LBA1000 **Oral Abstract Session**

Vepdegestrant, a PROTAC estrogen receptor (ER) degrader, vs fulvestrant in ER-positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer: Results of the global, randomized, phase 3 VERITAC-2 study.

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1001 Oral Abstract Session

Patient-reported outcomes (PROs) in patients with ER+, HER2- advanced breast cancer (ABC) treated with imlunestrant, investigator's choice standard endocrine therapy, or imlunestrant + abemaciclib: Results from the phase III EMBER-3 trial.

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Background: Imlunestrant (imlu) is a next-generation, brain-penetrant, oral selective estrogen receptor degrader. The EMBER-3 trial, in patients (pts) with ER+, HER2- ABC who had disease progression on or after aromatase inhibitor-based therapy, showed significant progression free survival (PFS) improvement with imlu vs standard therapy (SOC, fulvestrant or exemestane) in pts with *ESR1* mutations (*ESR1*m), and with imlunestrant+abemaciclib (imlu+abema) vs imlu in all pts, regardless of *ESR1*m. Exploratory PRO analyses are presented here. **Methods:** EORTC QLQ-C30 was administered at baseline (BL) and every 8 weeks until treatment discontinuation. Prespecified QLQ-C30 analysis used a longitudinal mixed model for repeated measures to calculate mean change from BL in pts with BL and ≥1 post-BL score. PRO-CTCAE (diarrhea frequency) was administered weekly, reporting 0 (never) to 4 (almost constantly). PRO-CTCAE (injection site reaction [ISR]) was administered to fulvestrant recipients weekly for 2 weeks post-injection, reporting yes/no (pain, swelling, redness). Descriptive analysis was used for PRO-CTCAE. **Results:** In pts with *ESR1*m, imlu monotherapy was associated with many improved or maintained EORTC QLQ-C30 scores, whereas scores with SOC were declined or maintained. Specifically, pts with *ESR1*m on imlu had improved global health status (GHS)/quality of life (QOL) and physical function (PF) scores, while scores with SOC declined (mean change differences between treatments: 9.9 [0.1, 19.7] and 6.2 [-0.8, 13.1], respectively). These PRO findings mirror the PFS findings in this group. In the overall population, GHS/QOL scores declined similarly with imlu vs SOC (mean change differences: 0.5 [-4.7, 5.7]), while PF scores were maintained with imlu vs a slight decline with SOC (mean change difference: 2.5 [-1.1, 6.1]). Most fulvestrant recipients (72%) reported ISR at any time while on treatment, with a mean of 31% during the first week of the first 6 cycles. Imlu+abema vs imlu showed broadly similar declines in all pts, with minimal mean change differences in GHS/QOL and PF scores (0.8 [-7.4, 5.9]; -2.2 [-6.6, 2.2], respectively). Pts reported similarly low rates of "frequent" or "almost constant" diarrhea with imlu (3%) and SOC (2%) and higher rates with imlu+abema (22%). **Conclusions:** PROs from EMBER-3 demonstrated that patients with *ESR1*m had better GHS/QOL and PF with imlu vs SOC, mirroring efficacy results. While the frequency of CTCAE defined ISRs was low, the high rate of PRO-CTCAE ISR demonstrates that this clinically relevant adverse event is underappreciated by physicians. Additionally, all pts had generally comparable GHS/QOL and PF with imlu+abema vs imlu. Overall, these results support the efficacy and safety of imlu compared to existing SOC. Clinical trial information: NCT04975308. Research Sponsor: Eli Lilly and Company, Indianapolis, IN, USA.

1003 Oral Abstract Session

INAVO120: Phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, hormone receptor-positive (HR+), HER2-negative (HER2−), endocrine-resistant advanced breast cancer (aBC).

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Background: INAVO, a highly potent and selective PI3Kα inhibitor that also promotes mutated p110α degradation, is FDA-approved in combination with PALBO + FULV for *PIK3CA*-mutated, HR+, HER2−, endocrine-resistant aBC, based on the primary analysis of INAVO120 (NCT04191499), which showed a statistically significant and clinically meaningful investigator-assessed progression-free survival (INV-PFS) benefit in the INAVO arm vs. the PBO arm (hazard ratio 0.43; 95% confidence interval [CI] = 0.32−0.59; $p < 0.0001$). At that analysis, interim OS results were immature. Here we report the final OS analysis, including updated efficacy and safety. **Methods:** Pts received INAVO (9 mg orally once daily [PO QD]; Days 1−28 of each 28-day cycle)/PBO + PALBO (125 mg PO QD; Days 1−21 of each cycle) + FULV (500 mg intramuscularly; Cycle 1 Days 1 and 15 then every ~4 weeks). OS and objective response rate (ORR) were formally tested; updated INV-PFS and safety analyses are descriptive. **Results:** Data cut-off was Nov 15, 2024, at 34.2 months (mo) of median follow-up. Median OS was 34.0 mo (95% CI = 28.4−44.8) in the INAVO arm and 27.0 mo (95% CI = 22.8−38.7) in the PBO arm (stratified hazard ratio 0.67; 95% CI = 0.48−0.94; p = 0.0190 [boundary = 0.0469]). The OS benefit was consistent across key subgroups. The survival probability at 6, 12, 18, 24, and 30 mo was 96.8%, 87.0%, 74.3%, 65.8%, and 56.5% in the INAVO arm and 90.1%, 76.7%, 67.2%, 56.3%, and 46.3% in the PBO arm. ORR was 62.7% (95% CI = 54.8−70.2) and 28.0% (95% CI = 21.3−35.6), respectively ($p < 0.0001$). Median time to chemotherapy (TTC) was 35.6 mo (95% CI = 25.4−not reached) in the INAVO arm and 12.6 mo (95% CI = 10.4−16.1) in the PBO arm (stratified hazard ratio 0.43; 95% CI = 0.30−0.60). Updated median INV-PFS was 17.2 mo (95% CI = 11.6−22.2) in the INAVO arm and 7.3 mo (95% CI = 5.9−9.2) in the PBO arm (stratified hazard ratio 0.42; 95% CI = 0.32−0.55), with landmark analyses supporting durable benefit. 90.7% of pts in the INAVO arm and 84.7% in the PBO arm had grade 3/4 adverse events (AEs); there were no new grade 5 AEs; 63.4% and 13.5% experienced any-grade hyperglycemia (grouped term); and AEs led to INAVO and PBO discontinuation in 6.8% and 0.6% of pts, respectively. **Conclusions:** INAVO + PALBO + FULV demonstrated a statistically significant and clinically meaningful OS benefit compared with PBO + PALBO + FULV. Improvement in INV-PFS was maintained during longer follow-up, along with a substantial and statistically significant improvement in ORR. TTC was also substantially delayed (by ~2 years) by the addition of INAVO to PALBO + FULV. With longer exposure to INAVO, no new safety signals, nor changes in the safety profile, were noted, supporting good tolerability (reflected in low discontinuation due to AEs). Clinical trial information: NCT04191499. Research Sponsor: F. Hoffmann-La Roche Ltd; The authors acknowledge the Memorial Sloan Kettering Cancer Center support grant (P30 CA008748).

Phase I/Ib study of inavolisib (INAVO) alone and in combination with endocrine therapy ± palbociclib (PALBO) in patients (pts) with *PIK3CA*-mutated, hormone receptor–positive, HER2-negative locally advanced/metastatic breast cancer (HR+, HER2– LA/mBC): Analysis of hyperglycemia (HG) in prediabetic/obese pts.

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Background: INAVO, a highly potent and selective PI3Kα inhibitor that also promotes degradation of mutated p110α, is approved by the FDA in combination with PALBO + fulvestrant (FULV) for *PIK3CA*-mutated, HR+, HER2–, endocrine-resistant advanced BC. HG is a common on-target side effect of PI3K inhibitors. There are limited data for PI3K inhibitors in prediabetic/obese pts. Data from prediabetic/obese pts with HR+, HER2– LA/mBC treated with INAVO from a Phase I/Ib study (GO39374; NCT03006172) are reported here. **Methods:** Adults ≥ 18 years of age received INAVO alone (Arm A), + letrozole (LET) + PALBO (Arm B), + LET (Arm C), + FULV (Arm D), + FULV + PALBO (Arm E), or + FULV + PALBO + primary prophylactic metformin (Arm F). Data are reported across all arms unless indicated. Pts with baseline risk factors for HG were defined by HbA_{1c} ≥5.7%, fasting blood glucose ≥ 100 mg/dL, or body mass index ≥ 30 kg/m^2. Adverse events (AEs) were reported using NCI-CTCAE v4, which utilizes fasting laboratory glucose values for HG severity grading, rather than clinical interventions used in v5. **Results:** Clinical cut-off was Jan 1, 2024. From190 pts treated, 110 (57.9%) were prediabetic/obese; their median time on INAVO was 222 days (range, 7 to 2,152) and mean cumulative dose intensity was 91.8%. Most prediabetic/obese pts discontinued INAVO due to progressive disease (82 [74.5%]); six (5.5%) discontinued INAVO due to an AE (one due to HG). HG was reported in 80.9% of prediabetic/obese pts (grade 3–4: 34.5%). In pts with two risk factors, 87.9% reported HG (grade 3–4: 39.4%). Among pts with HG, median time to onset was 14 days (range, 1 to 1,674) and 86.0% of events resolved by clinical cut-off. Median time to improvement or resolution of first worst grade ≥ 2 event was 8 days (range, 1 to 64). INAVO dose interruptions, reductions, and discontinuations due to HG were reported in 41.8%, 13.6%, and 0.9% of pts, respectively. The most common anti-HG medications were metformin (52.7%; biguanide; concomitant use in Arm F excluded), empagliflozin (25.5%; SGLT-2 inhibitor), sitagliptin (22.7%; DPP-4 inhibitor), and pioglitazone (13.6%; thiazolidinedione); insulin was used in 8.2% of pts. Median time to metformin start (excluding Arm F) was 14 days (range, 1 to 1,710); the median start dose was 1,000 mg total daily; and the highest daily start dose was 2,000 mg. More than one anti-HG medication was often needed. **Conclusions:** A high proportion of prediabetic/obese pts were included in GO39374. In most of these pts, HG was manageable with dose interruptions and oral anti-HG medications, most commonly metformin. Data support the use of INAVO in prediabetic/obese pts; further investigation of INAVO in pts with diabetes is warranted. Clinical trial information: NCT03006172. Research Sponsor: Genentech, Inc.; The authors acknowledge the Memorial Sloan Kettering Cancer Center support grant (P30 CA008748).

LBA1005 **Oral Abstract Session**

A double-blind placebo controlled randomized phase III trial of fulvestrant and ipatasertib as treatment for advanced HER2-negative and estrogen receptor positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor: The CCTG/BCT MA.40/FINER study (NCT04650581).

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Phase III of oral paclitaxel (DHP107) vs intravenous paclitaxel in HER2-negative recurrent or metastatic breast cancer (mBC): Primary analysis of a multinational optimal trial (NCT03315364).

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Background: DHP107 is a novel oral formulation of paclitaxel that is approved in South Korea and China for the treatment of gastric cancer. DHP107 had encouraging monotherapy anti-tumor activity with objective response rate (ORR) of 55% and median progression free survival (PFS) of 8.9 months (Mo) as first-line therapy in 31 patients with HER2 negative metastatic breast cancer (mBC) in the OPTIMAL phase II study (Kim *Ther Adv Med Oncol* 2021). The first primary analysis is reported herein. **Methods:** This phase III, open-label, randomized, controlled trial evaluated the non-inferiority of DHP107 to intravenous (IV) paclitaxel in mBC, with non-inferiority margin of 1.33. Patients (Pts) had received one or more lines of endocrine-based therapy and no chemotherapy for mBC. Pts from Korea, China, and Europe were randomized 1:1 to receive either DHP107 (200 mg/m^2 orally, twice daily) or IV paclitaxel (80 mg/m^2 weekly). The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival (OS), ORR, disease control rate (DCR), quality of life (QoL), and safety. **Results:** With the median follow-up of 38.8 Mo, the median age of the pts was 56 years. Of the 549 pts who underwent randomization, 481 pts had hormone receptor positive (HR+) disease and 68 pts had triple negative disease. Among all pts, DHP107 demonstrated non-inferiority to IV paclitaxel in PFS (mPFS: 10.02 vs. 8.54 Mo; HR 0.869, 95% CI 0.707–1.068). OS was comparable between groups (mOS: 32.95 vs. 32.46 Mo; HR 0.979, 95% CI 0.769–1.246). Among HR+HER2- pts, the mPFS was 10.74 Mo in the DHP107 arm, and 9.07 Mo in IV paclitaxel arm (HR 0.869, 95% CI 0.700-1.080). QoL outcomes showed no significant differences. ORR (45.8% vs. 39.7%) ad DCR (93.5% vs. 86.4%) were higher in the DHP107 group. DHP107 was associated with lower incidences of peripheral neuropathy (37.91% vs. 48.29%), hypersensitivity reactions, musculoskeletal and connective tissue disorders, and injection/infusion related reactions compared to IV paclitaxel. Neutropenia was the most common toxicity in both groups, occurring more frequently in the DHP107 group (81.6% vs. 59.3%) with higher rates of Gr≥3,4 neutropenia (67.15% vs. 29.66%), and febrile neutropenia (6.14% vs. 0.76%), but no grade 5 events were reported. Gastrointestinal toxicities were more frequent in the DHP107 group but were predominately Gr1. In this study, discontinuation rate due to AEs were comparable (12.27% vs. 8.75%, p=0.2081) and AEs leading to death occurred rarely in both groups (1.08% vs. 1.90%). **Conclusions:** DHP107 demonstrated comparable efficacy to IV paclitaxel with tolerable and manageable toxicity. These results establish DHP107 as an effective, convenient alternative to IV paclitaxel for patients with HER2-negative mBC, supporting its potential role in routine clinical practice. Clinical trial information: NCT03315364. Research Sponsor: DAEWHA PHARM. CO., LTD.

Circulating tumor DNA, pathologic response after neoadjuvant therapy, and survival: First results from TBCRC 040 (the PREDICT-DNA trial).

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Background: Patients with Stage II/III breast cancer that overexpresses the human epidermal growth factor-2 (HER2+) or is triple-negative (TNBC) generally receive upfront neoadjuvant therapy (NAT) before definitive surgery. Pathologic complete response (pCR) after NAT is associated with improved survival but a small proportion of patients remain at risk for recurrence. Circulating tumor DNA (ctDNA) in patients whose primary tumors have detectable mutations could improve the identification of patients who remain at risk after NAT. **Methods:** The Pathologic Response Evaluation and Detection In Circulating Tumor-DNA (PREDICT-DNA) trial was a prospective, multi-center study aimed at validating ctDNA as a biomarker for treatment response in Stage II/III HER2+ or TNBC. The primary aim was to determine the negative predictive value (NPV) of ctDNA for residual disease following NAT; secondary aims included five-year invasive disease-free survival (IDFS), which were fit to a Cox proportional hazards model. Mutations were identified from tumor tissue; ctDNA was then analyzed in pre- and post-NAT blood and compared with surgical pathology. Proposed sample size was 229 patients based on simulation to control expected half-width of a confidence interval on NPV to be ≤15% when NPV=90%. The Personalis NeXT Personal ctDNA assay was centrally performed. **Results:** 228 participants were enrolled in 24 sites between 2016 and 2018. 53% had TNBC, and 47% had HER2+ disease. 92.2% (n=166/180) had detectable ctDNA at baseline, and 46% of patients had pCR (42% TNBC, 50% HER2+). 54% of all post-NAT ctDNA detections were in the ultrasensitive range below 100 PPM. Among 112 subjects with undetectable ctDNA prior to surgery, 45 were found to have residual disease resulting in an NPV of 60% (CI 0.51-0.69). Patients with TNBC and detectable ctDNA prior to surgery were approximately 12 times more likely to experience a recurrence regardless of pCR (HR 12.8 [95% CI: 2.3-71.5]). See Table describing landmark IDFS analyses after surgery. **Conclusions:** While lack of ctDNA detection after NAT and before surgery did not predict pCR, initial analysis of predefined secondary objectives suggest that ctDNA-negative patients before surgery have excellent prognosis regardless of pCR, particularly if TNBC. This suggests that ctDNA may be a better biomarker for long term clinical outcomes than pCR. Further correlations and interactions will be presented. Clinical trial information: NCT02743910. Research Sponsor: Susan B. Komen Breast Cancer Foundation; Breast Cancer Research Foundation; Johns Hopkins Clinical Research Network Research Accelerator and Mentorship Program (RAMP); Commonwealth Foundation; NIH/NCI grant; R01CA194024; NIH/NCI grant; R01CA214494; NIH/NCI grant; R01CA289528; NIH/NCI grant; P50CA098131; NIH/NCI grant; P30CA06485; The Helen Golde Fund; NIH/NCI grant; P30CA006973; The Translational Breast Cancer Research Consortium (TBCRC).

Invasive disease-free survival (IDFS) by breast cancer subtype, according to ctDNA after NAT and pathologic response.

TNBC (total n=64)	3y IDFS (n=40)	4y IDFS (n=32)	5y IDFS (n=18)
ctDNA- & pCR (n=20)	94.1%	94.1%	94.1%
ctDNA- & RD (n=25)	95.8%	89.8%	89.8%
ctDNA+ & RD (n=19)	48.9%	48.9%	48.9%
HER2+ (total n=58)	3y IDFS (n=41)	4y IDFS (n=31)	5y IDFS (n=17)
ctDNA- & pCR (n=19)	94.1%	94.1%	94.1%
ctDNA- & RD (n=31)	92.6%	87.5%	87.5%
ctDNA+ & RD (n=8)	60.0%	60.0%	60.0%

Circulating tumor (ct)DNA monitoring of ER+/HER2- high-risk breast cancer during adjuvant endocrine therapy.

