of the Nuclear isoform was independently associated with significantly worse OS (median OS [mOS]=34.23 months [m] for low expression vs 25.72m for high expression;

adjusted HR=1.48; p-value=0.016). Phenotype analysis supported this finding, with Ph3 (N+/C+) and Ph4 (N-/C+) demonstrating the worst (mOS=19.55m) and best (mOS=37.19m) outcomes, respectively (using Ph1 as reference, Ph3 HR=2.92; p-value=0.0013). The interaction between the treatment arm and Cytoplasmic cyclin E expression was significant (p=0.0052). Patients with high expression of the Cytoplasmic isoform had significantly better PFS with CAPE (mPFS=14.8m) than with PALBO + ET (mPFS=5.73m) (HR=1.9, p-value=0.0418). Ph4 (N-/C+) had also significantly better PFS for CAPE (mPFS=22.67m) than for PALBO + ET (mPFS=8.51m) (HR=2.94; p-value=0.036).

Conclusions: This study confirms Cyclin E as a poor prognostic marker associated with worse overall survival in luminal MBC patients. Low molecular weight Cyclin E, detected as Cytoplasmic Cyclin E, identifies luminal MBC that benefit more from CAPE than from PALBO + ET. The low molecular weight Cyclin E isoform appears to be a promising predictive biomarker for the benefit of CAPE and resistance to PALBO + ET treatments in this population.

Circulating tumor DNA (ctDNA) monitoring of estrogen receptor-positive, human epidermal growth factor receptor 2-negative (ER+/HER2-) high risk breast cancer during adjuvant endocrine therapy

Author: Lajos pusztai
Citation: SABCS 2023:PS06-02

Background: ctDNA monitoring during adjuvant endocrine therapy provides an opportunity to detect molecular relapse before clinically apparent recurrence. The rate and dynamics of ctDNA positivity and the frequency of asymptomatic but imaging detectable metastatic disease at the time of ctDNA detection remain unknown in high-risk ER+/HER2- breast cancers. We present results of ctDNA positivity rates in 508 and imaging results in ctDNA+ patients from a prospective, multicenter, randomized ctDNA surveillance and intervention trial, DARE (NCT04567420).

Patients and methods: Patients receiving adjuvant endocrine therapy for > 6 months but < 7 years, with either (i) risk of recurrence > 15% calculated by PREDICT, RSPC, or CTS5, or (ii) > 4 positive axillary lymph nodes, or (iii) primary tumor > 5 cm, or (iv) 1-3 positive nodes with grade 3 histology, or > 3 cm tumor, or Oncotype Dx RS > 26, MammaPrint high risk, EndoPredict > 4, Prosigna score > 60 were eligible for ctDNA surveillance with the SignateraTM assay (Natera Inc.) every 4-6 months during routine follow up visits. ctDNA+ patients underwent systemic staging with imaging and randomized to continuation of adjuvant therapy versus switching to fulvestrant plus palbociclib if there was no evidence of distant metastatic disease. The primary objectives are to assess the incidence of ctDNA positivity in the surveillance phase and to assess if palbociclib plus fulvestrant improves relapse-free survival in 100 randomized patients. This is an updated, protocol-driven interim report to determine if screening eligibility criteria needs to be revised to keep randomization rate > 15% of the screened population.

Results: The trial is open at 15 sites and enrolled 508 patients between May 2021 and June 2023; 882 plasma ctDNA tests were performed successfully in 364 patients (72%). The most common reason for failure to generate a personalized ctDNA assay was insufficient tissue submitted, 78% of failed tests were due to preanalytical failure, the technical failure rate was 22%. Thirty patients, 8.2% of those with results available, had >1 positive ctDNA result, the overall positivity rate across all assays was 3.4% (n=30/882). Patient characteristics are shown in the table (not all patients have complete data), 47% of ctDNA+ cases had >4 + lymph nodes. ctDNA positivity rate in the first test was 3.8%, and anytime ctDNA detection rate among those with serial testing was 7.2%. Among ctDNA+ patients, the first ctDNA draw was positive in 23 of 30 cases (77%) with 36.5 months median time (range 6-102 months) from surgery to testing. Using 12 months interval brackets from surgery to 1st ctDNA positivity, annual detection rates were 2,3% (1/44), 8.5% (7/82), 10.8% (9/83), 7.5% (4/53), 13,2% (5/38), and 6.2% (4/64), at 1st, 2nd, 3rd, 4th and > 5th year post-surgery, respectively, due to small sample sizes, 95% confidence broadly overlap. Five ctDNA+ patients

(16.7%) had asymptomatic, imaging-detectable metastatic disease, 22 ctDNA+ patients were randomized, the goal is to accrue a total of 100 patients.

Conclusions: ctDNA surveillance of ER+/HER2- breast cancers during adjuvant endocrine therapy indicate 8.3% detection rate at patient level and 3.4% at assay level. Serial screening increases detection rates as 23% of positive ctDNA tests occurred after an initial negative result. 83% of ctDNA+ patients had true molecular relapse without imaging detectable metastatic disease. Eligibility for screening on the trial is now restricted to patients with >4 + lymph nodes, randomization is open for any patients who are ctDNA+ including routine commercial screening.

Table of patient characteristics

	with ctDNA result (n=364)	ctDNA+ (n=30)
Age < 50	29%	23%
Age >50	71%	77%
PR +	78%	73%
PR -	7%	17%
HER2 IHC negative	79%	77%
Grade 1	8%	7%
Grade 2	53%	50%
Grade 3	29%	37%
T 1	19%	17%
T2	43%	43%
T3	27%	27%
T4	2%	7%
0 +nodes	12%	12%
1 +node	24%	10%
2 +nodes	15%	13%
3 +nodes	8%	13%
>4 +nodes	0	47%

Results from a pilot study exploring ctDNA detection using a tumor-informed assay in the monarchE trial of adjuvant abemaciclib with endocrine therapy in HR+, HER2-, node-positive, high-risk early breast cancer

Author: Sherene Loi
Citation: SABCS 2023:PS06-01

Background: Two years of adjuvant abemaciclib + endocrine therapy (ET) resulted in significant and clinically meaningful improvement in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) in patients (pts) with HR+, HER2-, node-positive, high-risk early breast cancer (EBC) in the monarchE trial (NCT03155997). The benefit of abemaciclib was sustained beyond completion of treatment and deepened in magnitude at 4 years for IDFS and DRFS. This pilot study investigated the technical feasibility of ctDNA detection beginning prior to study treatment, as well as rates of persistence and clearance in a subset of EBC pts from monarchE using the clinically validated SignateraTM ctDNA assay.

Methods: Samples were analyzed from a selected subset of pts (n=178; 84 from abemaciclib+ET arm; 94 ET alone) who had blood collected both before initiating protocol directed therapy, Visit 1 (V1; randomization + ≤ 3 days) and near completion of the 2-year treatment period, Visit 27 (V27; 24 months +/- 5 days from V1). This cohort of pts was enriched for overall IDFS events compared to the total monarchE study population, however pts with relapses occurring prior to V27 were excluded. Primary tumors from selected pts were subjected to whole exome sequencing (WES). Selected samples included those from pts with a range of tumor mutation burden. Cell-free DNA was extracted from 356 plasma samples. A Signatera ctDNA assay was developed for each pt based on up to 16 variants detected by WES from each baseline tumor sample.

Results: The IDFS event rate for the selected subset (n=178) was 39.3% (abemaciclib+ET 34.5% [29/84] and ET alone 43.6% [41/94]). Ten pts (5.6%) were initially ctDNA+ and 42 pts (23.6%) were persistently (7 pts, 3.9%) or became (35 pts, 19.7%) ctDNA+ at V27. Notably, 70% of pts who were initially ctDNA+ and 100% of pts who were either persistently ctDNA+ or became ctDNA+ experienced recurrence (see Table 1). In contrast, none of the 3 pts that cleared ctDNA+ developed recurrence. In pts persistently ctDNA negative (neg), 28 (21.1%) experienced recurrence. Overall, 10% (7/70) of pts with IDFS events were initially ctDNA+ and 50% (35/70) had detectable ctDNA at V27.

Conclusions: Detection of ctDNA soon after completing neoadjuvant chemotherapy was infrequent, but also associated with a high-risk of recurrence. ctDNA positivity was common at the end of the 2-year treatment period and was highly prognostic with all pts subsequently developing disease recurrence. Importantly, ~30% of pts with early ctDNA detection ultimately dropped below detection limits during the 2-year treatment period and none developed recurrence. Although some pts remained persistently ctDNA neg during this study and experienced recurrence, the delay in recurrence may indicate longitudinal benefit from remaining ctDNA neg. Future planned analysis of an expanded cohort reflective of the intent to treat population including additional timepoints within the 2-year treatment period will further define how ctDNA dynamics may identify pts at high-risk of recurrence.

Prenatal BRCA1 epimutations is a major cause of triple-negative breast cancer

Author: Per Lonning
Citation: SABCS 2023:PS07-09

Background: Low level normal cell BRCA1 epimutations have been associated with an increased risk of triple-negative breast cancer (TNBC). However, the fraction of TNBCs that may have BRCA1 epimutations as their underlying cause is unknown. Neither are the time of occurrence and the potential inheritance pattern of BRCA1 epimutations established.

Methods: To address these questions, we analyzed BRCA1 methylation status in breast cancer tissue and matched white blood cells (WBC) from 411 patients with primary breast cancer, including 66 TNBCs. Samples were analyzed by a highly sensitive next-generation sequencing (NGS) assay on an Illumina MiSeq sequencer, allowing allele-resolved methylation assessment. Further, to assess the time of origin and the characteristics of normal cell BRCA1 methylation, we analyzed umbilical cord samples from 1260 newborn girls and 200 newborn boys.To assess potential Mendelian heritage, we analyzed BRCA1 methylation status in WBCs from 575 mothers and 531 fathers of newborn girls with (n = 102) and without (n = 473) WBC BRCA1 methylation.