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Background: ctDNA monitoring during adjuvant endocrine therapy is an opportunity to detect molecular relapse before clinically apparent recurrence. ctDNA positivity rates, dynamics and the frequency of asymptomatic imaging-detectable metastatic disease at the time of ctDNA detection remain unknown in high-risk ER+/HER2- BCs. We present ctDNA results from a prospective, multicenter, randomized ctDNA interventional trial, DARE (NCT04567420). **Methods:** Patients receiving adjuvant endocrine therapy for >6 months but <7 years, with either recurrence risk >15% (PREDICT, RSPC, CTS5), >4 positive axillary lymph nodes, (primary tumor >5 cm, or 1-3 positive nodes with grade 3 histology, or >3 cm tumor, or high molecular risk (Oncotype Dx RS >26, MammaPrint high risk, EndoPredict >4, Prosigna score >60) were eligible for ctDNA surveillance with the Signatera assay (Natera, Inc.) every 6 months. ctDNA+ patients had systemic staging with imaging and if there was no evidence of metastatic disease patients were randomized to switching to fulvestrant + palbociclib (Arm A) or to continuation of adjuvant therapy (Arm B). Negative predictive value (NPV) was calculated for recurrence in the screening group after each ctDNA- test. In randomized patients, early ctDNA dynamics were correlated with recurrence-free survival (RFS) and ctDNA clearance rates were calculated by trial arm. **Results:** 552 patients had tissue sent for assay design; 494 had ctDNA results; 52 failed WES and/or had incomplete tumor/normal/blood sets; 6 had pending reports. Among patients not randomized, 432 were ctDNA-, of these N=43 had one time point and 389 had >2 ctDNA- result, overall median screening time 27.4 months (0-45.5), 4 ctDNA- patients had recurrence (NPV 100% at 6 months and 99% at 12 months post-testing). Forty patients were randomized, 34 had post-randomization ctDNA result. Randomization rates were 53% and 76% for patients who tested ctDNA-positive on the first screening (N=19) versus those who turned positive in follow up testing (N=15). At any time post-randomization, ctDNA clearance rates were 63% (10/16) in Arm A and 22% (4/18) in Arm B. Among randomized patients, 6 of 9 patients with increased ctDNA levels from the pre-randomization to the 3-month on-treatment recurred (median time to recurrence 4.8 months, range: 3.3-24.3), among those with a decrease in ctDNA post-treatment only 1 of 6 experienced recurrence at 10.3 months (HR: 5.3, 95% CI: 1.1-53, p=0.04). **Conclusions:** This study demonstrates the ability of ctDNA to identify breast cancer patients at high risk of relapse for randomization in a prospective, multicenter, randomized clinical trial. Patients with serially ctDNA- results during surveillance had 99% RFS after a median f/u of 27.4 months. Interim analysis revealed higher clearance rates in Arm A compared to patients randomized to Arm B. Early on treatment ctDNA dynamics is prognostic of patient outcomes. Clinical trial information: NCT04567420. Research Sponsor: Pfizer; Natera Inc.

Circulating tumor DNA (ctDNA) dynamics as a predictor of treatment response in metastatic breast cancer (mBC).

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Background: ctDNA testing has emerged as a prognostic and predictive biomarker in the management of mBC. However, the relationship between ctDNA trends and real-world treatment outcomes has yet to be fully characterized. Here, we utilized a claims database to evaluate the association between ctDNA trends and the time to next treatment (TTNT) in patients with mBC. **Methods:** We utilized Natera's proprietary real-world database linked to commercially available claims data to identify patients who received treatment for mBC and had ctDNA testing performed commercially using a clinically validated, personalized, tumor-informed mPCR-NGS ctDNA assay (Signatera™, Natera, Inc.). Insurance claim codes for treatment regimens were used to determine BC receptor subtype and therapy dates. Treatment lines were included in the analysis if a ctDNA test result was available within 4 weeks before treatment initiation (T1) and a subsequent ctDNA test result was available 2-6 weeks after treatment initiation (T2). TTNT was calculated as the time from initiation of the first treatment to the subsequent treatment. T1 to T2 ctDNA dynamics were analyzed using the Student's t-test and were categorized as favorable (persistently negative, ctDNA-clearance, ctDNA-decrease) or unfavorable (ctDNA-negative to positive, ctDNA-increase). **Results:** A total of 7,222 treatment lines were assessed for duration of treatment and corresponding ctDNA dynamics, including3,117 lines (N=2,362 patients) for HR+/HER2- mBC, 3,717 lines (N=1,943 patients) for HER2+ mBC, and 888 lines (N=605 patients) for TNBC. Of these, 448 treatment lines met the inclusion criteria for ctDNA analysis. In HER2+ breast cancer, TTNT across 226 treatment lines was significantly longer in patients with favorable ctDNA dynamics (6.7 [3.18–10.3] months) relative to unfavorable dynamics (2.7 [1.4–5.1] months; $p<0.0001$). Among patients with HR+/HER2- mBC, TTNT across 156 treatment lines was longer in those with favorable ctDNA dynamics (median [Q1, Q3]: 7.51 [3.72–11.57] months) compared to unfavorable dynamics (5.02 [1.8–9.84] months; p=0.052). A similar trend was observed in TNBC, where TTNT across 66 treatment lines was longer with favorable ctDNA dynamics (6.03 [2.89–10.07] months) compared to unfavorable dynamics (2.7 [1.16–5.89] months; p=0.381), though this was not statistically significant. **Conclusions:** Early on-treatment ctDNA dynamics, assessed within the first 6 weeks of therapy, was associated with TTNT in a real-world ctDNA monitoring setting across different mBC subtypes and therapeutic regimens. An early rise in ctDNA levels correlated with the shortest TTNT, whereas ctDNA clearance was associated with the longest TTNT intervals. These findings highlight the potential of serial ctDNA testing in mBC for monitoring treatment response and informing clinical decisions. Research Sponsor: None.

Assessment of ctDNA somatic homologous recombination deficiency (HRD) in triple-negative breast cancer (TNBC) from SWOG S1416 trial.

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Background: HRD is observed in up to two-thirds of g*BRCA*-wildtype TNBC. S1416 (NCT02595905) showed that addition of a PARP inhibitor (veliparib) to cisplatin improved progression-free survival (PFS) in *gBRCA*-wildtype metastatic TNBC (mTNBC) with HRD phenotype ("*BRCA*-like"). In this study, we sought to evaluate concordance between circulating tumor DNA (ctDNA)-based detection of somatic homologous recombination repair (sHRR) alterations and tumor-based HRD and to assess if sHRR deficiency (sHRR+) was associated with benefit from veliparib in g*BRCA*-wild type mTNBC in SWOG S1416. **Methods:** S1416 enrolled patients with mTNBC who had received $\leq$ 1 line of prior therapy and randomized them to cisplatin plus veliparib or placebo. Central *gBRCA1/2* testing classified patients as *gBRCA*-mutated or -wildtype. An *a priori* defined biomarker panel classified *gBRCA*-wildtype patients into *BRCA*-like (HRD+) and non-*BRCA*-like (HRD-) groups. A third group with *gBRCA*-wildtype, but without tissue BRCA classification was also included. Pre-treatment and progression plasma samples were utilized for assessment of sHRR status. ctDNA was analyzed using the Guardant OMNI next-generation sequencing platform. sHRR+ was defined by detectable somatic alterations (SNVs, INDELs, fusions with a functional impact notation of deleterious, and/or CNVs with a functional characterization of homozygous deletion) in a 24 gene panel. **Results:** Among *N*=213 g*BRCA*-wildtype patients with evaluable pre-treatment blood samples, 25% were sHRR+. Among sHRR+ patients, alterations in *CHEK2* (18%), *BRCA1* (17%), *BARD1* (8%), *ATM* (7%), *BAP1* (7%), *CDK12* (7%), *NBN* (7%), *BRCA2* (5%), and *FANCA* (5%) accounted for 80% of sHRR alterations. Most sHRR+ patients (91%) had alterations in only one of 24 genes, suggesting mutual exclusivity of homologous recombination pathway alterations in ctDNA. sHRR+ status was numerically higher in *BRCA*-like compared to non-*BRCA*-like tumors or unclassified tumors (32% vs. 20% vs. 20%, respectively; *P*=0.12). Among *n*=98 patients with availability of evaluable pre-treatment and progression samples, 31% were sHRR+ at baseline and 28% were sHRR+ at progression. Numerically, conversion from sHRR+ to sHRR- was more common than conversion from sHRR- to sHRR+ (30% vs. 9%, respectively). sHRR was not prognostic for PFS (median 4.3 (sHRR+) vs. 4.1 (sHRR-) months, respectively; *P*=0.30) nor predictive of benefit from veliparib (*P*=0.40). **Conclusions:** One-fourth of *gBRCA*-wildtype mTNBC patients have ctDNA sHRR alterations, and there is incomplete overlap between tumor- and ctDNA-assessed HRD. ctDNA sHRR alterations were mostly mutually exclusive. Approximately one-third of patients with baseline sHRR+ converted to sHRR- at time of progression while receiving DNA damaging chemotherapy. sHRR was not prognostic and did not predict benefit from veliparib in S1416. Research Sponsor: NIH/NCI/NCTN; U10CA180888; NIH/NCI/NCTN; U10CA180819.

Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in HER2-low/ultralow, hormone receptor–positive (HR+) metastatic breast cancer (mBC) in DESTINY-Breast06 (DB-06).

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Background: DB-06 (NCT04494425), a Phase 3, randomized, open-label study, demonstrated a clinically meaningful progression-free survival (PFS; 13.2 vs 8.1 months [hazard ratio: 0.64]) benefit with T-DXd vs TPC (capecitabine, nab-paclitaxel, or paclitaxel) in patients with HR+, HER2-low (immunohistochemistry [IHC] 1+ or IHC 2+ / in situ hybridization–negative) or -ultralow (IHC 0 with membrane staining) mBC after ≥1 endocrine-based therapy (primary data cutoff: March 18, 2024). Here, we report an exploratory circulating tumor DNA (ctDNA) analysis based on baseline genomic status. **Methods:** Baseline ctDNA profiling in blood samples was assessed via Guardant OMNI 500-gene liquid biopsy assay. In total, 625 patients had evaluable ctDNA samples and putative tumor content, and comprised the biomarker evaluable population (BEP) presented herein. Baseline characteristics and efficacy outcomes were evaluated in key genomic subgroups (PI3K pathway, *ESR1*m, *BRCA1/2*m), including confirmed objective response rate (cORR) and PFS, both by blinded independent central review. **Results:** Genomic alterations were observed in 45.0% (PI3K pathway, n=281), 51.5% (*ESR1*m, n=322), and 7.7% (*BRCA1/2*m, n=48) of patients. The median PFS (mPFS) for each mutational subgroup was 13.2 (T-DXd) and 7.1 (TPC) months (PI3K pathway), 11.3 (T-DXd) and 7.0 (TPC) months (*ESR1*m), and 21.4 (T-DXd) and 5.6 (TPC) months (*BRCA1/2*m). T-DXd improved PFS and cORR outcomes compared with TPC across all mutational subgroups reported (Table). **Conclusions:** In this exploratory ctDNA analysis, T-DXd demonstrated a greater clinical benefit vs TPC regardless of PI3K pathway, *ESR1*, or *BRCA1/2* mutation. Clinical trial information: NCT04494425. Research Sponsor: AstraZeneca; Daiichi Sankyo.

BEP (N=625) subgroup (n=T-DXd/TPC)	T-DXd cORR, %	TPC cORR, %	T-DXd mPFS, mo*	TPC mPFS, mo*	PFS hazard ratio
PI3K pathway†	57.6	41.5	13.2	7.1	0.65
(139/142)	[48.9, 65.9]	[33.3, 50.1]	[9.9, 15.5]	[6.0, 9.5]	[0.48, 0.87]
***ESR1*m**	60.2	32.1	11.3	7.0	0.64
(166/156)	[52.4, 67.7]	[24.8, 40.0]	[9.8, 13.5]	[5.6, 9.3]	[0.49, 0.83]
***BRCA1/2*m**	80.0	39.3	21.4	5.6	0.14
(20/28)	[56.3, 94.3]	[21.5, 59.4]	[15.2, NE]	[4.1, 6.9]	[0.05, 0.33]

Square brackets = 95% CIs (based on the Clopper-Pearson [cORR] or Brookmeyer-Crowley method [PFS]). PFS hazard ratios and CIs based on Cox proportional hazards model with no stratification factors, and ties handled by Efron approach. A hazard ratio <1 favors T-DXd vs TPC. No formal testing of significance was performed; *Number of PFS events: 89 (T-DXd) and 92 (TPC) in the PI3K pathway group, 115 (T-DXd) and 107 (TPC) in the *ESR1*m group, and 7 (T-DXd) and 23 (TPC) in the *BRCA1/2*m group; †includes *AKT*m, *PIK3CA*m, and *PTEN*m; CI, confidence interval; m, mutation; mo, months; NE, non-evaluable.

Use of artificial intelligence–assistance software for HER2-low and HER2-ultralow IHC interpretation training to improve diagnostic accuracy of pathologists and expand patients' eligibility for HER2-targeted treatment.

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Background: The advent of HER2-targeted antibody-drug conjugates and the introduction of HER2-low and HER2-ultralow diagnostic categories have made precise HER2 IHC assessment crucial for optimal breast cancer treatment. However, reproducible and accurate HER2 IHC scoring, particularly in cases with low level of HER2 expression, remains challenging. Many patients with HER2-low or HER2-ultralow expression risk being misclassified as HER2 null, potentially missing access to effective HER2 targeted therapies. Artificial intelligence (AI) assisted HER2 assessment may improve pathologists' diagnostic accuracy and concordance during interpretation training, especially in challenging cases with minimal membrane staining. **Methods:** A training platform for AI-supported digital HER2 IHC assessment of breast cancer samples was developed for pathologists. A total of 105 pathologists from 10 countries participated in masterclass sessions, assessing 20 digital HER2 IHC-stained breast cancer cases both without and with AI assistance. Cases assigned ground-truth IHC scores by a central reference center, were divided into three exams: A (n = 5), B (n = 7), and C (n = 8). The masterclasses consisted of: (1) Exam A, (2) a lecture on HER2 IHC scoring, (3) Exam B, (4) discussion of results from Exams A and B, and (5) AI-assisted Exam C. The AI software was used for decision support only for Exam C. The HER2 IHC scoring followed ASCO/CAP 2023 guidelines, adapted to include the HER2-ultralow (IHC 0 with membrane staining) and HER2 null (IHC 0 with no membrane staining), and provided individual tumor cell classifications for explainability. **Results:** Across 1,940 readings, pathologists achieved an average agreement of 76.3% with reference scores without AI (Exams A+B), compared to 89.6% with AI-assistance (Exam C). For HER2 clinical categories (null, ultralow, low, positive) accuracy improved from 66.7% without AI to 88.5% with AI. Misclassification of HER2-ultralow cases as HER2 null occurred in 29.5% of readings without AI but decreased to 4.0% with AI assistance. **Conclusions:** AI-assisted training improved pathologists' accuracy in HER2 IHC scoring by 13.3%, compared to central reference scores. Furthermore, AI reduced the misclassification of HER2-low and HER2-ultralow cases as HER2 null by 25.5%, potentially enabling more patients to access HER2-targeted therapies. These findings highlight the value of AI systems in biomarker interpretation training, providing pathologists with enhanced decision-making tools at the individual cell level and improving diagnostic precision in HER2 IHC interpretation. Research Sponsor: AstraZeneca.

Treatment rechallenge after trastuzumab-deruxtecan–related interstitial lung disease: A multi-institution cohort study.

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Background: T-DXd is an antibody-drug conjugate approved for advanced HER2+/low/ultra-low breast cancer and multiple other solid tumors. T-DXd carries a rare but serious risk of ILD (incidence 12-15%), requiring frequent imaging and symptom evaluation. For > grade (G) 2 ILD, guidelines recommend permanent drug discontinuation. For asymptomatic G1 ILD, drug is held with the option for rechallenge (RC) if imaging findings resolve. Limited data exist on outcomes of RC after ILD in diverse real-world patients (pts). **Methods:** In this multi-center retrospective study, we analyzed pts with T-DXd related ILD treated from 2017-2024. Pts with ILD were identified via chart/ICD code review. Adjudication of T-DXd related ILD was based on treating providers' assessment and graded via CTCAE v5. We collected pt demographics, T-DXd and steroid dosing, imaging results, and outcomes after RC. Statistical analysis was performed using Wilcoxon rank sum and Fisher's exact tests. **Results:** Four centers treated 712 pts with T-DXd, with a 9.1% rate of any grade ILD (n=65). One other center reported only RC data in 18 pts with ILD. In total, 47 pts were RC; 38 after G1 ILD (81%), 9 after G2. Median (med) time to initial ILD was 145 days (d) after 1st dose (interquartile range [IQR] 78-205). Demographics for pts RC are shown in the table. Among 50 pts with G1 ILD, including pts not RC, 28/50 (56%) received steroids for a med of 36d (IQR 27-79). Radiographic improvement was seen at a med of 24d (IQR 19-63) for pts treated with steroids vs 82d (IQR 48-94) without ($p<0.01$); and a med of 35d (IQR 22-82) for pts RC vs 81d (IQR 68-105) for pts not RC (p=0.01). Among pts with G1 ILD, 38/50 (76%) were RC at a med of 42d (IQR 36-57) from last dose; 23/38 (61%) were dose reduced. After RC, pts remained on T-DXd for a med of 215d (IQR 60-334); 10/38 (26%) developed recurrent ILD (7-G1, 2-G2, 1-G3) at a med of 211d (IQR 47-273) from RC. No statistically significant differences were seen between ILD onset, time to RC, or demographics for pts with recurrent ILD vs not. Of the 9 pts RC after G2 ILD, T-DXd was continued for a med of 129d (IQR 49-171); 2/9 (22%) developed recurrent ILD (1-G2, 1-G3). No G5 toxicity was seen with RC. **Conclusions:** In this multi-center study, high RC rates were seen after G1 ILD with long duration of clinical benefit. Pts treated with steroids had faster radiographic ILD improvement, highlighting the importance of early steroid use. Among pts RC after G1 ILD, recurrent ILD rates were low, with the majority G1 and no G5 events. Notably, 9 pts with G2 ILD were RC, with a similar rate of recurrent ILD; this must be interpreted cautiously. Our large cohort data further supports the safety of T-DXd RC in diverse real-world settings. Research Sponsor: None.