Results: We found concordant tumor and mosaic WBC BRCA1 epimutations in 10 out of 66 patients with TNBC and in four out of six patients with estrogen receptor (ER)-low expression (< 10%) of tumors (combined 14 out of 72; 19.4%, CI: 11.1-30.5). These exceeded the number of tumors harboring germline (n = 5) or somatic (n = 4) BRCA1 mutations. Notably, BRCA1 methylation and BRCA1 mutations were mutually exclusive. Contrasting the findings in TNBC and ER-low exprssion tumors, we found WBC and tumor BRCA1 methylation concordance in only three out of 221 patients with ER >10+% tumors and zero out of 116 patients with HER2 positive tumors. Intraindividually, BRCA1 epimutations affected the same allele in normal and tumor cells. Assessing BRCA1 methylation in umbilical cord WBCs from newborn girls, we found mosaic, predominantly monoallelic BRCA1 epimutations, with qualitative features similar to those in adults, in 113/1260 (9.0%) of individuals. We found no correlation between WBC BRCA1 methylation in newborns and methylation status in their mothers, fathers, or any parent. Notably, WBC BRCA1 methylation occurred at a significantly lower frequency in newborn boys (9 / 200; 4.5%) as compared to newborn girls (p = 0.038). Similarly, WBC BRCA1 methylation was found less common among fathers (16 / 531; 3.0%), as compared to mothers (46 / 575; 8.0%; p = 0.0003).

Conclusions: Our findings suggest prenatal BRCA1 epimutations might be the underlying cause of around 20% of TNBC and low-ER expressing breast cancers. Such constitutional mosaic BRCA1 methylation likely arise through gender-related mechanisms in utero, independent of Mendelian inheritance.

P53 loss enables HR+ breast cancer escape from CDK4/6 inhibitor-induced quiescence via CDK2

Author: Rei Kudo
Citation: SABCS 2023:PS12-03

Background: Inhibition of CDK4/6 kinases has led to improved clinical outcomes in hormone receptor positive (HR+) breast cancer. While these are highly effective therapies, only a minority of patients experience long-term disease control. We sought to determine the genomic configurations and underlying mechanisms associated with long-term response.

Methods: To identify genomic patterns associated with clinical outcomes, we analyzed a cohort of 447 patients with metastatic HR+ breast cancer treated at MSK with first-line CDK4/6 inhibitors (CDK4/6i) for which tumor-normal sequencing and long-term clinical follow up were available. To identify the pattern of genomic features associated with longer, intermediate, and short response, we implemented an elastic net Cox regression on binary pathogenic variant status of each gene as well as select clinical features (prior endocrine therapy, endocrine therapy partner, de novo metastatic status). Our principal aim was variable interpretability over pure predictive accuracy. Human HR+ breast cancer models including human breast cancer organoids and cell lines were utilized for mechanistic studies. For validation in a clinical setting, we analyzed the association between Ki67 score after neoadjuvant ribociclib plus endocrine therapy and pre-treatment gene mutation from the FELINE trial [NCT02712723] using a Fisher exact test.

Results: Our model identified a "longer response" group (n = 124, 27.7%) from patients with a median progression free survival (PFS) of 32.5 months, compared with an "intermediate" (n = 224, 50.1%, median PFS = 13.7 months) and "short response" group (n = 99, 22.1%, median PFS = 5.84 months). TP53 and MDM2 pathogenic variant status were the most important variables to stratify between these groups, obtaining variable selection frequencies of 1.0 and 0.93 and mean hazard ratios of 2.02 and 1.38, respectively. To elucidate the mechanisms whereby the p53 pathway supports long term response, we generated isogenic and patient derived models of TP53 loss or MDM2 overexpression. Using immunoblotting and cell cycle assays, we found that drug-treated p53 KO cells and MDM2 overexpressing cells effectively suppressed RB1 phosphorylation and blocked in G1 after 24-48 hours. However, upon drug withdrawal, these cells could reenter the cell cycle and promote long-term tumor outgrowth. These effects we observed both in vitro and in vivo. Measures of long-term CDK4/6i response such as expression of senescence associated secretory phenotype genes was abrogated by TP53 loss. Mechanistically, we found persistent phosphorylation of the p130 RB1-like protein in the p53 KO cells. Phosphorylation of p130 impaired its interaction with E2F4, thereby blocking DREAM complex assembly and promoting cell cycle reentry. Inhibition of phosphorylation of p130 via p21 overexpression or by selective CDK2 inhibitors could restore irreversible cell cycle arrest in p53 KO cells. The combination of CDK2 and CDK4/6 inhibition led to long-term tumor growth suppression in models with mutant TP53. To validate the human relevance of TP53 mediating CDK4/6i response, we analyzed longitudinal samples from the FELINE trial that evaluated efficacy and feasibility of neoadjuvant ribociclib plus endocrine therapy. Of 45 evaluable patients, 13 (28.9%) harbored a pre-treatment TP53 loss of function variant. Of these 13 cases, 7 (53.8%) did not achieve a low (< 10%) Ki-67 upon surgical resection as compared to TP53 wildtype tumors (n=32), only one (3.2%) of which did not achieve a low Ki-67 [OR 32.1, 95% CI 3.28 – 1660.3, p = 0.00026].

Conclusion: Loss of p53 was strongly associated with lack of long-term response to CDK4/6i inpatients. Complete inhibition of both CDK4/6 and CDK2 appears to be necessary in order to convert quiescent HR+ tumors cells into durably inhibited and effectively dormant cancers.

Supportive Care

A randomized, open-label phase III trial Evaluating Low-Dose Vs standard-dose Olanzapine with triple Antiemetic therapy for Prevention of highly emetogenic chemotherapy- induced Nausea and vomiting in solid tumors (OLAnzaPiNE)

Author: Jyoti Bajpai
Citation: SABCS 2023:RF01-08

Background: Chemotherapy induced nausea and vomiting (CINV) is a major adverse event for cancer patients.Olanzapine (OLZ) in standard 10 mg dose along with triple antiemetics (TAE), has shown effectiveness in treating CINV with highly emetogenic chemotherapy (HEC), however, significant day time somnolence (DTS) precludes its widespread use. Steroids related side effects are another major concern. Hence, a lower dose of OLZ, with single dose (SD) steroid use is worth exploring in a randomized fashion.

Methods: Solid tumors planned for anthracycline-cyclophosphamide & high-dose cisplatin chemotherapy was randomized (1:1) to receive either 10mg OLZ (standard arm) or 2.5mg (experimental arm) till day 4 with TAE regimen [5-hydroxytryptamine type 3 (5-HT3) receptor antagonists, dexamethasone (SD, without delayed doses), and neurokinin-1 (NK1) receptor antagonists] in both arms.Primary objective was to evaluate Complete control rate (CCR) defined as proportion of subjects with no emetic episodes (EE), no use of rescue medications (RM), no or mild nausea assessed in overall phase (OP) =0-120 hours(h) in both groups.Secondary objectives were to compare two groups for the CCR in acute(AP) and delayed phase(DP);Complete response rate (CRR)=no EE and no use of RM in AP(0- 24h), DP(25-120h) and OP; Total control rate(TCR)= no EE, no use of RM, and no nausea) in AP, DP, OP; Time to treatment failure(TTF), defined as mean duration from chemotherapy initiation to first episode of nausea, EE, use of RM; Incidence of significant daytime somnolence(DTS).Tertiary objectives were effect on appetite loss. Subjects

maintained a daily record of nausea, EE, RM use with the severity graded on a four-category scale.

Statistical analysis: CCR, CRR, TCR are given in counts and proportions. Occurrence of nausea, EE, DTS and their grades were compared using Chi-square test.

Results: A total of 275 subjects were enrolled, among them 267 were analyzable, inclusive of 132 subjects in 2.5mg and135 in 10mg arms with well-balanced baseline characteristics (Table 1) Proportion of patients with CCR in OP (Primary end point) in 2.5mg vs. 10mg arms were, 44.7 % vs. 43.7 % (P = 0.87) respectively.CCR in 2.5mg vs. 10mg arms in AP, DP were 50% vs. 48.9%(p=0.856) and 50.8% vs. 58.5% (P=0.203) respectively. CRR in 2.5mg vs. 10mg in AP, DP and OP were 56.1% vs. 57 % (P=0.872), 55.3% vs. 63% (P = 0.203), and 50.8 % vs. 51.1% (P=0.954), respectively. TCR in2.5mg vs. 10mg in AP, DP, and OP were25% vs. 23 % (P=0.697), 20.5% vs. 22% (P = 0.725), and 13.6 % vs. 15.6% (P=0.657), respectively.Subjects receiving 2.5 mg as compared with those receiving 10 mg, had statistically significant decreased DTS on overall grades 65.2%vs 89.6% vs. ($p < 0.001$); severe grade DTS was more on day1 i.e., 4.5%vs. 40% ($p < 0.001$) and although successively reduced from day 2-5 in both the arms, however, 2.5 mg fared better on all the days (table 1). No statistically significant effect of reduced appetite noted in 2.5mg vs. 10mg i.e., 17.4% vs. 24.4 %(p=0.208)

Conclusion : Low dose olanzapine (2.5mg) is non inferior to 10mg olanzapine in controlling CINV without requirement of delayed steroids, and is superior with respect to DTS (all days, all grades, severe grades) in subjects receiving HEC.This merits wide recognition as a new steroid sparing antiemetic regimen of choice with HEC.

Psychological interventions during breast cancer rehabilitation: a randomized controlled trial comparing structured short-term psychotherapy versus non-specific group discussion

Author: David Fauser
Citation: BMC Cancer. 2023 Nov 21;23(1):1133.

Purpose: Psycho-oncological treatment is recommended in cancer rehabilitation as it improves fatigue, anxiety, depression, and quality of life in breast cancer patients. The aim of our study was to compare a structured short-term psychotherapy and a non-specific group discussion provided during breast cancer rehabilitation.

Methods: Breast cancer patients were randomly assigned to structured group short-term psychotherapy or a non-specific group discussion during breast cancer rehabilitation. The patients completed questionnaires at the beginning and end of rehabilitation and three months after rehabilitation. The primary outcome was anxiety. Secondary outcomes were depression, distress, fatigue and health-related quality of life domains.