RC Pt Characteristics (n=47)	n (%) or Median (IQR)
Cancer type	
Breast	43 (91)
GI	3 (6)
Gyn	1 (2)
Age (yrs)	57 (52-68)
Prior # therapy lines in the advanced/metastatic setting	3 (1-5)
Renal impairment (CrCl < 60 mL/min)	8 (17)

Phase IB and II study of ribociclib with trastuzumab plus endocrine therapy in HR+/HER2+ advanced breast cancer patients: Korean Cancer Study Group BR 18-2 MINI trial.

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Background: In HER2+ advanced breast cancer (ABC), standard treatment has been anti-HER2 therapy with chemotherapy, regardless of hormone receptor status. While prior studies support the use of CDK4/6 inhibitors with anti-HER2 and endocrine therapy in pretreated HR+/HER2+ ABC, data on their first line use without chemotherapy are limited. This study investigates ribociclib, trastuzumab, and letrozole as a first-line combination in HR+/HER2+ ABC. **Methods:** This multicenter, single-arm, prospective trial was conducted across 17 academic institutions in South Korea (NCT03913234). Eligible patients were HR+/HER2+ ABC with no prior systemic therapy for metastatic disease. The Phase IB study used a 3+3 design to determine the recommended Phase II dose (RPIID) of ribociclib with fixed doses of letrozole (2.5 mg QD) and trastuzumab (8 mg/kg loading, then 6 mg/kg every 3 weeks). The Phase II trial evaluated efficacy and safety at the RPIID. The primary endpoint was progression-free survival (PFS), targeting an improvement from 8 to 12 months. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DOR), and safety. PAM50 testing assessed correlations between intrinsic subtype and treatment efficacy. **Results:** Phase IB (n = 13) identified the RPIID as ribociclib 600 mg QD, with one dose-limiting toxicity (Grade 3 ALT elevation) at 400 mg. In Phase II, 77 patients were enrolled, with a median age of 61 years (range 31–85), 18.2% (14/77) premenopausal, 66.2% (51/77) HER2 IHC 3+ and recurrent disease in 64.9% (50/77). 66.2% (51/77) had visceral metastases. At a median follow-up of 15.8 months (95% CI: 12.9-19.1) months, the median PFS was 30.4 months (95% CI: 19.6–NA), meeting the primary endpoint. The median OS was not reached. The ORR was 61.1%, including 3 complete and 41 partial responses, with a DOR of 11.8 months (95% CI: 7.6-13.4). Common adverse events included neutropenia (66.7%), pruritus (24.4%), and nausea (22.2%). There was a death reported due to aortic aneurysm. PAM50 analysis in 75 patients (phase IB/II) showed no significant correlation between intrinsic subtype and efficacy. **Conclusions:** Ribociclib, trastuzumab, and letrozole as first-line therapy in HR+/HER2+ ABC demonstrated a median PFS of 30.4 months with a manageable safety profile, supporting its potential as a chemotherapy-free option. Clinical trial information: NCT03913234. Research Sponsor: None.

HER2-ADC trastuzumab rezetecan (SHR-A1811) in HER2-positive breast cancer with brain metastases: Update results from REIN trial.

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Background: HER2-directed antibody-drug conjugates (ADCs) have been demonstrated to be of intracranial activity in patients with HER2+ breast cancer (BC) with brain metastases (BM). Our prospective, non-randomized phase 2 trial (NCT05769010) aimed to assess the feasibility of SHR-A1811, a novel HER2-target ADC, with or without other anti-tumor agents in HER2-expressing BCBM. Here we report the data of SHR-A1811 combined with bevacizumab in HER2+ BCBM, and update the results of SHR-A1811 in HER2+ BCBM (preliminary ORR data of the first 25 patients in Arm 1 has been published at 2024 ASCO), presenting the efficacy and safety of SHR-A1811 alone or in combination in the treatment of HER2+ BCBM. **Methods:** Patients with HER2-positive or -low BC with at least one radiotherapy-naïve measurable intracranial lesion were eligible for our trial. The patients with HER2+ disease enrolled in Arm 1 received SHR-A1811 6.4 mg/kg every 3 weeks, while those in Arm 3 were assigned to SHR-A1811 4.8 mg/kg and bevacizumab 15 mg/kg every 3 weeks until disease progression, unaccepted toxicity, or no further benefit. The primary endpoint was the intracranial overall response rate (ORR-IC) per RANO-BM. **Results:** Between March 30, 2023, and June 3, 2024, 58 patients were enrolled in Arm 1 (n = 33) and Arm 3 (n = 25). Among these, 56 patients (96.6%) had received anti-HER2 therapy previously, and the median number of prior systemic therapies in advanced setting was 2 (range: 0-9). 54 patients received at least one efficacy assessment and the confirmed ORR-IC in Arm 1 and Arm 3 were 84.4% (27/32) and 72.7% (16/22) respectively, which were numerically identical to the overall ORR in each arm, and all patients achieved intracranial disease control. As of December 31, 2024, the median PFS of Arm 1 was 13.2 (95% CI: 10.0-15.4) months, while the median PFS of Arm 3 was not mature. 78.8% (26/33) of patients in Arm 1 and 48.0% (12/25) in Arm 3 experienced treatment-related adverse events (TRAEs) of grade 3 or 4, and the frequencies of grade 4 TRAEs were 36.4% and 4% respectively. The grade 3/4 TRAEs that occurred in more than one patient included decreased neutrophil counts (Arm 1 / Arm 3: 69.7% / 36.0%), decreased leucocyte counts (51.5% / 16.0%), decreased platelet counts (30.3% / 0%), anemia (21.2% / 8.0%), decreased lymphocyte counts (21.2% / 0%), and nausea (6.1% / 0%). **Conclusions:** Our findings showed that SHR-A1811 6.4 mg/kg solely or SHR-A1811 4.8 mg/kg combined with bevacizumab both can attain high intracranial remission rates, while the lower-dose combination regimen might exhibit a better safety profile. The long-term outcomes will continue to be followed up. Clinical trial information: NCT05769010. Research Sponsor: None.

A phase II clinical study of adebrelimab and bevacizumab combined with cisplatin/carboplatin in triple-negative breast cancer patients with brain metastases.

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Background: Brain metastases (BMs) of triple-negative breast cancer (TNBC) is a lethal disease often associated with a limited life span of approximately 6 months and local therapy is usually the first treatment choice due to lack of effective anti-tumor agents. Here reported a triplet, anti-PD-L1 (Adebrelimab, SHR-1316), bevacizumab plus cisplatin/carboplatin in BMs of triple negative breast cancer. **Methods:** This is a single center, single-arm, phase II clinical trial involving triple-negative breast cancer patients with active brain metastases. A total of 35 participants were administered a triplet treatment consisting of Adebrelimab, bevacizumab and cisplatin/carboplatin. Prior use of bevacizumab or anti-PD-1/PD-L1 was not allowed. Prior use of platinum was allowed only in cases with platinum-sensitive disease. The primary endpoint was the objective response rate in the central nervous system (CNS-ORR), and the secondary endpoints included the clinical benefit rate in CNS (CNS-CBR), progression-free survival (PFS), overall survival (OS), the first progression site and safety. **Results:** The data cutoff for this analysis was on December 20, 2024. A total of 35 patients enrolled in this study from August 2020 to October 2024. Among all patients, 42.9% (15/35) had neurological symptoms at baseline, and 80% (28/35) had not received any local treatment for their brain metastases. The median number of previous lines of therapy for metastatic disease was 2 (range 0-4), with 40% (14/35) patients having received a prior platinum agent. In the intention-to-treat population,which comprised patients who received at least one cycle of study treatment, the CNS-ORR was 77.1% (27/35), with 5 complete responses (CR), 22 partial responses (PR) and the confirmed CNS-ORR was 71.4%(25/35). Among the 23 patients who progressed, the brain was the site of first progression in 69.6% (16/23) of patients. The median PFS was 7.6 months (95% CI, 5.7-11.5), while CNS-PFS was 10 months (95%CI, 7.4-12.6), and median OS was 16 months (95%CI, 11.7 to not reached). Treatment-related adverse events (TRAEs) were reported in 100% (35/35) of patients, with the incidence of grade≥3 TRAEs being 48.6% (17/35), including neutropenia (8.6%, 3/35) and platelet count decreased (8.6%, 3/35). Adebrelimab related serious adverse events (SAEs) occurred in one patient (facial nerve disorder), no treatment-related deaths were reported. **Conclusions:** The triplet treatment of anti-PD-L1 Adebrelimab, bevacizumab and cisplatin/carboplatin, was the first regimen demonstrating a high intracranial anti-tumor activity, a prolonged CNS-PFS and OS with a good safety profile. Warranting further investigation in this highly aggressive disease. Clinical trial information: NCT04303988.
Research Sponsor: None.

Sacituzumab tirumotecan (sac-TMT) as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): Initial results from the phase II OptiTROP-Breast05 study.

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Background: TROP2 (trophoblast cell surface antigen 2) is highly expressed in TNBC and associated with poor survival. Sac-TMT (MK-2870/SKB264) is a TROP2 ADC developed with a novel linker to conjugate the payload, a belotecan-derivative topoisomerase I inhibitor. It is approved in China for pts with a/mTNBC who have received at least two prior chemotherapies, including one for metastatic disease. The Phase II OptiTROP-Breast05 study (NCT05445908) evaluated sac-TMT as first-line treatment for pts with a/mTNBC. The study also explored the impact of PD-L1 combined positive score (CPS) status. Pts with CPS < 10 (PD-L1-negative, IHC 22C3 pharmDx) have limited treatment options, representing a critical unmet need. **Methods:** Pts with a/mTNBC who had not received prior treatment for advanced disease were enrolled, regardless of PD-L1 or TROP2 status, to receive sac-TMT at 5 mg/kg Q2W until disease progression or unacceptable toxicity. For pts with recurrent TNBC, a disease-free interval (DFI) of at least 6 months was required for eligibility. Tumor assessment was performed every 6 weeks per RECIST v1.1 as assessed by investigator. **Results:** As of 18 Nov 2024, a total of 41 pts (median age 55 yrs; 43.9% ECOG PS 1; 78.0% PD-L1 CPS < 10) were enrolled; 61.0% of pts had visceral metastases at baseline, 29.3% of pts had de novo metastasis, 19.5% of pts had a DFI of 6-12 months (mos), and 51.2% of pts had a DFI > 12 mos. The median follow-up was 18.6 mo. The objective response rate (ORR) was 70.7% (29/41, 3 unconfirmed PR) and the disease control rate (DCR) was 92.7%. Median duration of response (mDoR) was 12.2 mo, while the median progression-free survival (mPFS) was 13.4 mo, and the 12-mo PFS rate was 64.6% (95% CI: 45.0%, 78.7%). Among the 32 pts with PD-L1 CPS < 10, the ORR was 71.9% (23/32, 3 unconfirmed PR) and the DCR was 93.8%. The mPFS in this subgroup was 13.1 mo, with a 12-mo PFS rate 59.1% (95% CI: 37.1%, 75.7%). Treatment-related adverse events (TRAEs) of grade 3 or higher occurred in 63.4% of pts. The most common $\geq$ grade 3 TRAEs (occurred in $\geq$5% of pts) were neutrophil count decreased (46.3%), WBC count decreased (34.1%), anemia (12.2%), stomatitis (9.8%), lymphocyte count decreased (7.3%) and fatigue (7.3%). No treatment-related deaths occurred, and there were no reports of neuropathy or interstitial lung disease/pneumonitis. **Conclusions:** Sac-TMT demonstrated promising anti-tumor activity with a manageable safety profile as a first-line treatment for pts with a/mTNBC, independent of the PD-L1 status. A Phase 3 study comparing sac-TMT vs investigator's choice of chemotherapy in first-line PD-L1-negative (CPS < 10) a/mTNBC is currently underway (NCT06279364). Clinical trial information: NCT05445908. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2− metastatic breast cancer (mBC): Results from phase 1 study to support the recommended phase 3 dose (RP3D).

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Background: PF-07248144 is a selective catalytic inhibitor of KAT6, a histone lysine acetyltransferase. To inform the RP3D, we evaluated two pharmacokinetically distinguishable doses of PF-07248144 in combination with fulvestrant (FUL) from a phase 1 study in ER+/HER2− mBC in a dose expansion phase. **Methods:** Pts with ER+/HER2− mBC after prior CDK4/6i and endocrine therapy (ET) received PF-07248144 at recommended doses for expansion (RDEs) of 5 mg QD alone, 5 mg QD plus FUL, or 1 mg QD plus FUL (N = 107) and were followed up (at least 6 months across all cohorts) to assess for safety and efficacy. Primary objective wassafety/tolerability per CTCAE 5.0 and RDE selection. Other objectives included antitumor activity per RECIST 1.1, PK, PD, and predictive biomarkers. **Results:** 5 mg QD was identified as the RDE for both PF-07248144 monotherapy (35 pts treated) and FUL combination (43 pts treated) based on safety, PK, PD, and antitumor activity. 1 mg PF-07248144 plus FUL (29 pts treated) was selected as the lower RDE based on a distinguishable PK and safety profile while achieving maximal blood and tumor PD marker reduction and efficacious concentrations supported by preclinical models. As of Oct 11, 2024, a total of 107 pts were treated at RDEs. Baseline pt characteristics from the two RDEs plus FUL were comparable. All pts received prior CDK4/6i and ET in the metastatic setting. Positive dose-response relationships were identified for both safety (neutropenia) and efficacy (objective response rate [ORR]) endpoints. At 5 mg and 1 mg doses plus FUL, the most common treatment-related adverse event (TRAE) was dysgeusia (G1+G2: 83.7% vs 89.7%). The most common G≥3 TRAE was neutropenia (G3: 39.5% vs 20.7%; G4: 7.0% vs 0.0%). The neutropenia was reversible and manageable with dose modifications. No febrile neutropenia was observed. The safety profile of 5 mg PF-07248144 monotherapy was consistent with 5 mg RDE plus FUL. No events of pneumonitis were reported in the 107 pts treated. For FUL plus 5 mg and 1 mg PF-07248144, ORR was 37.2% (95% CI: 23.0–53.3) vs 24.1% (10.3–43.5); median duration of response was 15.8 mos (9.2–not estimable [NE]) vs 4.6 mos (3.4–NE); clinical benefit rate was 55.8% (39.9–70.9) vs 37.9% (20.7–57.7). With median duration of follow-up 21.9 mos and 11.0 mos for pts receiving FUL plus 5 mg and 1 mg PF-07248144, the median progression-free survival was 10.7 mos (95% CI: 5.3–13.8) vs 3.6 mos (1.8–5.6), respectively. **Conclusions:** Based on a thorough benefit–risk assessment of two pharmacokinetically distinguishable doses with sufficient number of pts and follow up, 5 mg QD PF-07248144 was identified as the optimal dose in combination with FUL with acceptable safety and encouraging activity. A pivotal phase 3 trial is planned to address the high unmet medical need in ER+/HER2− mBC after progression on CDK4/6i plus ET. Clinical trial information: NCT04606446. Research Sponsor: Pfizer Inc.

Phase II study of trastuzumab-pkrb plus gedatolisib in patients with HER2-positive metastatic breast cancer who progressed after 2 or more HER2-directed chemotherapies (KM-10A/KCSG BR18-13).

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Background: The prognosis of patients with HER2 positive metastatic breast cancer (MBC) has dramatically improved with the advent of HER2-targeted therapy. However, resistance to anti-HER2 therapies remains inevitable. Aberrations in the PI3K-AKT-mTOR pathway are recognized as a key mechanism of resistance to HER2 directed therapies. This study is a multicenter, prospective, single-arm, phase II study to evaluate the antitumor activity and safety of trastuzumab-pkrb plus gedatolisib in patients with HER2 positive MBC who progressed after 2 or more HER2 directed chemotherapy. **Methods:** The primary endpoint was the overall response rate (ORR), assumed to be 25% with a type I error rate of 0.05 and a power of 0.9. Although the target enrollment was 62 patients, the study was prematurely terminated after 44 patients due to the drug supply issue of gedatolisib. Patients with HER2-positive MBC and PI3K pathway genomic aberrations, identified via tumor-targeted sequencing or cfDNA analysis, were enrolled after disease progression on at least two HER2-directed therapies. The treatment regimen included trastuzumab-pkrb and gedatolisib. Safety and efficacy outcomes were evaluated, with a data cutoff of December 31, 2024. **Results:** Primary efficacy and safety data were evaluable in 44 patients. The median age was 59 years (range: 28-72), and the median number of prior palliative treatment lines was 4 (range: 2-10). Genomic aberrations included mutations kinase domain (26 patients), helical domain (11), amplification (1) of *PIK3CA*, deletion of *PTEN* (2), and other mutations (4). Among the 44 evaluable patients, the best overall responses were complete response (CR) in 2 patients (4.5%), partial response (PR) in 17 (38.6%), stable disease (SD) in 19 (43.2%), progressive disease (PD) in 5 (11.4%), and non-evaluable (NE) in 1 (2.3%), resulting in an objective response rate (ORR) of 43.2% and a disease control rate (DCR) of 86.4%. The median progression-free survival (mPFS) was 5.8 months. After a median follow-up of 32.5 months, 22 deaths were recorded, and 19 patients were alive. The median overall survival (mOS) after study enrollment was 18.4 months. Common treatment-related adverse events (TRAEs) included oral mucositis (32.3%; 4.1% ≥ grade 3) and skin reactions (14.1%; 1.8% ≥ grade 3). Hyperglycemia was reported in 6.8% (0.5% ≥ grade 3). No fatal adverse event related to trial medications were reported. **Conclusions:** In this phase II study, the combination of trastuzumab-pkrb and gedatolisib demonstrated a 43.2% response rate with manageable toxicity in patients with HER2 positive MBC and *PIK3CA* mutations. A translational research study focused on the analysis of cfDNA and PBMC is currently being planned. Clinical trial information: NCT03698383. Research Sponsor: Korea Health Industry Development Institute; HI17C2206.

Longitudinal tissue analysis and correlation of microenvironmental changes with combined immunotherapy and targeted therapy response in metastatic breast cancer.