Results: In total, 160 patients (80 in both groups) were recruited and included in the analysis. There was no significant difference between both groups in the primary outcome anxiety at the end of rehabilitation (difference = -0.2; 95% CI -1.2 to 0.7) and three months after rehabilitation (difference = 0.2; 95% CI -0.9 to 1.3) and in any secondary outcome. Patients in the short-term psychotherapy group with high anxiety levels at baseline reported fewer depressive symptoms at the end of rehabilitation.

Conclusions: Our study showed no difference between structured short-term psychotherapy and a non-specific group discussion. Patients with high baseline anxiety levels were more likely to benefit from short-term structured psychotherapy. Early identification of this subgroup and symptoms of mental illness should occur after initial treatment in breast cancer patients in order to offer a structured treatment for anxiety and depressive symptoms during rehabilitation.

Efficacy and safety of mirogabalin for chemotherapy-induced peripheral neuropathy: a prospective single-arm trial (MiroCIP study)

Author: Sonoko Misawa
Citation: BMC Cancer 23, 1098 (2023).

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a painful, dose-limiting adverse effect of commonly used chemotherapeutic agents. The purpose of this exploratory study was to evaluate the efficacy and safety of mirogabalin in patients with moderate to severe CIPN during chemotherapy and the effects of 12 weeks' intervention on chemotherapy completion and CIPN severity.

Methods: Patients experiencing moderate to severe CIPN while undergoing oxaliplatin- or taxane-containing chemotherapy for colorectal, gastric, non-small-cell lung, or breast cancer received mirogabalin at between 5 and 15 mg twice daily. The primary endpoint was change in numeric rating scale (NRS) score for pain from baseline to week 12. Secondary endpoints included NRS scores for tingling and sleep, completion of chemotherapy, severity of CIPN, and quality of life (QOL) scores. The safety endpoint was incidence of adverse events.

Results: Of 58 patients who consented to participation, 52 were eligible and constituted the full analysis set and safety analysis set. From baseline to week 12 (last observation carried forward [LOCF]), NRS score decreased by 30.9%: mean change (95% confidence interval [CI]), - 1.7 (- 2.4 to - 1.0) ($p < 0.001$). Patients with baseline NRS of ≥ 6 experienced a 44.0% reduction in score from baseline to week 12 (LOCF): mean change (95% CI), - 3.3 (- 5.0 to - 1.5) ($p = 0.002$). Chemotherapy was discontinued in 18 (34.6%) patients; CIPN led to discontinuation in only 2 (3.8%). There was no notable worsening of CIPN severity in terms of Common Terminology Criteria for Adverse Events grade or Modified Total Neuropathy Score-reduced, although use of pain medications during chemotherapy might cause worsening of CIPN due to underestimation

of subjective symptoms. QOL score based on the EuroQol five-dimensional descriptive system did not worsen during the 12 weeks. Thirty-one percent of patients experienced adverse drug reactions, and the most common event was somnolence (13.5%). Serious adverse events and death occurred in 3 patients and 1 patient, respectively; however, they were unrelated to mirogabalin treatment.

Conclusions: Intervention with mirogabalin during chemotherapy may be effective and safe for cancer patients with moderate to severe CIPN. It can contribute to completion of chemotherapy without worsening of CIPN.

International Pooled Analysis of Leisure-Time Physical Activity and Premenopausal Breast Cancer in Women From 19 Cohorts

Author: Iain R Timmins
Citation: J Clin Oncol. 2023 Dec 11:JCO2301101.

Purpose: There is strong evidence that leisure-time physical activity is protective against postmenopausal breast cancer risk but the association with premenopausal breast cancer is less clear. The purpose of this study was to examine the association of physical activity with the risk of developing premenopausal breast cancer.

Methods: We pooled individual-level data on self-reported leisure-time physical activity across 19 cohort studies comprising 547,601 premenopausal women, with 10,231 incident cases of breast cancer. Multivariable Cox regression was used to estimate hazard ratios (HRs) and 95% CIs for associations of leisure-time physical activity with breast cancer incidence. HRs for high versus low levels of activity were based on a comparison of risk at the 90th versus 10th percentiles of activity. We assessed the linearity of the relationship and examined subtype-specific associations and effect modification across strata of breast cancer risk factors, including adiposity.

Results: Over a median 11.5 years of follow-up (IQR, 8.0-16.1 years), high versus low levels of leisure-time physical activity were associated with a 6% (HR, 0.94 [95% CI, 0.89 to 0.99]) and a 10% (HR, 0.90 [95% CI, 0.85 to 0.95]) reduction in breast cancer risk, before and after adjustment for BMI, respectively. Tests of nonlinearity suggested an approximately linear relationship (Pnonlinearity = .94). The inverse association was particularly strong for human epidermal growth factor receptor 2-enriched breast cancer (HR, 0.57 [95% CI, 0.39 to 0.84]; Phet = .07). Associations did not vary significantly across strata of breast cancer risk factors, including subgroups of adiposity.

Conclusion: This large, pooled analysis of cohort studies adds to evidence that engagement in higher levels of leisure-time physical activity may lead to reduced premenopausal breast cancer risk.

Mepitel Film for the Prevention of Acute Radiation Dermatitis in Breast Cancer: A Randomized Multicenter Open-Label Phase III Trial

Author: Tara Behroozian
Citation: J Clin Oncol. 2023 Feb 20;41(6):1250-1264.

Purpose: Radiation dermatitis (RD) is common in patients undergoing breast radiotherapy. Mepitel film (MF) can reduce RD, but the results from two randomized controlled trials are conflicting. We aimed to conduct a confirmatory randomized controlled trial in patients at risk of RD.

Methods: Patients were randomly assigned to receive MF or standard care (2:1 ratio). Patients with large breasts after lumpectomy (bra size ≥ 36 inches or cup size ≥ C) or after mastectomy were eligible. Stratification factors included surgery type, dose fractionation, and administration of boost/bolus. The primary end point was grade (G) 2 or 3 RD using the Common Terminology Criteria for Adverse Events v5.0. Secondary end points included patient- and clinician-reported outcomes.

Results: Between January 2020 and May 2022, 376 patients were included in the modified intention-to-treat analysis. The incidence of G2 or 3 RD was significantly lower in MF patients compared with standard care (n = 39/251, 15.5%; 95% CI, 11.3 to 20.6% v n = 57/125, 45.6%; 95% CI, 36.7 to 54.8% respectively, odds ratio (OR): 0.20, P < .0001). Benefits of MF remained significant in patients who developed G 3 RD (n = 7, 2.8%; 95% CI, 1.1 to 5.7% v n = 17, 13.6%; 95% CI, 8.1 to 20.9%, OR: 0.19) and moist desquamation (n = 20, 8.0%; 95% CI, 4.9 to 12.0% v n = 24, 19.2%; 95% CI, 12.7 to 27.1%, OR: 0.36). When evaluating the combined patient and health care provider score using Radiation-Induced Skin Reaction Assessment Scale, the MF arm had significantly lower scores (P < .0001). Individual items on the Radiation-Induced Skin Reaction Assessment Scale also favored the MF for both patient- and clinician-reported outcomes. Blistering/peeling, erythema, pigmentation, and edema were significantly reduced in the MF arm. Three patients removed the film prematurely because of rash (n = 2) and excessive pruritus (n = 1).

Conclusion: MF significantly reduces RD in patients undergoing breast radiotherapy.

Randomized Trial of Exercise and Nutrition on Chemotherapy Completion and Pathologic Complete Response in Women With Breast Cancer: The Lifestyle, Exercise, and Nutrition Early After Diagnosis Study

Author: Tara Sanft
Citation: J Clin Oncol. 2023 Dec 1;41(34):5285-5295.

Purpose: Successful completion of chemotherapy is critical to improve breast cancer outcomes. Relative dose intensity (RDI), defined as the ratio of chemotherapy delivered to prescribed, is a measure of chemotherapy completion and is associated with cancer mortality. The effect of exercise and eating a healthy diet on RDI is unknown. We conducted a randomized trial of an exercise and nutrition intervention on RDI and pathologic complete response (pCR) in women diagnosed with breast cancer initiating chemotherapy.

Methods: One hundred seventy-three women with stage I-III breast cancer were randomly assigned to usual care (UC; n = 86) or a home-based exercise and nutrition intervention with counseling sessions delivered by oncology-certified registered dietitians (n = 87). Chemotherapy dose adjustments and delays and pCR were abstracted from electronic medical records. T-tests and chi-square tests were used to examine the effect of the intervention versus UC on RDI and pCR.

Results: Participants randomly assigned to intervention had greater improvements in exercise and diet quality compared with UC (P < .05). RDI was 92.9% ± 12.1% and 93.6% ± 11.1% for intervention and UC, respectively (P = .69); the proportion of patients in the intervention versus UC who achieved ≥85% RDI was 81% and 85%, respectively (P = .44). The proportion of patients who had at least one dose reduction and/or delay was 38% intervention and 36% UC (P = .80). Among 72 women who received neoadjuvant chemotherapy, women randomly assigned to intervention were more likely to have a pCR than those randomly assigned to UC (53% v 28%; P = .037).

Conclusion: Although a diet and exercise intervention did not affect RDI, the intervention was associated with a higher pCR in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative and triple-negative breast cancer undergoing neoadjuvant chemotherapy.

Pregnancy After Breast Cancer in Young BRCA Carriers: An International Hospital-Based Cohort Study

Author: Matteo Lambertini
Citation: JAMA. 2023 Dec 7:e2325463.

Importance: Young women with breast cancer who have germline pathogenic variants in BRCA1 or BRCA2 face unique challenges regarding fertility. Previous studies demonstrating the feasibility and safety of pregnancy in breast cancer survivors included limited data regarding BRCA carriers.

Objective: To investigate cumulative incidence of pregnancy and disease-free survival in young women who are BRCA carriers.

Design, setting, and participants: International, multicenter, hospital-based, retrospective cohort study conducted at 78 participating centers worldwide. The study included female participants diagnosed with invasive breast cancer at age 40 years or younger between January 2000 and December 2020 carrying germline pathogenic variants in BRCA1 and/or BRCA2. Last delivery was October 7, 2022; last follow-up was February 20, 2023.