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Background: The ability to interrogate changes within the tumor microenvironment before, during and following therapeutic intervention could yield important understanding of treatment response and causes for disease progression.Here we conducted a multicenter phase II clinical trial (NCT04521179) examining the effect of a novel CTLA-4/PD-L1 bispecific (KN046) antibody in combination with a a novel anti-HER2 bispecific (KN026) antibody in treatment resistant metastatic breast cancer. Our on-going trial demonstrated that in advanced HER2-positive breast cancer (HER2+ BC) patients, who have progressed after prior anti-HER2 combinational therapies, the objective response rate (ORR) of this chemo-free therapy of KN026 in combination of KN046 was about 47.2% (95% CI: 30.4-64.5). To explore the underlying mechanism of this regimen, we collected tumor specimens from patients before and after receiving this combinational treatment for emerging multi-modal molecular analyses (''Multi-omics'') to provide an in-depth description of the tumor immune microenvironment and its correlation with treatment response. **Methods:** We performed matched pre- and on-treatment investigative biopsies on index tumors and performed single-cell RNA sequencing (scRNA-seq) and single-cell T cell receptor sequencing (scTCR-seq) analysis. **Results:** We performed comprehensive scRNA-seq on tumor biopsies obtained from a total of 17 patients that evaluable for overall response. Among them, 13 patients had two biopsies taken, and four patients had one biopsy collected either before or during treatment. Single-cell RNA and T cell receptor sequencing from 334,183 cells from site-matched tumors reveal significant temporal shift of various immune cell populations and phenotypes within the tumor microenvironment associated with treatment responses. In-depth analysis of subpopulations revealed that $CD8^+$ T cells are activated in responsive patients during treatment, and T_{REG} cells, one of $CD4^+$ T cell subtypes, are activated in non-responsive patients after therapy. Moreover, we also found that combined-therapy activates cDCs and induces an inflammation shift in $M\phi$s of responsive patients. **Conclusions:** We identified that regulatory T cells are activated while effector T cells, natural killer cells, and dendritic cells were significantly depleted in non-responding tumors. The immune response in responsive patients was effectively enhanced, whereas in nonresponsive patients, it was significantly diminished. And higher baseline levels of $M\phi$s were associated with therapeutic resistance. These results support that longitudinal analysis of tumor microenvironment to generate multi-omics data that can lead to rich insight disease process and to provide clinical value in evaluating treatment responses. Clinical trial information: NCT04521179. Research Sponsor: Guangdong Science and Technology Department (2023B1212060013, 2022B1515020100, 2022A1515012238); the Natural Science Foundation of China (82273033, 82072924, 82072906).

Zongertinib in HER2-altered breast cancer: Preclinical activity and preliminary results from a phase Ia dose-escalation study.

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Background: Preclinical studies have demonstrated that zongertinib, an irreversible TKI, selectively and potently inhibits oncogenic HER2 in a variety of cancer models. An ongoing Phase (Ph) Ia/Ib dose escalation/expansion trial (NCT04886804) has demonstrated preliminary clinical activity of zongertinib across a range of HER2-driven solid tumors. Here we present comparative preclinical data for zongertinib in breast cancer (BC) cell lines and cell line-derived xenograft (CDX) models, as well as clinical data from patients (pts) with HER2-driven BC who received zongertinib during Phase Ia dose escalation. **Methods:** Cell proliferation assays were undertaken in *HER2*-amplified BC cell lines (relative copy numbers ranging from 3.2–10.1) exposed to serial dilutions of zongertinib and tucatinib. Antitumor activity of zongertinib (5–40 mg/kg QD) *in vivo* was assessed in three *HER2*-amplified BC CDX models. Ph Ia of the trial enrolled pts with confirmed HER2 alterations (mutations, amplification or overexpression) who had exhausted all other treatment (Tx) options. In Ph Ia, zongertinib was administered at 15–150 mg BID or 60–360 mg QD in 21-day cycles. Primary endpoints were maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs). Efficacy (objective response, OR) was evaluated as a secondary endpoint using RECIST v1.1. **Results:** Zongertinib inhibited tumor cell growth *in vitro* with greater potency (4.5–16.4-fold) than tucatinib (zongertinib IC_{50}: 2.6–40.6 nM; tucatinib IC_{50}: 13.2–664.0 nM). In mice, zongertinib was well tolerated and led to a dose-dependent inhibition of BC tumor growth, with tumor regressions at higher doses (≥ 20 mg/kg QD). As of August 29, 2024, 121 pts had been treated in the Ph Ia trial. Two DLTs occurred during the MTD evaluation period; the MTD was not reached. Treatment-related adverse events (TRAEs; all/grade ≥3) occurred in 82.6%/12.4% of pts; the confirmed OR rate was 31.4% across all doses and tumor types. In total, 15 pts with Stage IV BC (HER2 overexpression/amplification: n = 10; *HER2* mutations: n = 4; both: n = 1) received zongertinib (100 mg BID: n = 1; 240–360 mg QD: n = 14). Most were white (60.0%) and had an ECOG PS of 1 (66.7%). Mean (standard deviation, SD) age was 58.1 (7.4) years. Mean (SD) Tx duration was 4.0 (3.4) months. TRAEs (any/grade ≥3) occurred in 93.3%/0.0% of pts. In pts with BC, the confirmed OR rate was 26.7% (4 partial responses). The confirmed disease control rate was 73.3%. Regardless of confirmation, the OR rate was 46.5%. At the time of data cut-off, 2 pts with responses were still on treatment, and an additional 3 patients had a response lasting longer than 4 months. **Conclusions:** Zongertinib potently inhibits HER2-driven BC growth in preclinical models *in vitro* and *in vivo*. Preliminary Ph Ia data indicate that zongertinib has encouraging clinical activity and manageable safety in pts with advanced, HER2-driven BC. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

Transcriptomic analysis of HER2 expression in metastatic breast cancer: Insights from a UAE patient cohort.

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Background: HER2-low metastatic breast cancer (mBC) has emerged as a clinically significant subgroup since approval of trastuzumab deruxtecan. However, its relevance as a distinct subtype remains debated. We aimed to identify HER2-related gene signatures, examine the molecular characteristics of HER2-low mBC, and investigate the potential for classifying HER2-low mBC into subgroups with profiles resembling either HER2-positive (HER2+) or HER2-negative (HER2-) mBC. **Methods:** We performed differential gene expression (DGE) analysis using the TCGA-BRCA dataset, comparing HER2+ and HER2- samples to identify a 17-gene HER2 expression signature. The findings were validated on archival samples from a UAE clinical center, where DGE analysis was repeated to compare HER2+ and HER2-zero mBC. HER2-low samples were then classified into two subsets; positive-like and zero-like based on their HER2 signature gene expression level. Lastly, Gene Set Enrichment Analysis (GSEA) was conducted to evaluate the molecular characteristics of these subsets. **Results:** In the TCGA-BRCA dataset (n = 409; median age 59 years, range 26–90), 20.5% of samples were HER2+, and 79.5% were HER2-. DGE analysis identified a 17-gene HER2 signature that effectively separated HER2+ and HER2- mBC. These 17 genes including GSDMB, ERBB2, and MED1, are associated with HER2 expression. In the UAE cohort (n = 69; median age 52 years, range 24–84), comprising 7.25% HER2+, 60.87% HER2-low, and 31.88% HER2-zero mBC, 7 genes (GSDMB, GRB7, ERBB2, STARD3, PGAP3, MIEN1, TCAP) from the 17-gene HER2 signature were similarly upregulated in the HER2+ samples. We observed an increasing trend in HER2 signature expression across the groups, from HER2-zero to HER2-low and then HER2+ mBC showing the highest expression. This trend was supported by separation across HER2 status with gene-level expression, Gene Set Variation Analysis scores and Principal Component Analysis (PCA). Next, HER2-low mBC were classified into two distinct subgroups based on distance-to-centroid approach with PCA. Based on distance to HER2+ and HER2-zero centroids, HER2-low mBC were classified into positive-like and zero-like subgroups respectively. Separation of the positive-like and zero-like samples were observed with DGE analysis and expression of the HER2 signature genes. GSEA of HER2-low positive-like samples indicate increased activation of ERBB2 oncogenic pathway and suppression of gene sets involved in immune-mediated pathways compared to HER2-low zero-like mBC. **Conclusions:** This study reveals the potential utility of transcriptomic HER2 signature to characterize HER2-related molecular features in mBC, revealing a gradient of HER2 signature expression across HER2+, HER2-low, and HER2-zero. Identification of suppressed immune-mediated pathways in HER2-low positive-like mBC suggests combination with immune mediators as potential treatment strategy. Research Sponsor: None.

Phase I summary of the C406 (CART) efficacy and safety for an HER-2–positive breast cancer population.

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Background: C406 is a chimeric antigen receptor (CAR) modified autologous T cell, which is a CART targeting HER-2. Here we present the breast cancer results in Phase 1 study. **Methods:** This phase 1 trial to evaluate the safety and efficacy of chimeric antigen receptor (CAR) modified autologous T cells (C406) for pts with Her2-positive recurrent or refractory breast cancer. C406 is administered intravenously at a fixed dose. Response was evaluated by RECIST v.1.1 every 4 weeks. **Results:** As of Jan 18, 2025, 8 (F) breast cancer pts have received C406 at doses of $3*10^7$/kg (n = 6), $1*10^8$/kg (n = 2). Two patients in the $3*10^7$/kg -dose group received the second transfusion. Overall, the median age was 59 years, the median number of priortreatment lines was 3.125 and the median number of anti-HER-2 treatment lines was 2. The histological type was invasive breast cainoma, 7 cases of ductal carcinoma and 1 case of mucous carcinoma. These breast cancer hormone receptor types include ER+/PR+, ER-/PR-, and ER+/PR-. Cyclophosphamide combined with fludarabine was the regimen for lymphocyte clearance in all patients. Among them, 1 patient did not receive bridging therapy. Bridging treatment options for other patients were as follows, attillizumab bridging therapy (n = 1), albumin-bound paclitaxel combined with carboplatin and attillizumab (n = 1), albumin-bound paclitaxel combined with Attillizumab (n = 2), gemcitabine combined with attillizumab (n = 1), Albumin-bound paclitaxel + epirubicin + cyclophosphamide + Attilizumab + local radiotherapy (n = 1), docetaxel + Attilizumab + local radiotherapy (n = 1). Among the 8 pts having imaging tumor assessment, the DCR was 75%, which includes 0 partial responses (PR), 6 stable disease (SD), and 2 progressive disease (PD) according to RECIST v1.1. Among the 6 SD pts, 1 pt's progression-free survival (PFS) is 8 months. All the 8 pts experienced a treatment related adverse events (TRAEs). The most common TRAEs included white blood cell count decrease (100%, 8/8), neutrophil count decrease (100%, 8/8), lymphocyte count decrease (100%, 8/8) and cytokine release syndrome (25%, 2/8). No TRAE leading to discontinuation and death. **Conclusions:** C406 therapy showed an acceptable safety profile anti-tumor activity for advanced HER-2 positive breast cancer, but the antitumor activity needs to be further explored. Clinical trial information: ChiCTR2500096093. Research Sponsor: None.

Decoding HER2 dynamics: Exploring HER2 expression across a real-world breast cancer cohort.

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Background: HER2 expression in breast cancer (BC) has evolved from a binary scoring system to a continuum-based approach, driven by the therapeutic benefits of trastuzumab deruxtecan (T-DXd) in patients with HER2-Low tumors. Our understanding of HER2 expression is complicated by several factors, including tumor heterogeneity, altered expression as tumors progress, and variations in assay technique and scoring. Here we describe HER2 expression patterns in a large cohort of patients with BC, including a subset with longitudinal results. **Methods:** HER2 expression levels were determined by IHC using the VENTANA 4B5 antibody. HER2 copy number and HER2/CEP17 ratios were determined using a validated dual-probe ISH assay. Tumors were retrospectively identified as HER2-Zero (IHC 0), HER2-Low (IHC 1+ or 2+ with negative ISH) or HER2-positive (IHC3+ or IHC2+ with positive ISH) based on the established IHC and ISH values scored at the time of reporting (Apr 2013 to Nov 2024). Estrogen and progesterone receptor (HR) levels were determined using validated IHC assays. All testing was performed in a CAP/CLIA accredited referral laboratory. Tumor histology, specimen collection site (CS), and patient demographics were abstracted from test requisition forms. Results are descriptive and presented in aggregate. **Results:** A total of 30,023 BC specimens from 27,055 patients were included in the analysis. Most patients were female (99%; 26,687) with a median age at testing of 63.5 years. Among HER2-Low specimens, 87% were HR-positive (HR+) and 13% were HR-negative/HR-Low (ER IHC $<$ 10%). Longitudinal specimens were available for 1,267 patients with a median of 77 days between collection dates. 69% (869) of longitudinal specimens demonstrated the same level of HER2 expression, including in 69% (597/868) of cases where both specimens were collected from breast and 69% (203/294) of cases where the first specimen was collected from breast and the second was collected from another site. Among 398 patients who had HER2 expression levels changes, 46% went from HER2-Low to HER2-Zero and 33% went from HER2-Zero to HER2-Low. **Conclusions:** HER2-Low status is common in BC, especially among HR-positive cases.HER2 expression status changed between longitudinal specimens in 31% of patients, which may inform therapeutic eligibility. This reaffirms current guidelines recommending a biopsy at first distant recurrence and suggests that serial biopsies might be helpful in detecting HER2 expression in an originally HER2-Zero tumor. Research Sponsor: None.

Longitudinal HER2 expression levels changes.

HER2 Expression Level Change	Both CSs Breast	Breast to Other CS	Other CS combinations	Total
Positive to Low	27	3	3	33
Positive to Zero	5	2	1	8
Low to Positive	23	6	3	32
Low to Zero	116	51	17	184
Zero to Positive	6	3		9
Zero to Low	94	26	12	132
No Change (Positive)	71	32	7	110
No Change (Low)	365	104	41	510
No Change (Zero)	161	67	21	249

A phase Ib/IIa study of BAT8010+BAT1006, an anti-HER2 monoclonal antibody-exatecan conjugate combined with an ADCC-enhanced HER2 mAb in patients with advanced solid tumors.

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Background: BAT8010 is an ADC argeting HER2, while BAT1006 is a humanized monoclonal antibody targeting another epitope of HER2, with ADCC enhancement activity via completely devoid of fucose. This study investigates the combination of BAT8010 and BAT1006 in patients with advanced solid tumors. **Methods:** Patients in this open-label, multicenter clinical trial received BAT8010 +BAT1006 on day 1 of a 21-day cycle until intolerable or disease progression occurred. The study objectives included assessing tolerability, safety, pharmacokinetic characteristics, immunogenicity, and preliminary efficacy. **Results:** As of January 15, 2025, 20 patients with metastatic breast cancer (mBC, n=14) and gastric cancer (GC, n=6) were enrolled in three cohorts: BAT8010 (2.1mg/kg) + BAT1006, BAT8010 (2.4mg/kg) + BAT1006 and BAT8010 (2.7mg/kg) + BAT1006, with BAT1006 fixed at 15 mg/kg. HER2 positivity on tumor tissue was categorized as IHC2+/FISH+ or IHC3+. Two dose-limiting toxicity (grade 4 thrombocytopenia and neutropenia) were reported in the BAT8010 (2.7mg/kg) + BAT1006 group. The maximum tolerated dose was determined to be BAT8010 (2.4mg/kg) + BAT1006, and expansion studies have been proceeded at this dose. Safety: Among the 20 patients who received at least one dose of BAT8010 + BAT1006, 17/20 (85%) reported at least one treatment-emergent adverse events (TEAEs). The most common TEAEs (≥5%) included neutropenia, leukopenia, nausea, thrombocytopenia and anemia. Most TEAEs were Grade 1 or 2; however, 55% of the patients experienced Grade 3 or greater AEs, including neutropenia 7/20 (35%), thrombocytopenia 5/20 (20%), infusion-related reaction 1/20 (5%) and febrile neutropenia1/20 (5%). The infusion-related reaction was mild, and one subject discontinued the study treatment due to TEAEs. No cases of interstitial lung disease (ILD)/pneumonitis were reported. Efficacy: Fourteen mBC patients were recruited across the dose cohorts: BAT8010 (2.1 mg/kg)+BAT1006 (n=3), BAT8010 (2.4 mg/kg)+BAT1006 (n=7) and BAT8010 (2.7 mg/kg)+BAT1006 (n=4). Most had previously undergone 3-7 lines of systemic treatments, including trastuzumab and HER2 ADC regimens. Six GC patients were included in the BAT8010 2.4mg/kg + BAT1006 (n=4) and BAT8010 2.7mg/kg + BAT1006 (n=2) cohort. Sixteen patients had at least one tumor assessment, yielding an ORR of 43.7% (7/16) and a DCR of 87.5% (14/16). Among the 12 mBC patients, the ORR is 50% (6/12) with a DCR of 91.66% (11/12), including one CR. In the 4 GC patients, the ORR was 25% (1/4) with a DCR of 75% (3/4). **Conclusions:** The combination of BAT8010 and BAT1006 was well-tolerated, with manageable toxicity, and demonstrated promising preliminary antitumor activity in metastatic breast cancer and gastric cancer. Dose expansion studies are ongoing to further detect the safety and efficacy in these population. Clinical trial information: CTR20241120. Research Sponsor: None.

JSKN003, a biparatopic HER2-targeting ADC, in heavily pretreated HER2-positive breast cancer: A pooled analysis of early-phase studies.