Exposure: Pregnancy after breast cancer.

Main outcomes and measures: Primary end points were cumulative incidence of pregnancy after breast cancer and disease-free survival. Secondary end points were breast cancer-specific survival, overall survival, pregnancy, and fetal and obstetric outcomes.

Results: Of 4732 BRCA carriers included, 659 had at least 1 pregnancy after breast cancer and 4073 did not. Median age at diagnosis in the overall cohort was 35 years (IQR, 31-38 years). Cumulative incidence of pregnancy at 10 years was 22% (95% CI, 21%-24%), with a median time from breast cancer diagnosis to conception of 3.5 years (IQR, 2.2-5.3 years). Among the 659 patients who had a pregnancy, 45 (6.9%) and 63 (9.7%) had an induced abortion or a miscarriage, respectively. Of the 517 patients (79.7%) with a completed pregnancy, 406 (91.0%) delivered at term (≥37 weeks) and 54 (10.4%) had twins. Among the 470 infants born with known information on pregnancy complications, 4 (0.9%) had documented congenital anomalies. Median follow-up was 7.8 years (IQR, 4.5-12.6 years). No significant difference in disease-free survival was observed between patients with or without a pregnancy after breast cancer (adjusted hazard ratio, 0.99; 95% CI, 0.81-1.20). Patients who had a pregnancy had significantly better breast cancer-specific survival and overall survival.

Conclusions and relevance: In this global study, 1 in 5 young BRCA carriers conceived within 10 years after breast cancer diagnosis. Pregnancy following breast cancer in BRCA carriers was not associated with decreased disease-free survival.

Interrupting Endocrine Therapy to Attempt Pregnancy after Breast Cancer

Author: Ann H Partridge
Citation: N Engl J Med. 2023 May 4;388(18):1645-1656.

Background: Prospective data on the risk of recurrence among women with hormone receptor-positive early breast cancer who temporarily discontinue endocrine therapy to attempt pregnancy are lacking.

Methods: We conducted a single-group trial in which we evaluated the temporary interruption of adjuvant endocrine therapy to attempt pregnancy in young women with previous breast cancer. Eligible women were 42 years of age or younger; had had stage I, II, or III disease; had received adjuvant endocrine therapy for 18 to 30 months; and desired pregnancy. The primary end point was the number of breast cancer events (defined as local, regional, or distant recurrence of invasive breast cancer or new contralateral invasive breast cancer) during follow-up. The primary analysis was planned to be performed after 1600 patient-years of follow-up. The prespecified safety threshold was the occurrence of 46 breast cancer events during this period. Breast cancer outcomes in this treatment-interruption group were compared with those in an external control cohort consisting of women who would have met the entry criteria for the current trial.

Results: Among 516 women, the median age was 37 years, the median time from breast cancer diagnosis to enrollment was 29 months, and 93.4% had stage I or II disease. Among 497 women who were followed for pregnancy status, 368 (74.0%) had at least one pregnancy and 317 (63.8%) had at least one live birth. In total, 365 babies were born. At 1638 patient-years of follow-up (median follow-up, 41 months), 44 patients had a breast cancer event, a result

that did not exceed the safety threshold. The 3-year incidence of breast cancer events was 8.9% (95% confidence interval [CI], 6.3 to 11.6) in the treatment-interruption group and 9.2% (95% CI, 7.6 to 10.8) in the control cohort.

Conclusions: Among select women with previous hormone receptor-positive early breast cancer, temporary interruption of endocrine therapy to attempt pregnancy did not confer a greater short-term risk of breast cancer events, including distant recurrence, than that in the external control cohort. Further follow-up is critical to inform longer-term safety.

Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer

Author: Lauren McVicker
Citation: JAMA Oncol. 2023 Nov 2:e234508.

Importance: Genitourinary syndrome of menopause can be treated with vaginal estrogen therapy. However, there are concerns about the safety of vaginal estrogen therapy in patients with breast cancer.

Objective: To determine whether the risk of breast cancer-specific mortality was higher in females with breast cancer who used vaginal estrogen therapy vs females with breast cancer who did not use hormone replacement therapy (HRT).

Design, setting, and participants: This cohort study analyzed 2 large cohorts, one each in Scotland and Wales, of females aged 40 to 79 years with newly diagnosed breast cancer. These population-based cohorts were identified from national cancer registry records from 2010 to 2017 in Scotland and from 2000 to 2016 in Wales and were followed up for breast cancer-specific mortality until 2020. Females were excluded if they had a previous cancer diagnosis (except nonmelanoma skin cancer). Data analysis was performed between August 2022 and August 2023.

Exposure: Use of vaginal estrogen therapy, including vaginal tablets and creams, was ascertained from pharmacy dispensing records of the Prescribing Information System for the Scotland cohort and from general practice prescription records for the Wales cohort.

Main outcomes and measures: The primary outcome was time to breast cancer-specific mortality, which was obtained from national mortality records. Time-dependent Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% CIs for breast cancer-specific mortality, comparing vaginal estrogen therapy users with HRT nonusers and adjusting for confounders, including cancer stage and grade.