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Background: JSKN003 is a biparatopic HER2-targeting antibody-drug conjugate (ADC) conjugated to a topoisomerase I inhibitor (TOP1i) via a tetrapeptide linker, designed to enhance serum stability and anti-tumor activity. The efficacy and safety of JSKN003 in advanced ovarian cancer and other solid tumors have been highlighted in previous reports, and this analysis provides updated insights into its performance in HER2-positive breast cancer. **Methods:** JSKN003-101 is a dose-escalation and -expansion study in Australia, and JSKN003-102 is a phase I/II study in China, both involving patients with advanced solid tumors. A pooled analysis was performed to assess its efficacy and safety in HER2-positive advanced breast cancer. **Results:** As of November 29, 2024, the median follow-up duration was 3.52 months (range: 2.99-3.71). A total of 71 patients with HER2-positive breast cancer were enrolled, with the majority receiving 6.3 mg/kg or 8.4 mg/kg doses. The median age was 54 years (range: 32-79), with 78.9% ECOG 1. All patients had stage IV disease, with 76.1% having visceral metastases. All patients had prior anti-HER2 therapy, including 87.3% with prior ADCs or TKIs, and 56.3% having ≥3 prior lines. Among 62 evaluable patients, 56 were T-DXd naïve. In these 56 patients, the overall response rate (ORR) was 67.9% (95%CI: 54-79.7), and the disease control rate (DCR) was 94.6% (95%CI: 85.1-98.9). In the RP2D subgroup (6.3mg/kg, n = 30), the ORR was 70.0% (95%CI:50.6-85.3). Of 6 patients with prior T-DXd exposure, 1 achieved a partial response (PR), 3 had stable disease (SD), and tumor shrinkage was observed in 3. Both median progression-free survival (PFS) and median overall survival (OS) were immature. Treatment-related adverse events (TRAEs) ≥Grade 3 occurred in 11.3% of patients, and serious adverse events (SAEs) in 9.9%, with 2 drug-related. No TRAEs led to death or treatment discontinuation. The most common TRAEs (≥20%) included nausea, elevated liver enzymes, vomiting, decreased appetite, fatigue, diarrhea, and anemia. No≥Grade 3 neutropenia was observed. Grade ≥3 anemia and decreased platelet count were each reported in 1 patient (1.4%), both being Grade 3. Interstitial lung disease (ILD) occurred in three patients (4.2%), all Grade 1-2, with no Grade ≥3 events. **Conclusions:** JSKN003 demonstrated promising efficacy and manageable safety in heavily pretreated HER2-positive breast cancer, including T-DXd-experienced patients. The biparatopic HER2 antibody design likely enhanced its binding efficiency and contributed to the observed clinical benefit. These findings support the planned Phase 3 trial to further evaluate its therapeutic potential. Clinical trial information: NCT05494918; NCT05744427. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

IBI354 (anti-HER2 antibody-drug conjugate [ADC]) in patients (pts) with HER2-positive breast cancer (BC) and other solid tumors: Updates from a phase 1 study.

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Background: HER2 has been established as an important therapeutic target for BC. IBI354 consists of trastuzumab (anti-HER2 antibody) conjugated to a camptothecin derivative. In a global, multicenter, phase 1 study, IBI354 was well tolerated and showed promising efficacy in BC and other solid tumors (2024 ESMO 345MO/720MO/576P). Here, we report updated safety and efficacy of IBI354. **Methods:** Eligible pts with advanced solid tumors who had failed or were intolerant to standard treatment were enrolled. Positive HER2 was defined as immunohistochemistry (IHC) 2+/in situ hybridization (ISH)+ or IHC 3+. IBI354 was administered intravenously at 6-15 mg/kg Q3W or Q2W. Primary endpoint was safety. Secondary endpoints were objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progress-free survival (PFS) assessed by investigators per RECIST v1.1 and overall survival (OS). **Results:** As of Nov 12, 2024, a total of 368 pts with solid tumors were enrolled in China and Australia (females: 89.4%, median age: 56.0 years [range: 27-82], ECOG PS 1: 75.0%). Median follow-up time was 11.3 months (range: 5-19). Median treatment duration was 25.0 weeks (range: 3.1-63.3) and 124 (33.7%) pts remain on treatment. Treatment-related adverse events (TRAEs) occurred in 331 (89.9%) pts while ≥grade 3 (G3) TRAEs occurred in 93 (25.3%) pts. Most common TRAEs included white blood cell count decreased (48.6%, with 7.1% ≥G3), anemia (46.7%, with 4.9% ≥G3), nausea (46.2%, with 0.8% ≥G3) and neutrophil count decreased (38.3%, with 9.8% ≥G3). Interstitial lung disease occurred in 8 (2.2%) pts (5 treatment-related and 3 treatment-unrelated, all G1-2). TRAEs led to dose reduction in 5 (1.4%) pts and treatment discontinuation in 4 (1.1%) pts. No TRAE led to death. Efficacy was evaluable in 88 pts with HER2-positive BC (stage IV: 97.7%; prior systemic therapy regimens≥5: 65.9%; IHC 2+/ISH+: 19.3%, IHC 3+: 80.7%). The overall confirmed ORR was 58.0% (95% CI: 47.0-68.4) and DCR was 90.9% (95% CI: 82.9-96.0). Among 51 pts with confirmed responses, median DoR was not reached (events rate: 19.6%) and 12-month DoR rate of 71.8% (95% CI: 52.9-84.2). Median PFS was not reached with events rate of 37.5%. Median OS was not reached with events rate of 5.7% and 9-month OS rate of 96.2% (95% CI: 88.7-98.8). **Conclusions:** IBI354 continues to demonstrate favorable safety profiles with no new safety signals. Encouraging efficacy was observed in HER2-positive BC. Clinical trial information: NCT05636215. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Efficacy of tucatinib, trastuzumab, and capecitabine (TTC) following trastuzumab-deruxtecan (T-DXd) in HER2-positive metastatic breast cancer (MBC): Updated results and subgroup analyses from the UNICANCER multicenter retrospective cohort.

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Background: T-DXd is the standard second-line treatment for HER2-positive MBC with TTC being the preferred third-line option. However, the efficacy of TTC following T-DXd remains unclear. Here, we provide an updated and subgroup analysis of a French cohort comprising 101 patients who received TTC after T-DXd. **Methods:** We conducted a retrospective study across 12 French comprehensive cancer centers, including patients with HER2-positive MBC treated with TTC after T-DXd exposure. The primary endpoint was progression-free survival (PFS), while secondary endpoints included overall survival (OS) and time to next treatment (TTNT). **Results:** A total of 101 patients who initiated TTC between August 2020 and December 2022 were included in the analysis. The median age was 56.4 years (range: 30.8–84.8). Patients had received a median of 4 prior MBC therapies (range: 2–15), which included pertuzumab (81%) and T-DM1 (93%). 82 patients (81%) experienced progression on T-DXd, while 19 discontinued due to toxicity or other reasons. The data cutoff date was December 1, 2024. For the whole population, with a median follow-up of 29.6 months (95% CI [26.0–34.0]), the median PFS was 4.7 months (95% CI [3.9–5.8]), the median TTNT was 5.2 months (95% CI [4.5–6.6]), and the median OS was 13.9 months (95% CI [12.4–19.0]). For the 86 patients who initiated TTC immediately after T-DXd, the median PFS and TTNT were 5.2 months (95% CI [4.4–6.4]) and 5.5 months (95% CI [4.7–7.2]), respectively. HR+ disease was identified in 71.3% (n=72) of the cohort, with 84.7% receiving TTC immediately post-T-DXd. With a median follow-up of 29.6 months (95% CI [25.1–NR]), the HR+ population had a median PFS of 4.1 months (95% CI [3.5–5.6]) and a median OS of 13.4 months (95% CI [12.3–19.0]). The median TTNT was 4.7 months (95% CI [4.0–6.3]). Among the 65 RECIST-evaluable HR+ patients, best response included progressive disease in 40%, stable disease in 29%, partial response in 29%, and complete response in 2%. With a median follow-up of 29.3 months (95% CI [26.0–NR]), the HR- population had a median PFS of 5.8 months (95% CI [4.4–10.5]) and a median OS of 17.5 months (95% CI [10.6–22.9]). The median TTNT was 6.0 months (95% CI [4.9–10.7]). Among the 24 RECIST-evaluable HR- patients, best response included progressive disease in 25%, stable disease in 38%, partial response in 33%, and complete response in 4%. **Conclusions:** This large retrospective cohort with extended follow-up highlights the efficacy of TTC in HER2-positive MBC patients previously treated with T-DXd. These findings support the role of TTC as a viable treatment option post-T-DXd and provide insights for optimizing therapeutic strategies in this setting. Research Sponsor: None.

Eribulin plus pyrotinib In trastuzumab-resistant HER2-positive advanced breast cancer: A single-arm, multicenter phase II trial (EPIC trial).

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Background: This study (ChiCTR2000038832) aimed to evaluate the efficacy and safety of combining eribulin with pyrotinib in patients with advanced HER2-positive breast cancer who had developed resistance to trastuzumab. These patients typically face a poor clinical prognosis, and evidence-based guidance for treatment decisions remains limited. **Methods:** Eligible patients were those with pathologically confirmed HER2-positive metastatic breast cancer, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and prior treatment with trastuzumab and taxanes. Participants received oral pyrotinib (400 mg once daily) and intravenous eribulin (1.4 mg/m^2 on days 1 and 8 of each 21-day cycle) for up to six cycles. Pyrotinib was continued until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). The secondary endpoints include the objective response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), and safety. **Results:** Between February 2021 and September 2023, 30 patients were enrolled, with a median age of 57 years (range: 30–76). All had received prior trastuzumab and taxane therapies. As of November 30, 2024, the median follow-up was 20.1 months. Disease progression or death occurred in 15 patients, and the median PFS was 13.73 months (95% confidence interval [CI]: 11.1–14.8). The 12-month PFS rate was 61.7% (95% CI: 44.2%–86.0%). The 12-month OS rate was 75.3% (95% CI: 66.2%–84.4%). The objective response rate (ORR) was 53.3% (16/30), and the disease control rate (DCR) was 80.0% (24/30). Median overall survival was not reached. Common adverse events (AEs) of any grade occurring in $>$ 15% of patients included diarrhea (40%), nausea (20%), anorexia (16%), and vomiting (16%), with grade 3 diarrhea reported in 3% of patients. No treatment-related deaths were observed. **Conclusions:** The combination of eribulin and pyrotinib shows promise as a therapeutic option for patients with HER2-positive advanced breast cancer resistant to trastuzumab. While advancements in anti-HER2 therapies continue, further studies are needed to address unresolved challenges in this clinical context. Clinical trial information: ChiCTR2000038832. Research Sponsor: None.

Quantitative pre-treatment assessment of trastuzumab deruxtecan (T-DXd) antibody target (HER2) and payload target (topoisomerase 1, Topo1) to predict outcomes in metastatic breast cancer (MBC).

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Background: The antitumor activity of T-DXd for MBC is sub-optimally predicted by HER2 immunohistochemistry (IHC). We evaluated novel assays to quantify the expression of T-DXd antibody and payload targets and their association with outcomes. **Methods:** We retrieved pre-treatment FFPE tumor samples for patients (pts) with MBC receiving T-DXd at Dana-Farber Cancer Institute between 2017 and 2023. Patients were categorized by HER2 IHC status at start of T-DXd. The RPPA-based protein assessment of HER2 and Topo1 was performed in a CLIA lab after laser capture microdissection enrichment of tumor epithelium. The HER2DX standardized assay was performed after RNA extraction. We evaluated the association of each marker, continuously and by tertiles/quartiles, with time to next treatment (TTNT) with T-DXd. Cox proportional hazards models were utilized to estimate hazard ratios and log-rank test p-values were reported. The Kaplan-Meier method was used to calculate median estimates. **Results:** HER2DX and RPPA testing were conducted for 41 (25 with HER2+, 16 with HER2- MBC) and 38 pts (24 with HER2+, 14 with HER2- MBC), respectively.Both HER2DX and RPPA HER2 quantitative testing significantly predicted outcomes with T-DXd (Table). The HER2DX HER2 amplicon mRNA signature was significantly associated with TTNT with T-DXd (p=0.001), including when divided into tertiles, with a range of 4.7 months in the lowest vs 12.03 months in the highest tertile (p=0.02). Similarly, the RPPA-based HER2 protein expression was significantly associated with TTNT when divided into quartiles (p=0.02). Pre-treatment Topo1 protein expression was significantly associated with outcomes in pts with HER2-negative MBC (n=14), with higher expression of TOPO1 associated with worse TTNT with T-DXd (p=0.04). **Conclusions:** Higher pre-treatment HER2 mRNA signature (HER2DX) and protein (RPPA) expression predicted improved outcomes with T-DXd for MBC, whereas higher Topo1 expression was associated with worse outcomes with T-DXd among pts with HER2- MBC. Research Sponsor: Terri Brodeur Breast Cancer Foundation; Saverin Award; Susan G. Komen Breast Cancer Foundation; Breast Cancer Research Foundation.

Association of pre-treatment HER2 amplicon mRNA signature, HER2 RPPA and Topo1 RPPA expression with outcomes among patients receiving T-DXd.

	Group	Median TTNT (months)	95% CI	HR	95% CI	p-value
HER2 amplicon mRNA expression n=41	1 unit increase	-	-	0.70	0.56-0.87	**0.001**
HER2 amplicon tertiles n=41	Low (ref)	4.70	3.27-NA	0.71	0.33-1.55	Log-Rank
	Med	5.33	4.7-NA	0.23	0.08-0.69	p=**0.019**
	High	12.03	7.37-NA			
HER2 RPPA protein expression n=38	10 unit increase	-	-	0.95	0.90-1.01	0.083
HER2 RPPA quartiles n=38	≤ 25% (ref)	4.03	2.87-NA	0.64	0.25-1.61	Log-Rank
	>25%-50%	5.83	2.13-NA	0.28	0.10-0.74	p=**0.019**
	>50%-75%	8.00	5.33-NA	0.30	0.12-0.75	
	>75%	9.07	5.83-NA			
Topo1 RPPA expression (HER2- only) n=14	< median (ref)	5.87	4.90-NA	3.49	1.02-11.96	Log-Rank
	≥ median	2.70	2.47-NA			p=**0.036**

Efficacy and safety results of TQB2930, a HER2-targeted bispecific antibody combined with chemotherapy in patients with HER2-positive breast cancer (BC) previously treated with ≥2 line treatments: Results from a phase 1b/2 study.

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Background: TQB2930 is a HER2-targeted bispecific antibody designed to bind two distinct HER2 epitopes: the extracellular domain 4 (ECD4), and the extracellular domain 2 (ECD2). In an ongoing phase 1b/2 clinical trial, TQB2930 has demonstrated favorable tolerability alongside durable responses in patients with heavily pretreated metastatic HER2-positive BC. In this context, Cohort 4 of the trial was designed to evaluate the safety and efficacy of TQB2930 in combination with chemotherapy for patients with HER2-positive BC who had received at least two prior lines of treatment. **Methods:** Cohort 4 enrolled patients aged ≥18 years with recurrent or metastatic HER2-positive BC who had undergone at least two prior systemic therapies. Patients with stable brain metastases were permitted. All enrolled patients received TQB2930 intravenously at a dose of 30 mg/kg every three weeks (Q3W), administered in combination with one of four investigator-selected chemotherapies (capecitabine, eribulin, gemcitabine, or vinorelbine). The primary endpoint was the overall response rate (ORR), while secondary endpoints encompassed disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and immunogenicity. **Results:** As of December 15, 2024, 55 patients (pts) had been treated with TQB2930 combined with chemotherapy. The median follow-up duration was 4.14 months (95% CI: 3.55–4.31). Out of 52 patients evaluable for efficacy, the ORR was 48.1% (25/52), with 88.5% (46/52) experiencing a reduction in target lesion size. Among patients who had progressed on prior T-DM1 therapy, the ORR was 36.8% (7/19), whereas patients who had failed other HER2-ADC therapies exhibited an ORR of 50% (8/16), including RC48, DS-8201, and so on. Notably, the median PFS and OS had not yet been reached, while the 6-month PFS rate was estimated at 71%. Grade ≥3 TRAEs were primarily hematological, encompassing decreased white blood cell count, neutropenia, thrombocytopenia, and infusion-related reactions. Importantly, there were no grade ≥3 cardiac toxicities, and the incidence of sinus bradycardia or QT interval prolongation was < 3%. **Conclusions:** The combination of TQB2930 with chemotherapy demonstrates encouraging antitumor efficacy and an acceptable safety profile in patients with HER2-positive BC who have undergone at least two prior lines of treatment. These results support the potential of TQB2930 as a novel therapeutic strategy for HER2-positive BC and underscore the need for further clinical exploration. This study was funded by Chia Tai Tianqing Pharmaceutical Group Nanjing Shunxin Pharmaceutical Co., Ltd. Clinical trial information: NCT06202261. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Nanjing Shunxin Pharmaceutical Co., Ltd.

Association of germline homologous recombination deficiency mutations with HER2 status conversion from negative to positive following neoadjuvant chemotherapy in breast cancer.

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Background: Neoadjuvant therapy (NT) is well established in breast cancer management, with subsequent adjuvant therapy guided by biomarker status and tumor response. While rare, biomarker status can change post-NT. The mechanisms driving conversion and optimal treatment strategies remain unclear. This study aimed to investigate clinicopathological characteristics, including germline mutations, in patients who underwent HER2 status conversion from negative to positive (N-P) after NT. **Methods:** Patients treated with NT for breast cancer between 2012 and 2023 were retrospectively identified from the Stanford STRIDE database. Clinicopathological features, including demographics, genetic data, treatment history, pathological characteristics, and recurrence, were collected through chart review. ER, PR, and HER2 status were assessed using immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH), with HER2 interpretation following ASCO/CAP guidelines relevant at the time of testing. Per institutional policy, both IHC and FISH were routinely performed for HER2 assessment. **Results:** A total of 28 patients with HER2 status change were identified; 26 (93%) were female and 2 (7%) male, with a median diagnosis age of 47 years (IQR 39–58). Most patients were ER-positive (N=24, 86%) at diagnosis. Among 25 patients who underwent germline testing, 56% harbored mutations in homologous recombination deficiency genes, including BRCA2 (5, 20%), BRIP1 (4, 16%), PALB2 (2, 8%), ATM (2, 8%), and BRCA1 (1, 4%). Post-NT, patients were classified into HER2 groups: 36% (10/28) in Group 1, 46% (13/28) in Group 1b (HER2 low amplified with HER2/cell <6 and ratio >2), 14% (4/28) in Group 3, and 4% (1/28) in Group 4. Adjuvant HER2-directed therapy was administered to 24 patients (89%): trastuzumab in 8 (29%), trastuzumab and pertuzumab in 12 (43%), and trastuzumab emtansine in 4 (14%); 4 patients (14%) did not receive adjuvant HER2 therapy. Recurrence occurred in 8 patients (29%), including 3 with germline mutations. One non-mutated case involved discordant HER2-positive recurrence with ipsilateral in-breast recurrence and liver metastases, testing HER2-positive by FISH despite IHC 0. **Conclusions:** This study highlights that a majority of patients who underwent HER2 status conversion after NT harbored homologous recombination deficiency mutations, suggesting a potential mechanistic basis. Furthermore, while 85.8% of patients received adjuvant HER2-directed therapy, the rarity of HER2-positive recurrences underscores the potential for overtreatment. Further studies are needed to elucidate the mechanisms of HER2 status conversion from negative to positive after NAT which will improve the efficacy of treatment strategies and patient outcomes. Research Sponsor: None.

Recurrence risk prediction model in HER2-positive early breast cancer after HER2-targeted therapy.

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Background: HER2-positive breast cancer patients treated with adjuvant targeted therapy, including trastuzumab or pertuzumab have demonstrated improved outcomes. However, a part of patients still experience recurrence despite targeted therapy. This study aims to develop a time-dependent model to predict recurrence risk in HER2-positive early breast cancer patients following targeted therapy, utilizing data from the APHINITY trial. **Methods:** The APHINITY trial included two arms: trastuzumab-only arm (n = 2,400) and trastuzumab + pertuzumab dual-target therapy arm (n = 2,404). Each group was randomly divided into training (70%) and validation (30%) cohorts, resulting in 3,363 patients in the training set and 1,441 patients in the validation set. The Cox proportional hazards model and two machine learning models, Random Survival Forest (RSF) and XGBoost (XGB), were used to predict invasive disease-free survival. Model performance was evaluated using Harrell`s C-index and area under the curve (AUC). **Results:** After selecting clinical variables provided by the APHINITY trial, 12 variables were included in the model training. The predictive performance of Cox model, RSF and XGB machine learning models was assessed. Among them, the RSF model demonstrated the best predictive effectiveness. In the training set, the RSF model achieved a C-index of 0.66, with AUCs of 0.78 for 1-year recurrence risk, 0.70 for 3-year recurrence risk, and 0.66 for 5-year recurrence risk. In the validation set, the RSF model achieved a C-index of 0.68, with AUCs of 0.79 for 1-year recurrence risk, 0.73 for 3-year recurrence risk, and 0.71 for 5-year recurrence risk. The XGB model performed slightly worse than RSF, and the machine learning methods significantly outperformed the Cox model. **Conclusions:** In this study, a time-dependent recurrence prediction model was established based on large-sample randomized controlled trial, demonstrating a favourable short-term recurrence prediction effect, which can serve as a clinical decision assistant for screening patients at high risk of recurrence for intensified adjuvant therapy or follow-up monitoring. Research Sponsor: None.

Racial and ethnic disparities in clinical outcomes of HER2-positive metastatic breast cancer treated with antibody-drug conjugates: A TriNetX real-world evidence study.

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Background: HER2-positive breast cancer (HER2+ BC) is an aggressive BC subtype driven by overexpression of the human epidermal growth factor receptor 2 (HER2). Antibody drug conjugates (ADCs), such as trastuzumab deruxtecan (T-DXd) and ado-trastuzumab emtansine (T-DM1), both approved for metastatic HER2+ BC, have significantly improved survival in this population. However, racial and ethnic disparities in outcomes with ADCs remain unclear. **Methods:** De-identified data from TriNetX, a global federated health research network, were analyzed for patients with metastatic HER2+ BC receiving HER2-directed ADCs. Kaplan-Meier analysis assessed overall survival. Statistical comparisons of survival rates between groups were made using log-rank tests. Propensity matching was used to adjust for age, comorbidities and lines of treatment. Two-sided P $\leq$0.05 was used to determine statistical significance. **Results:** A total 7,462 patients were included in this analysis. The median age was 56.2 years (range: 43-69), 68% were Non-Hispanic White (NHW), 17% Black, 5% Asian, and 10% Hispanic. 4,774 pts received TDM-1, 1,547 received T-DXd, and 1,141 received both. 37.6% patients treated with TDM-1 and 64.3% treated with T-DXd received >2 lines of prior therapy. Overall, the survival rate was 96% at 1 year, 89.3% at 3 years, and 83.7% at 5 years. At 3 years, the survival varied significantly by race: 90.3% in NHWs, 87.1% in Black, 92.9% in Asians, and 91.3% in Hispanics ($p < 0.001$). Similar differences extended to 5 years: NHW 85.0%, Black 80.9%, Asian 89.5%, Hispanic 86.7% ($p<0.001$) (Table). Among patients receiving T-DM1, the 3-year survival rate was 71.9%, compared to 45.7% in the T-DXd cohort ($p<0.05$). After adjusting for age and comorbidities, there was no difference in survival between patients who received T-DXd and TDM1 (not including who received both) (HR 2.55 (95% CI: 2.20–2.96; p = 0.75). **Conclusions:** Our study shows better outcomes with use of ADCs in heavily pretreated metastatic HER2-BC, with 83.7% of patients surviving beyond 5 years. However, significant racial disparities were observed, with Asian patients showing the highest survival while Black patients had the poorest survival which could be due to multi-level factors. Future studies are needed to understand the underlying mechanisms behind this racial disparity in outcomes with HER2-directed ADCs to inform strategies to improve patient outcomes. Research Sponsor: None.

Survival rates and hazard ratios by race.

Race	3-year survival probability (%)	5-year survival probability (%)	Hazard Ratio
NHW	89.60	83.96	1.00
Black	86.90	80.30	1.33 (95% CI: 1.26–1.40)
Asian	92.26	88.92	0.69 (95% CI: 0.6–0.75)
Hispanic	91.20	86.27	0.89 (95% CI: 0.83–0.95)

NHW (Non-Hispanic White).

Characterization of the immune microenvironment and spatial phenotypes across HER2 subtypes in advanced or metastatic breast cancer.

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Background: Breast cancer is defined by HER2 and hormone receptors (HR) status, which influence the clinical outcomes. HER2-positive has been traditionally defined as HER2 overexpression on immunohistochemistry (IHC score of 3+) or 2+ and *ERBB2* amplification on *in situ* hybridization (ISH). $HER2^{low}$ (IHC 1+ or 2+ and non-amplified ISH) accounts for nearly half of tumors. There is a paucity of data regarding immune subpopulations and spatial phenotypes in HER2 subtypes. We have investigated the characteristics of tumor immune microenvironment contexture across HER2 groups ($HER2^{+}$ vs $HER2^{low}$ vs $HER2^{-}$ (0 by IHC)) focusing tumor infiltrating lymphocytes (TIL) and on immune cell dynamics, including the distribution and spatial proximity to tumor cells to potentially inform treatment selection. **Methods:** Formalin-fixed paraffin-embedded (FFPE) samples of patients with metastatic breast cancer who had HER2 IHC/ISH testing according to ASCO-CAP guidelines were stained and analyzed using an 8-plex immunofluorescence (mIF) panel (CD3, CD8, CD69, FOXP3, Ki67, PD-L1, PD1, PanCK). For neighborhood analysis, samples with an area > 2 mm^2 and a phenotypes density with > 2 cells/mm^2 were considered. A novel spatial analysis method was used to quantify the Euclidian distance between tumor cells and surrounding immune cell populations. The clustering coefficient was used to determine the connectivity of immune cell node neighbors. These findings were analyzed in relation to the clinical characteristics. **Results:** Tumor and stromal compartment analysis was done on 44 FFPE samples (10 $HER2^{-}$, 19 $HER2^{low}$, and 15 $HER2^{+}$) with 84% collected from metastatic sites. HER2 status was not significantly associated HR status or overall TIL infiltration into the tumor compartment. The dominant TIL subset identified was non-regulatory CD3+ T cells as defined as $CD3^{+}/FOXP3^{-}/CD8^{-}$. $HER2^{-}$ samples were more associated with lack of PD-L1 expression on intratumoral myeloid cells and PD-L1 low expression on tumor cells as compared with $HER2^{low}$ and $HER2^{+}$ ($p = 0.06$). For spatial analysis, 33 samples (6 $HER2^{-}$, 16 $HER2^{low}$ and 11 $HER2^{+}$) were considered. Macrophages and proliferating tumor cells were more abundant in $HER2^{-}$ samples than $HER2^{low}$ or $HER2^{+}$ ($p = 0.006$ and p-0.027, respectively). Median distances from tumor cells to macrophages and T_{regs} were shorter in $HER2^{-}$ cases compared to $HER2l^{ow}$ ($p < 0.001$). Although the clustering coefficient were similar between HER2 groups, $HER2^{low}$ group clustered mostly around macrophages while $HER2^{+}$ group preferred cytotoxic T cells ($CD8^{+}$). **Conclusions:** The spatial organization and density of immune cells in the $HER2^{low}$ and $HER2^{+}$ breast cancer microenvironment may provide insight into prognosis and guide therapeutic approaches for combination therapies and HER2-targeted immunotherapies. Research Sponsor: None.

Risk of radiation necrosis with concurrent antibody-drug conjugates and radiotherapy in HER2-positive breast cancer with brain metastases: A meta-analysis.

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Background: Antibody-drug conjugates (ADCs) have transformed the outcomes of HER2-positive breast cancer (BC), particularly in patients with brain metastases (BM) due to the use of ADCs like trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), which have demonstrated intracranial efficacy. Radiotherapy (RT), especially stereotactic radiosurgery (SRS), remains a cornerstone for BM management. However, combining ADCs with RT may increase the risk of symptomatic radiation necrosis (SRN). This meta-analysis evaluates SRN outcomes in patients receiving concurrent (C-ADC) versus non-concurrent ADCs with RT (NC-ADC). **Methods:** A systematic search was performed in January 2025 across PubMed, Cochrane, and conference proceedings from ASCO, SNO, ESMO, and SABCS. Eligible studies included randomized controlled trials and cohort studies (CS) of C-ADC and NC-ADC in HER2-positive BC patients with BM. Studies reporting SRN rates or related outcomes were included. A random-effects model was used to calculate pooled proportions and risk ratios (RR) with 95% confidence intervals (CIs). Heterogeneity across studies was assessed using the I^2 statistic, with values of 0–25% considered low, 26–50% moderate, and greater than 50% high. **Results:** Out of 884 studies screened, 9 CS (N = 421) were included. The median age was 56.3 years (IQR: 49.8–57). Patients receiving prior intracranial RT was 41.28%, 19.28% underwent SRS, and 19.58% received prior whole brain radiotherapy (WBRT). The median time of C-ADC was 8.75 days (IQR: 8.0–18.0) and NC-ADC was 273.5 days (IQR: 225.75–327.75). The pooled proportion of SRN in the C-ADC group was 19.5% (95% CI: 9.2%–29.8%; I^2 = 39.19%, τ^2 = 0.0061, P = 0.1382) indicating moderate heterogeneity. NC-ADC group experienced a pooled SRN proportion of 6.9% (95% CI: 2.5%–11.2%; I^2 = 51.98%, τ^2 = 0.0014, P = 0.0089), signifying high heterogeneity. The pooled RR showed a significantly increased SRN risk in the C-ADC group (RR = 2.726, 95% CI: 1.454–5.109, P = 0.002). Heterogeneity for the pooled RR was negligible (I^2 = 0.0%, Q = 0.20, P = 0.977), indicating consistent findings across studies. **Conclusions:** C-ADC is associated with a significantly higher risk of SRN. This risk is concerning but must be balanced against potential improvements in local control and efficacy outcomes. Prospective studies are needed to optimize treatment schedule and sequences to minimize toxicity and optimize survival. Research Sponsor: None.

Meta-analytical findings.

Analysis/Measure	Effect Size	95% CI	I^2	P-Value	Notes
Pooled Proportion (Overall)	0.110	0.050–0.169	76.53%	0.0003	High heterogeneity (τ^2=0.0047)
C-ADC Proportion	0.195	0.092–0.298	39.19%	0.0002	Moderate heterogeneity (τ^2=0.0061)
NC-ADC Proportion	0.069	0.025–0.112	51.98%	0.0021	High heterogeneity (τ^2=0.0014)
Risk Ratio (C-ADC vs. NC-ADC)	2.726	1.454–5.109	0.0%	0.002	No heterogeneity (τ^2=0.0000)

Molecular and clinical insights of trastuzumab deruxtecan efficacy in advanced breast cancer (aBC).

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Background: In aBC, trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in HER2-positive, HER2-low, and HER2-ultralow disease subtypes. However, the impact of molecular markers on treatment outcomes requires further investigation, particularly in the context of HER2 status across biopsies, genetic alterations, and the tumor micro-environment (TME). **Methods:** We retrospectively analyzed 477 patients (pts) with aBC (DFCI = 369; Yale = 108) treated with T-DXd. HER2 immunohistochemistry (IHC) discordance was defined as a shift in HER2 status across the last two tumor samples prior to T-DXd (HER2 0 to 1, 2, or 3+ or vice versa). Concordance was defined as consistent HER2-0, HER2-low (1 or 2+) or HER2 3+ across samples. Outcomes included time-to-next treatment (TTNT) and overall survival (OS); multivariable Cox proportional hazards models were performed. Targeted tumor sequencing was conducted on 163 pts with aBC treated with T-DXd. TME analysis of 97 patients used machine learning on H&E slides to classify tumors as inflamed, desert, or altered. **Results:** Pts with discordant HER2 (n = 118, 25%) showed similar outcomes to those with concordant HER2-0 (n = 32) expression, both of which had significantly worse OS and TTNT compared to concordant HER2-low (both 1 or 2+) (n = 202) or HER2-3+ (n = 111) tumors (Table). *PTEN* mutations (mut; n=13) were associated with significantly shorter TTNT. *ERBB2* amplifications or gains (n= 31) correlated with improved outcomes. CDK12 deletions or loss (n = 14) were linked to poorer TTNT (Table). *PTEN* mut and *ERBB2* amplifications were predictive of outcomes with T-DXd, as neither alteration was associated with TTNT in pts receiving non-T-DXd first-line systemic therapy. Tumors with inflamed TME had the worst outcomes, followed by deserts and altered TMEs (Table). **Conclusions:** We identify favorable biomarkers of T-DXd efficacy in aBC, including concordant HER2-low or HER2-3+ status, absence of PTEN mut, and an altered or desert TME. These findings require validation to refine treatment strategies across HER2-driven malignancies. Research Sponsor: None.

	OS T-DXd: HR (95% CI)	p/q-value	TTNT T-DXd: HR (95% CI)	p/q-value	TTNT 1st Line: HR (95% CI)	p/q-value
Concordant HER2-0 (n = 32) vs discordant (n = 118)	1.07 (0.65-1.75)	0.789	1.17 (0.76-1.79)	0.474	-	-
Concordant HER2-low (n = 202) vs discordant	0.67 (0.49-0.92)	0.012	0.65 (0.50-0.85)	0.002	-	-
Concordant HER2-3+ (n = 111) vs discordant	0.23 (0.14-0.38)	< 0.001	0.27 (9.18-0.4)	< 0.001	-	-
PTEN mutations (n = 13) vs wild-type (WT) tumors (n =150)	-	-	2.20 (1.20-4.0)	0.068	0.99 (0.76-1.35)	0.93
ERBB2 amplifications/gains (n = 31) vs ERBB2 WT (n = 132)	0.43 (0.26-0.72)	0.045	-	-	1.1 (0.77 - 1.71)	0.51
CDK12 loss/deletions (n = 14) vs CDK12 WT (n = 116)	-	-	2.56 (1.39-4.76)	0.014	1.42 (1.04-1.86)	0.016
Altered (n = 28) vs Desert (n = 34)	0.58 (0.26-1.30)	0.18	0.97 (0.52-1.80	0.91	-	-
Inflamed (n = 35) vs Desert (n = 34)	2.21 (1.20-4.05)	0.011	2.13 (1.21-3.74)	0.0084	-	-

1041 Poster Session

Transcriptomic biomarkers of therapeutic response to antibody-drug conjugates in metastatic breast cancer: A comprehensive multi-center study.

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Background: The three antibody-drug conjugates (ADCs) — sacituzumab govitecan (SG), trastuzumab deruxtecan (T-DXd), and trastuzumab emtansine (T-DM1) — that are FDA-approved for treatment of metastatic breast cancer (MBC) have markedly improved patient outcomes. However, most patients with MBC treated with ADCs ultimately have disease progression via either primary or acquired ADC resistance. Here, we characterized the transcriptomic profile of drug efflux genes in MBC prior to ADC treatment (tx) to elucidate biomarkers of response and resistance to SG, T-Dxd, and T-DM1. **Methods:** We analyzed the transcriptomic tumor profile of six drug efflux pump genes (*ABCB1*, *ABCC1-4*, *ABCG2*) generated from pre-tx biopsies collected from patients with MBC (N = 453; 36% TNBC, 26% HR+/HER2-, 20.5% HER2+, 19% NOS) 1 year prior to or up to 15 days post-tx with SG (n = 204), T-DXd (n = 178), or T-DM1 (n = 71). RNA-sequencing data were generated and processed with the Tempus xR assay. The correlation between duration of treatment (DoT) and gene expression was tested for all genes of interest using Pearson's correlation coefficient. Cox proportional hazards models with risk set adjustment were used to test for associations between pre-tx gene expression and overall survival (OS), where gene expression was modeled as a continuous linear predictor. The proportional hazards assumption for OS was tested, and Cox modeling results were omitted when evidence of non-proportional hazards was detected. Given the exploratory nature of the analyses, all p-values are uncorrected and nominal statistical significance was set at $p < 0.05$. **Results:** This diverse cohort had a median age of 52 and a range of races (55% White, 14% Black, 7.1% Other, 24% Unknown). Median DoT across all patients was 130 days. Higher expression of drug efflux pump genes was associated with shorter DoT for T-DXd (*ABCB1*: -0.290, p = 0.017; *ABCC1*: -0.274, p = 0.025). Additionally, higher expression of *ABCB1* was associated with worse OS for T-DXd (HR: 1.30, 95% CI: 1.10 - 1.53, p = 0.002). In the SG cohort, no significant associations between efflux pump expression and DoT were found, but higher pre-tx *ABCC1* and *ABCC4* gene expression was associated with worse OS (HR: 1.34, 95% CI: 1.02-1.75, p = 0.034; HR:1.19, 95%CI: 1.00-1.41, p = 0.042). In the T-DM1 cohort, no significant associations were found between efflux pump gene expression and DoT or OS. **Conclusions:** Multi-modal analysis identified drug efflux pump gene expression as a potential biomarker of resistance, primarily to T-DXd. These findings should be further validated, and combinatorial clinical trial strategies may be explored. Research Sponsor: Tempus AI, Inc.

Integrating dynamic analysis of serial ctDNA testing to enhance diagnostic and prognostic assessments in patients with metastatic breast cancer.