Results: The 2 cohorts comprised 49 237 females with breast cancer (between 40 and 79 years of age) and 5795 breast cancer-specific deaths. Five percent of patients with breast cancer used vaginal estrogen therapy after breast cancer diagnosis. In vaginal estrogen therapy users compared with HRT nonusers, there was no evidence of a higher risk of breast cancer-specific mortality in the pooled fully adjusted model (HR, 0.77; 95% CI, 0.63-0.94).

Conclusions and relevance: Results of this study showed no evidence of increased early breast cancer-specific mortality in patients who used vaginal estrogen therapy compared with patients who did not use HRT. This finding may provide some reassurance to prescribing clinicians and support the guidelines suggesting that vaginal estrogen therapy can be considered in patients with breast cancer and genitourinary symptoms.

Association of Staphylococcus aureus Colonization With Severity of Acute Radiation Dermatitis in Patients With Breast or Head and Neck Cancer

Author: Yana Kost
Citation: JAMA Oncol. 2023 Jul 1;9(7):962-965.

Importance: Pathogenesis of acute radiation dermatitis (ARD) is not completely understood. Pro-inflammatory cutaneous bacteria may contribute to cutaneous inflammation after radiation therapy.

Objective: To evaluate whether nasal colonization with Staphylococcus aureus (SA) before radiation therapy is associated with ARD severity in patients with breast or head and neck cancer.

Design, setting, and participants: This prospective cohort study with observers blinded to colonization status was conducted from July 2017 to May 2018 at an urban academic cancer center. Patients aged 18 years or older with breast or head and neck cancer and plans for fractionated radiation therapy (≥15 fractions) with curative intent were enrolled via convenience sampling. Data were analyzed from September to October 2018.

Exposures: Staphylococcus aureus colonization status before radiation therapy (baseline).

Main outcomes and measures: The primary outcome was ARD grade using the Common Terminology Criteria for Adverse Event Reporting, version 4.03.

Results: Among 76 patients analyzed, mean (SD) age was 58.5 (12.6) years and 56 (73.7%) were female. All 76 patients developed ARD: 47 (61.8%) with grade 1, 22 (28.9%) with grade 2, and 7 (9.2%) with grade 3. The prevalence of baseline nasal SA colonization was higher among patients who developed grade 2 or higher ARD compared with those who developed grade 1 ARD (10 of 29 [34.5%] vs 6 of 47 [12.8%]; P = .02, by $\chi 2$ test).

Conclusions and relevance: In this cohort study, baseline nasal SA colonization was associated with development of grade 2 or higher ARD in patients with breast or head and neck cancer. The findings suggest that SA colonization may play a role in the pathogenesis of ARD.

Bacterial Decolonization for Prevention of Radiation Dermatitis: A Randomized Clinical Trial

Author: Yana Kost
Citation: JAMA Oncol. 2023 Jul 1;9(7):940-945.

Importance: Evidence-based approaches for the prevention of acute radiation dermatitis (ARD) are limited, and additional strategies are necessary to optimize care.

Objective: To determine the efficacy of bacterial decolonization (BD) to reduce ARD severity compared with standard of care.

Design, setting, and participants: This phase 2/3 randomized clinical trial was conducted from June 2019 to August 2021 with investigator blinding at an urban academic cancer center and enrolled patients with breast cancer or head and neck cancer receiving radiation therapy (RT) with curative intent. Analysis was performed on January 7, 2022.

Interventions: Intranasal mupirocin ointment twice daily and chlorhexidine body cleanser once daily for 5 days prior to RT and repeated for 5 days every 2 weeks through RT.

Main outcomes and measures: The primary outcome as planned prior to data collection was the development of grade 2 or higher ARD. Based on wide clinical variability of grade 2 ARD, this was refined to grade 2 ARD with moist desquamation (grade 2-MD).

Results: Of 123 patients assessed for eligibility via convenience sampling, 3 were excluded, and 40 refused to participate, with 80 patients in our final volunteer sample. Of 77 patients with cancer (75 patients with breast cancer [97.4%] and 2 patients with head and neck cancer [2.6%]) who completed RT, 39 were randomly assigned BC, and 38 were randomly assigned standard of care; the mean (SD) age of the patients was 59.9 (11.9) years, and 75 (97.4%) were female. Most patients were Black (33.7% [n = 26]) or Hispanic (32.5% [n = 25]). Among patients with breast cancer and patients with head and neck cancer (N = 77), none of the 39 patients treated with BD and 9 of the 38 patients (23.7%) treated with standard of care developed ARD grade 2-MD or higher (P = .001). Similar results were observed among the 75 patients with breast cancer (ie, none treated with BD and 8 [21.6%] receiving standard of care developed ARD grade ≥2-MD; P = .002). The mean (SD) ARD grade was significantly lower for patients treated with BD (1.2 [0.7]) compared with patients receiving standard of care (1.6 [0.8]) (P = .02). Of the 39 patients randomly assigned to BD, 27 (69.2%) reported regimen adherence, and only 1 patient (2.5%) experienced an adverse event related to BD (ie, itch).

Conclusions and relevance: The results of this randomized clinical trial suggest that BD is effective for ARD prophylaxis, specifically for patients with breast cancer.