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Background: The monitoring of circulating tumor DNA (ctDNA) in patient with metastatic breast cancer (MBC) plays a critical role in predicting therapy resistance, metastasis, and prognosis. Our previous studies have highlighted the importance of dynamic ctDNA analysis correlated with treatment resistance and prognosis in MBC (ASCO 2022 (#1057), AACR 2023 (#1031), and CCR Zhang Q., 2024). Here, we report that multivariable analysis of ctDNA mutations including P53, Myc, and BRAF, provides a significantly greater prognostic impact on survival. **Methods:** This study included 391 MBC patients who received systemic treatment between 2016 and 2022 (IRB-approved non-interventional trial, NU16B06) at the Robert H. Lurie Cancer Center, Northwestern University. Blood samples (15 ml each) were collected from patients at 3 time points: before treatment, and 3 and 6 months after treatment. Plasma ctDNA was analyzed by Guardant 360 using NGS for a 74-gene panel. The median follow-up was 26.6 months since enrollment. Causal Inference-Ensemble Learning was used for statistical analyses. **Results:** Among 391 patients (54.4% Luminal-like, 17.7% HER2-positive, 27.9% Triple-negative), the most common ctDNA mutations were $TP53^{Mut}$ (160 patients, 40.92%), $PIK3CA^{Mut}$ (39 patients, 29.4%), and Myc^{Mut} (53 patients, 13.55%) at any time point. Other notable mutations included $HER2^{Mut}$ (49 patients, 12.5%), $FGFR1^{Mut}$ (45 patients, 11.5%), $PTEN^{Mut}$ (39 patients, 9.9%), and $BRAF^{Mut}$ (35 patients, 8.95%). Less frequent mutations were $FGFR2^{Mut}$ (13 patients, 3.3%), $MAPK^{Mut}$ (8 patients, 2.0%), $BRCA1^{Mut}$ (20 patients, 5.1%), $BRCA2^{Mut}$ (17 patients, 4.3%), and $CDH1^{Mut}$ (21 patients, 5.37%). Patients in mutation groups showed significantly shorter median overall survival (OS) compared to wild-type groups: $TP53^{Mut}$ vs $TP53^{WT}$, Hazard Ratio (HR) = 1.91 (P = 0.0002); Myc^{Mut} vs Myc^{WT}, HR = 3.24 ($P < 0.0001$); and $BRAF^{Mut}$ vs $BRAF^{WT}$, HR = 2.45 (P = 0.007). No significant correlations were found between other gene mutations and OS. Analysis of multiple ctDNA mutations (TP53, Myc, and BRAF) revealed significant prognostic differences. Cohort 1 (no mutations, 231 patients) had a significantly longer median OS of 32.2 months compared to 20.5 months in cohort 2 (at least one mutation, 119 patients) and 15.3 months in cohort 3 (two or more mutations, 59 patients). Cohort 3 exhibited the worst prognosis compared to both cohort 1 and cohort 2 (Chi-square = 13.3, P = 0.0003). These findings suggest that combined analysis of ctDNA mutations enhances the ability to predict prognosis. **Conclusions:** In this study, we identified multiple ctDNA mutations during long-term follow-up, which are associated with prognosis. The synergy of multivariable analysis of ctDNA mutations during treatment enhances the role of single ctDNA alterations in monitoring metastatic prognosis, thereby supporting clinical decision-making. Research Sponsor: Robert H Lurie Cancer Center, Northwestern University.

TP53 genomic alterations including targetable *TP53* Y220C mutation in clinically advanced breast cancer.

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Background: Recent studies demonstrating the ability of drugs such as Rezatapopt to target the *TP53* Y220C mutation motivated us to assess the *TP53* mutation landscape in clinically advanced breast cancer (CABC). **Methods:** FFPE blocks of 23,760 CABC were analyzed by hybrid capture-based comprehensive genomic profiling that evaluated broad types of genomic alterations (GA) including mutations, amplifications, deletions, and fusions. MSI-high (MSI-H) status, tumor mutational burden (TMB), genomic ancestry, mutational signature, and homologous recombination deficiency signature (HRDsig) were determined from sequencing data. PD-L1 expression was determined by IHC (Dako 22C3, TPS scoring system). GA were compared using Fisher's exact test with the Benjamini-Hochberg multiplicity adjustment. **Results:** Among analyzed cases of CABC, 12,653 (53%) had *TP53* GA and 254 (1.1%) were the Y220C mutation. When compared with *TP53* wild type (wt) cases, *TP53* GA group were younger (56 vs 60 years; $p < .0001$) and had a higher median GA (6 vs 5; $p < .0001$). Both *TP53* Y220C group (15.7% vs 11.2%; not significant [NS]) and *TP53* non-Y220C group (18.3% vs 11.2%; $p < .0001$) were more frequently of African genetic ancestry than *TP53*wt group. The *TP53* non-Y220C had significantly less European (*TP53* non-Y220C: 65.2% vs 74.7%; $p < .0001$) genetic ancestries. MSI-H was rare in all groups, but slightly higher in *TP53* Y220C than *TP53*wt cases (1.7% vs 0.3%; $p = .036$). Median TMB was low for all groups (range 2.41-2.61; NS). An APOBEC genomic signature was more common in *TP53* non-Y220C mutant than *TP53*wt (6.2% vs 5.0%; $p = .0002$) but not in *TP53* Y220C (4.3% vs 5.0%; NS). GA more frequent in *TP53* Y220C and non-Y220C groups versus *TP53*wt included *BRCA1*, *ERBB2*, *PTEN,* and *RB1*. GA more frequent in the *TP53*wt group included *BRCA2*, *CCND1*, *CDH1*, *ESR1,* and *PIK3CA*. More *TP53* Y220C than *TP53* non-Y220C mutant cancers had *CDH1* mutations (6.3% vs 2.8%; NS) suggesting the Y220C GA may be more frequent in lobular carcinomas. **Conclusions:** *TP53* Y220C is a relatively rare event in CABC. The *TP53* mutant group was associated with GA in tumor suppressor genes, including *BRCA1*, *PTEN*, and *RB1*, whereas the *TP53*wt group was associated with GA in pathways associated with endocrine resistance, including *PIK3CA* and *ESR1.* Research Sponsor: None.

	*TP53*wt (N=11107)	Y220Cmut (N=254)	P-value†	*TP53* wt (N=11107)	*TP53* non-Y220Cmut (N=12399)	P-value†	*TP53* Y220Cmut (N=254)	*TP53* non-Y220Cmut (N=12399)	P-value†
BRCA1	1.4%	7.5%	<.0001	1.4%	6.0%	<.0001	7.5%	6.0%	NS
BRCA2	5.2%	4.7%	NS	5.2%	3.6%	<.0001	4.7%	3.6%	NS
CCND1	24.3%	7.5%	<.0001	24.3%	11.3%	<.0001	7.5%	11.3%	NS
CDH1	23.8%	2.8%	<.0001	23.8%	6.3%	<.0001	2.8%	6.3%	NS
ERBB2	10.1%	16.5%	0.003	10.1%	13.5%	<.0001	16.5%	13.5%	NS
ESR1	11.5%	3.1%	<.0001	11.5%	4.2%	<.0001	3.1%	4.2%	NS
PIK3CA	44.3%	23.6%	<.0001	44.3%	28.2%	<.0001	23.6%	28.2%	NS
PTEN	9.4%	18.9%	<.0001	9.4%	15.4%	<.0001	18.9%	15.4%	NS
RB1	2.6%	10.6%	<.0001	2.6%	11.8%	<.0001	10.6%	11.8%	NS

†Benjamini/Hochberg adjustment.

Comprehensive results of ESG401, a TROP2-targeting ADC: Updated phase 1 analysis in advanced solid tumors.

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Background: ESG401 is a novel ADC comprising a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to the Topoisomerase I inhibitor SN-38 via a stable cleavable linker. ESG401-101 is a phase 1, open-label, dose-escalation (1a) and dose-expansion(1b) study evaluating the safety and antitumor activity of ESG401 in advanced solid tumors. This report summarizes the comprehensive phase 1 results. **Methods:** Patients (pts) aged 18–75 years with locally advanced/metastatic solid tumors received ESG401 until unacceptable toxicity, progressive disease, or consent withdrawal. Phase 1a results (n = 40) have been reported previously. Phase Ib comprised three parallel cohorts: late-stage TNBC, late-stage HR+/HER2-, and first-line TNBC. **Results:** As of Oct 23, 2024, 156 pts were enrolled at 13 sites across China (40 in 1a; 116 in 1b). Most pts had metastatic HR+/HER2-BC (n = 65; median prior lines: 3; range: 1–10), followed by late-line TNBC (n = 47; median prior lines: 3; range: 1–12), first-line TNBC (n = 40), HER2+BC (n = 2), and one case each of endometrial cancer (EC) and adenoid cystic carcinoma (ACC). All pts had distant metastases at baseline; 13%, 57%, and 54% had brain, liver, and lung metastases, respectively. ESG401 demonstrated efficacy in pts with solid tumor(Table), including those with brain metastases. The safety profile remained consistent with no new or unexpected signals. The most common any-grade TEAEs were leukopenia, neutropenia, anemia, nausea, and vomiting. Grade ≥3 TRAEs were primarily neutropenia and leukopenia, none leading to permanent discontinuation. TRAEs led to delayed dosing, dose reduction, and discontinuation in 38.5%, 7.1%, and 2.6% of pts, respectively. **Conclusions:** ESG401 demonstrated favorable safety and efficacy benefits due to its enhanced linker, showing good safety and promising antitumor activity in advanced solid tumors across settings. These results warrant further clinical investigation. Clinical trial information: NCT04892342. Research Sponsor: Shanghai Escugen Biotechnology Co., Ltd.

	Late-line					First-line
	HR+/HER2−BC	TNBC	HER2+BC	EC	ACC	TNBC
n	58	37	2	1	1	35
ORR% (95% CI)	34.5 (22.5, 48.1)	35.1 (20.2, 52.5)	0	0	0	83.0 (66.4, 93.4)
DCR% (95% CI)	77.6 (64.7, 87.5)	62.2 (44.8, 77.5	100	100	100	100 (90.0, -)
mPFS Mons (95% CI)	7.4 (4.0, 9.2)	3.7 (2.1, 4.9)	3.8, 21.3[a]	8.3 [b]	3.7 [b]	NR
mDOR Mons (95% CI)	6.6 (4.6, 14.2)	4.5 (3.1, 13.6)	NA	NA	NA	NR

[a]The actual value for these two patients is listed.
[b]The actual value for one patient is listed.
NA, not applicable. NR, not reached.

Effect of ERBB2 activating mutations on enhanced internalization and activity of trastuzumab deruxtecan in HER2-non-amplified metastatic breast cancer.

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Background: Trastuzumab Deruxtecan (T-DXd) is a HER2-targeting antibody drug conjugate approved for the treatment of HER2 low metastatic breast cancer (MBC). Whether HER2 activating mutations define a distinct clinical subset within HER2 low MBC is unknown. Here we present a single institution retrospective study of patients treated with T-DXd and report real world progression free survival (PFS), in patients with mutant vs. wild type (wt) HER2. We further modeled the impact of various HER2 mutations on T-DXd internalization and activity preclinically to characterize mechanistic and mutation-specific differences. **Methods:** All patients who had received T-DXd for HER2-low and HER2-null MBC at Memorial Sloan Kettering Cancer Center were eligible for inclusion. Clinicopathologic data were abstracted from patient records. PFS was determined clinically and calculated using the Kaplan-Meier method. Univariable and multivariable associations between PFS and patient characteristics were assessed using Cox-proportional hazards models. *ERBB2* mutations were modeled in breast cell lines and examined for kinetics of fluorescence-labeled T-DXd cell internalization and potency of T-DXd antitumor effects. **Results:** We found 278 patients who received T-DXd for HER2 non-amplified MBC. Thirty-one had triple negative breast cancer and 247 had estrogen receptor positive MBC. Median age was 59 and TDXd was the median 6^{th} line of systemic treatment for MBC. Median PFS for all patients was 6.97 months (95%CI 5.73-8.4). *ERBB2* mutations were found in 23 (8.2%) patients on genomic sequencing via MSK-IMPACT. Among mutations, 20 were known oncogenic mutations per OncoKB (eg D769Y, L755S, S310F, V777L), while 3 were variants of unknown significance (L35R, P378L, R1169K). *ERBB2* activating mutations were significantly associated with prolonged T-DXd PFS; median 6.28 months in the wt population vs 10.58 months with an *ERBB2* mutation (HR 0.55, 95%CI 0.31-0.98, p = 0.04). After adjusting for age, treatment line, and ER status, *ERBB2* mutations were independently associated with longer PFS. Among patients with *ERBB2* activating mutations, 9 had HER2 IHC 0 disease, while the remaining 14 were at least HER2 IHC 1+. There was no statistically significant difference in PFS between patients with HER2 IHC 0 vs 1+ (HR 1.74, 95%CI 0.53-5.7, p = 0.35) among those with *ERBB2* mutations. Finally, expression of the most common *ERBB2* mutants in MCF10A cells lead to more rapid internalization of labeled TDX-d into cells and lower IC50 for inhibition of proliferation. **Conclusions:** *ERBB2* activating mutations are associated with longer T-DXd PFS in HER2-non-amplified MBC, even when HER2 IHC was 0, likely due to enhanced ADC internalization. The data imply that *ERBB2* mutant breast cancers may be uniquely sensitive to T-DXd, independent of HER2 expression levels. Research Sponsor: National Cancer Institute; CA009512-34A1; Brian Piccolo Cancer Research Fund; Sussman Family Fund.

Differences in genomic profiles, targeted treatment use, and overall survival in patients with metastatic breast cancer by Area Deprivation Index.

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Background: We previously showed racial differences in circulating tumor DNA (ctDNA) profiles and PI3K inhibitor (PI3Ki) use in patients (pts) with metastatic breast cancer (mBC); however, these findings may be influenced by socioeconomic disadvantage. A validated measure to explore this is the Neighborhood Atlas Area Deprivation Index (ADI, Kind et al NEJM 2018), which includes 17 measures of neighborhood disadvantage such as poverty, employment, and education. We sought to determine differences in genomic profiles, PI3Ki use, and overall survival (OS) in pts with mBC by ADI. **Methods:** This retrospective cohort study analyzed 1127 pts with mBC and ctDNA testing using the Guardant360 assay who were treated at Washington University in St. Louis (N = 634), Massachusetts General Hospital (N = 313), Weill Cornell (N = 109), and Northwestern University (N = 71). 9-digit zip codes were converted into national ADI ranks (0-100) divided into high deprivation (HDep, rank $\geq$60) and low deprivation (LDep, rank $<$ 60) groups based on prior studies. Multivariate models were designed to determine genomic and prognostic differences by ADI. Pts with *PIK3CA* mutations were evaluated by ADI and use of PI3Ki in the second line or beyond, either through clinical trial enrollment or after FDA approval. OS from time of first ctDNA test was stratified by ADI and self-reported race. **Results:** The cohort included 165 Black pts (14.6%) and 335 pts (29.7%) from HDep zip codes. Black pts were more likely to be from HDep areas (Odds ratio [OR] 3.82, 95% confidence interval [CI] 2.62-5.57, P $<$ 0.001). There were no differences in mBC subtype between ADI groups. Pts with HR+ HER2- mBC in the HDep group were significantly less likely to receive PI3Ki vs LDep (8/46, 17.4% vs 33/90, 36.7%, P = 0.02) despite equal incidence of *PIK3CA* mutations. Pts in the HDep group were more likely to have *TP53* single nucleotide variants (snv) (OR 1.58, 95% CI 1.18-2.10, P = 0.002) and less likely to have *AKT1* snv (OR 0.29, 95% CI 0.11-0.80, P = 0.017). Among pts in the HDep group, worse prognosis was seen in pts who self-identified as Black (hazard ratio [HR]1.51, 95% CI 1.02-2.25, P = 0.04), had *PIK3CA* snv (HR 1.73, 95% CI 1.23-2.44, P = 0.002), or *TP53* snv (HR 1.56, 95% CI 1.12-2.17, P = 0.009). Median OS was significantly shorter in the HDep vs LDep group (24 months [mos] vs 28 mos, P = 0.04) and significantly lower for Black pts in the HDep vs Black pts with LDep or White pts with HDep or LDep (15 mos vs 25-28 mos, P = 0.02). **Conclusions:** In this multi-institutional cohort, we identified significant disparities in the use of PI3Ki in HDep neighborhoods and higher rates of *TP53* snv, which are associated with aggressive tumor biology. Pts with mBC in HDep areas, especially Black pts, had shorter OS. Further research is needed to validate these findings, determine the root causes of these disparities, and implement change to achieve equity in precision medicine use. Research Sponsor: None.

Dissecting primary endocrine resistance through ctDNA profiling of a hybrid real-world and clinical trial dataset in hormone receptor-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC).

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Background: New targeted therapies, including novel endocrine agents and antibody drug conjugates, are revolutionizing the treatment of HR+/HER2- metastatic breast cancer (MBC). However, questions surrounding primary and secondary endocrine resistance (R1 and R2, respectively) still hinder the development of personalized treatment strategies. This study aimed to investigate R1 by leveraging liquid biopsy in a hybrid real-world and clinical trial dataset. **Methods:** This study used the nationwide (US-based) deidentified Flatiron Health-Foundation Medicine MBC clinicogenomic database (FH-FMI CGDB), comprising data originated from ~280 US cancer clinics (~800 sites of care), and analyzed a cohort of 855 patients (pts) profiled through the FoundationOne Liquid CDx NGS panel, combining it with the first 65 pts enrolled in the GIM-24-PalboBP study (NCT04318223). R1 was defined as 1-line PFS of < 6 months. A 1:3 Propensity Score Matching was applied to balance key factors (i.e. age, ECOG performance status, visceral, lymph node, multiple metastasis, type of CDK6/4i). Pathogenic alterations with a $> 10\%$ prevalence were tested singularly and according to oncogenic pathways based on Sanchez-Vega F et al, Cell. 2018. Associations between ctDNA alterations, R1, and R2 were assessed using logistic regression, while prognosis was evaluated through Cox regression. **Results:** A set of 528 pts (respectively 132 and 396 for R1 and R2) was selected from the original cohort of 855 pts. Top detected alterations were PIK3CA SNV (46%), TP53 SNV (33%) and ESR1 SNV (24%). R1 was associated with TP53 SNV (OR = 2.30, $P < 0.001$), CCND1, FGF19, FGF3 and FGF4 CNVs (respectively OR = 1.75, P = 0.018; OR = 1.62, P = 0.044; OR = 1.80, P = 0.015; OR = 1.73, P = 0.024). On the other hand, ESR1 SNV was associated with R2 (OR = 0.47, P = 0.005). CCND1, FGF19, FGF3 and FGF4 CNVs were significantly co-occurring ($P < 0.001$) and located in the chromosome (chr)11q13.3 region. In multivariable analysis, TP53 SNV, ESR1 SNV and chr11q13.3 CNV maintained their association with R1 (respectively OR = 2.22, $P < 0.001$; OR = 0.47, P = 0.006 and OR = 1.94, P = 0.006). Pathway analysis was consistent, showing a significant association between R1 and SNVs in the P53 and in the ER pathways (respectively OR = 1.92, P = 0.002; OR = 0.58, P = 0.024) and CNVs in the cell cycle pathway (OR = 2.18, P = 0.001). No differences were observed for 2-line (PFS2) across R1 and R2 (median PFS2 8.89 vs 8.03 months P = 0.589). Chemotherapy was prevalent in the R1 group (35% vs 15%). Within pts receiving 2-line endocrine therapy, TP53 SNV was the only prognostic factor in R1 (HR = 2.02, P = 0.008), while SNVs in TP53 and ESR1 had an impact on PFS2 in R2 (respectively HR = 1.50, P = 0.003 and HR = 1.45, P = 0.008). **Conclusions:** This study confirms TP53 and ESR1 as key factors for R1 and R2, respectively, with ESR1 showing a prognostic impact on PFS2 in R2 only. Additionally, chr11q13.3 emerges as a new candidate region for R1. These results provide critical data for both decision making and 2-line clinical trial design. Research Sponsor: None.

Genomic alterations (GAs) associated with durability of benefit from trastuzumab deruxtecan (T-DXd), trastuzumab emtansine (T-DM1) and sacituzumab govitecan (SG) in metastatic breast cancer (MBC).

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Background: Predictive biomarkers are needed to guide use of T-DXd, T-DM1 and SG in MBC. We used real-world comprehensive genomic profiling (CGP) of tumor tissue and circulating tumor DNA (ctDNA) to describe pre- and post-treatment somatic GAs in patients receiving these antibody-drug conjugates (ADCs) and evaluated the predictive value of *ERBB2* amplification (*ERBB2*amp) in MBC treated with T-DXd and T-DM1. **Methods:** MBC patients with FoundationOne CDx or FoundationOne Liquid CDx who received T-DXd, T-DM1 or SG monotherapy were included. Clinical data originated from 280 cancer clinics (~800 sites of care) between 1/2011-4/2024 included in the US-wide de-identified Flatiron Health-Foundation Medicine MBC clinicogenomic database. For each ADC and MBC subtype, we characterized the GA profile of pre-ADC samples. Pre- and post-treatment GAs were then compared by chi-square, adjusted for multiple comparisons. For patients who received T-DXd or T-DM1, time to next treatment (TTNT) was compared between patients with or without *ERBB2*amp by tissue CGP by Cox models, adjusted for age, ECOG status, HR status, and line of therapy. **Results:** We identified 1,177 pre-ADC samples (n = 972 tissue, n = 205 liquid biopsy; T-DXd n = 492, T-DM1 n = 167, SG n = 518). *TP53* (59.7%), *PIK3CA* (34.4%), and *ERBB2* (20.6%) were most commonly altered across all samples. Median TTNT for T-DXd in HER2+ MBC (n = 106) was 16.6 mo; *ERBB2* alterations were present in 84.6% of cases above the median vs 47.5% below. Median TTNT for cases with somatic *BRCA1/2* mutations (n = 6) was 8.48 mo vs 18 mo for *BRCA1/2* wildtype. Formal statistical analyses of baseline GAs and associations with TTNT on each ADC will be presented at the conference. GAs in *ATM* (24% vs 3.7%, $p < 0.0001$), *GNAS* (6% vs 2%, $p < 0.0001$), *EGFR* (4% vs 0.2%, $p < 0.01$) and *ERCC4* (2% vs 0, $p = 0.02$) were more prevalent in samples post-T-DXd (n = 50, 15 tissue/35 liquid) vs pre-T-DXd (n = 492, 378 tissue/114 liquid). GAs in *ERCC4* (3.3% vs. 0, $p = 0.001$) were more prevalent in samples post-SG (n = 60, 31 tissue/29 liquid) vs pre-SG (n = 518, 439 tissue/79 liquid). HER2+ MBC with *ERBB2*amp by CGP (n = 54) had more favorable TTNT on T-DXd vs non-amplified HER2+ (n = 30; 22.5 vs 6.4 mo, HR 0.10, 95% CI 0.04-0.24, $p < 0.0001$). HER2-low MBC with *ERBB2*amp by CGP (n = 6) had more favorable TTNT on T-DXd vs non-amplified HER2-low (n = 263; NR vs 7.4 mo, HR 0.22, 95% CI 0.05-0.90, $p = 0.035$). HER2+ MBC with *ERBB2*amp by CGP (n = 102) had more favorable TTNT on T-DM1 vs non-amplified HER2+ (n = 45; 8.3 vs 2.6 mo, HR 0.50, 95% CI 0.33-0.75, $p < 0.001$). **Conclusions:** This real-world analysis provides insight into baseline GAs and associations with TTNT on T-DXd, T-DM1 and SG in MBC as well as GAs that emerge on treatment. *ERBB2*amp by CGP carried additional predictive value to IHC/FISH HER2 status in both HER2+ and HER2-low MBC treated with T-DXd and HER2+ MBC treated with T-DM1. Research Sponsor: None.

Macroscale genomic alterations in histomolecular invasive lobular carcinoma compared to other breast cancer subtypes.

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Background: Although invasive lobular carcinoma (ILC) is often classified as a separate breast cancer (BC) subtype with distinct molecular features, options for diagnosis and treatment remain similar to other BCs. Using an integrated histomolecular approach to classify 617 BC samples into either histomolecular ILC (hmILC) or histomolecular no special type (hmNST) subsets, we compared their macroscale genomic alterations to describe biological traits of the ILC BC subtype, which may lead to improved approaches in BC therapies. **Methods:** A total of 617 BC FFPE samples were subject to whole-exome and bulk RNA sequencing analysis. hmILC subset was defined based on CDH1 truncation/deletion or low CDH1 expression (z-score $<$ $-2.5\times$MAD), while all other samples were classified as hmNST. Copy number variations (CNVs) were assessed using Sequenza to detect recurrent amplifications/gains and deletions; homologous recombination deficiency (HRD) scores were calculated based on large-scale state transitions and loss-of-heterozygosity events; tumor mutational burden (TMB) scores were evaluated as percent of mutations per megabase; and mutational signatures were deconvoluted using maftools R package. **Results:** Genome-wide CNV analysis revealed distinct patterns in hmILC compared to hmNST. hmILC showed hallmark deletions at regions harboring *CDH1* (16q), while gains were observed significantly more frequently at regions harboring *FCGR3A* (1q) compared to hmNST. Elevated APOBEC activation signature expression was found in 32% hmILC vs. 19% hmNST samples ($p = 0.002$, chi-squared test). HRD-positive cases were less frequent in the hmILC subset (25%) compared to hmNST (42%) ($p = 0.001$). In contrast, hmILC tumors more frequently demonstrated high TMB scores compared to hmNST (10% vs. 2%, $p = 0.0003$). Moreover, TMB-positive hmILC samples were mostly HRD-negative.Genetic alterations in genes like *FANCA*, *FANCD2* and *PALB2* were more frequently enriched in hmILC tumors compared to hmNST ($p < 0.1$). Furthermore, hmILC subset with high HRD scores frequently harbored additional DNA repair gene mutations (e.g., *BRCA2*) compared to the subset with low HRD scores ($p = 0.02$). **Conclusions:** This study revealed macroscale genomic alterations, such as unique CNV patterns, altered distributions of HRD- and TMB-positive cases and increased APOBEC-driven mutational processes, in the hmILC BC subset. These distinct genomic architectures highlight the need for innovative trials using inhibitors of DNA repair and related pathways for hmILC BC patients, particularly in those with high HRD-high tumors. Research Sponsor: None.

Landscape analysis of proteins in the development of breast cancer brain metastasis.

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Background: Breast cancer brain metastasis(BCBM) is a major cause of mortality in advanced breast cancer patients, and treatment options are limited. In this project, we investigated the proteomic landscape of primary breast cancer and brain metastasis. **Methods:** We conducted high-throughput proteomic analysis on primary and brain metastatic breast cancer tissues surgically resected from 21 patients. Following screening and sample processing using pressure cycle technology (PCT) for peptide extraction, we used the data-independent acquisition (DIA) mass spectrometry (MS) method to acquire the data. Additionally, we used biological function assays, co-culture experiments, and transcriptome sequencing analysis to further investigate the differentially expressed proteins. **Results:** Patients were mostly in clinical stage II, with two excluded from analysis due to no surgery. Breast cancer classifications included 47.6% HER2+/HR-, 28.6% HER2+/HR+, 9% HER2-/HR+, and 14.3% TNBC. All patients received chemotherapy, with 57% undergoing neoadjuvant therapy and 12 receiving targeted therapy (all with trastuzumab). A total of 9430 protein groups were identified, with 692 showing differential expression in BCBM. Notably upregulated proteins included CRYAB, GFAP, STXBP1 and significantly downregulated proteins included CACNA1A, AOC3, PMP2, OGN. Most differentially expressed proteins were involved in extracellular matrix (ECM) and cell-cell interactions, with collagen family proteins (e.g., COL14A1, COL22A1) playing key roles in BCBM. HER2+ BCBM was associated with ECM pathways, while TNBC impacted the immune microenvironment. Regardless of the subtype, we identified 11 proteins that collectively contribute to the development of BCBM, including CRYAB, ATP6V0A1, HLA-DQB1, TPM2, SERPINB9, NFATC2, GRAP, ALDH1L2, DHRS4L2, SEPTIN1 and SAMHD1. We found that high ACOX1 and low KRT9/KRT14 expression were linked to poor prognosis in BCBM. Analyzing whether patients had undergone targeted therapy, we found that resistance might be acquired through the oxidative phosphorylation pathway, promoting brain metastasis in HER2+ breast cancer. Interestingly, CRYAB expression was prominent across all subtypes of BCBM and targeted therapy groups, suggesting it may serve as an essential biomarker for BCBM. We have confirmed that CRYAB can promote the proliferation and migration of HER2+BCBM, and preliminarily verified that CRYAB is closely related to immune infiltration through CXCL5, CXCL8 and CCL3 in tumor microenvironment, which may promote the occurrence of HER2+BCBM by affecting the NF-κB pathway. **Conclusions:** Leveraging high-throughput proteomics, we present a detailed analysis that elucidates the biological processes involved in developing and progressing BCBM from multiple angles. This work offers new directions for early prediction, treatment, and prognosis of BCBM in clinical practice. Research Sponsor: National Natural Science Foundation of China; 81602716.

Evaluation of tumor immune microenvironment in Hispanic and African American breast cancer.

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Background: Hispanics or Latinos (HL) and African Americans or Black (AA) have a higher prevalence of advanced-stage breast cancer (BC) at diagnosis compared to Non-Hispanic Whites (NHW). To understand the role of immune system, we evaluated the tumor immune microenvironment (TIME) by race/ethnicity among HL, AA, and NHW BC patients. **Methods:** 15544BC samples were tested by NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). Race/ethnicity data is self-reported. Immune cell were estimated using WTS deconvolution (Quantiseq). Gene expression profiles were analyzed for T-cell inflammation score (TIS) and interferon-gamma (IFN-gamma) score. Real-world overall survival (OS) was obtained from insurance claims and calculated from date of tumor biopsy to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square and Mann-Whitney U test with *p*-values adjusted for multiple comparisons ($q < .05$). **Results:** 7170 NHW (35.3%, N = 2528) biopsied (bx) from primary breast cancer (pBC), 64.7% (N = 4642) metastatic bx (mBC), 1,508 AA (pBC 39.3% N = 592, mBC 60.7% N = 916), and 1,754 HL (pBC 44.1% N = 774, mBC 55.9% N = 980) cases were included. By subtype, there were 1,956 (60.4% NHW, 20.7% NHB, 18.9% HL) TNBC, 3425 HR+/HER2- (72.6% NHW, 11.9% NHB, 15.6% HL), and 694 HER2+ (64.6% NHW, 15.7% NHB, 19.7% HL). Across all cases, AA (20.5%) and HL (20.4%) had greater incidence (%) of PD-L1+ cases versus (vs) NHW (17.4%), all $q < .05$. TMB-High (³10 mut/Mb) was similar in NHW (11.5%), AA (10.8%), and HL (10.9%). AA tumors had lower median % cell infiltration of M2-like macrophages (M2 Mφ), B cells, and neutrophils vs NHW (Table). HL had a lower fraction of M2 Mφ and higher CD8+ T cells (Table). AA had lower TIS (-8 vs 1, p = .02) while HL had lower IFN-gamma (-0.38 vs. -0.35, $q < .05$) vs NHW. By subtype, AA had lower neutrophils (4% vs 4.3%) and increased DC fractions (3.1% vs 2.8%) in TNBC vs NHW, all $q < .05$; no significant changes seen in HL vs NHW. AA had worse mOS than NHW overall (31.8 vs 36.8 months (mo)), HR 1.1, 95% CI 1 – 1.2, p = < .01), in pBC (40.3 vs 49.9 mo, HR 1.3, 95% CI 1.1 – 1.5, p = < .01), but not mBC (27.4 vs 29.1 mo, HR 1, p = 0.2). HL had similar mOS vs NHW overall (37.4 vs 36.8 mo, HR 0.9, p = 0.9) and in mBC (29.1 vs 31 mo, HR 0.96, p = 0.4), but worse mOS in pBC (44.7 vs 50.0 mo, HR 1.1, 95% CI 1 – 1.3, p = .01). **Conclusions:** Our study shows worse mOS in AA and HL pBC cases vs NHW, possibly from a less inflamed TIME in AA and HL and lower fraction of neutrophils and M2 Mφ despite higher % of PD-L1+. Targeting Mφ and CD8+ T cells and converting cold to hot TIME may lessen race/ethnic disparities, especially in early-stage BC. Research Sponsor: None.

Immune cell fraction of NHW, AA and HL BC.

	NHW (median %)	AA (median %)	HL (median %)	q-value NHW vs AA	q-value NHW vs HL
B cell	5.2	4.8	5.0	<.05	0.7
DC	2.6	2.7	2.6	0.08	0.4
M1 Mφ	2.5	2.4	2.4	0.4	0.9
M2 Mφ	4.6	3.7	4.2	<.05	<.05
Neutrophils	3.7	3.5	3.4	<.05	<.05
NK cell	2.9	2.9	2.9	0.7	0.6
CD8+ T cell	0.1	0.15	0.26	0.8	<.05
Treg	1.5	1.5	1.6	0.6	<.05

Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) measured by Guardant Reveal in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with long-term disease control on first-line trastuzumab-pertuzumab.

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Background: The CLEOPATRA and PERUSE trials established the combination of a taxane with the antiHER2 monoclonal antibodies trastuzumab and pertuzumab (HP) as the gold standard first-line treatment for HER2+ mBC. In both studies, the progression events reached a plateau after 4 years and up to 30% of pts remained long-term progression-free, hypothesizing HP maintenance can be safely discontinued. We therefore evaluated whether epigenomic-based ctDNA MRD analysis can potentially identify pts with a higher chance of permanent remission. PRE-PHENIX is a multi-center observational study that explores the prevalence of MRD measured by Guardant Reveal in HER2+ mBC pts on long-term first-line HP maintenance. **Methods:** A total of 40 pts with HER2+ mBC on first-line treatment with HP maintenance for a minimum of 4 years were included. Confirmation of no progressive disease by CT or PET-scan in the last 3 months previous to study entry was mandatory. Plasma samples were analysed using Guardant Reveal powered by the Guardant Infinity platform, a tissue-free epigenomic assay interrogating differentially methylated regions of DNA optimized to detect breast cancer DNA from normal cell-free DNA. Two ctDNA tests were performed on each patient within a 6 – 12-week interval. Additionally, 11 pts with confirmed disease progression on antiHER2 therapy for mBC were included as case controls. The primary objective was to establish the prevalence of positive MRD in both populations and the agreement between the two tests for the Long-Term responders. **Results:** Median age was 63.2 years (range 30.8 – 84.4). The median duration of first-line HP treatment was 6.9 years (range 4.2 - 11.1). At diagnosis, 26 pts (65%) presented with "de novo" mBC and 20 (50%) had visceral disease. The last radiological evaluation categorized 6 pts (15%) as having stable disease (SD), 2 pts (5%) with partial response (PR), and 32 pts (80%) with complete response (CR). Among the 11 pts with confirmed progression, 2 presented exclusive Central Nervous System (CNS) disease. Guardant Reveal identified MRD in 4 long-term responders (10%), 3 out of 6 pts (50%) with SD, 1 of 2 pts (50%) with PR, and no MRD among the 32 pts with CR. A perfect agreement was observed between the two tests (Kappa-index of 1). Ten out of the 11 pts (91%) with disease progression had MRD, including the two with exclusive CNS involvement. **Conclusions:** Our study demonstrates clinically significant performance of a tissue-free MRD test, Guardant Reveal, as a potential non-invasive monitoring tool to guide de-escalation strategies in pts HER2+ mBC pts with long-term remissions on HP treatment. A prospective study (PHENIX) to guide HP interruption by ctDNA monitoring is planned. This study was funded by a Fundación Contigo full grant (Spain) and Guardant Health. Research Sponsor: None.

Antibody drug conjugates treatment response score (ADC TRS) for sequencing trastuzuamb deruxtecan (T-DXd) and sacituzumab govitecan (SG) in advanced breast cancer (aBC).

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Background: T-DXd, targeting HER2, is approved in hormone receptor positive or negative (HR+/-) HER2-low (1-2+ by immunohistochemistry [IHC]) and HR+/HER2-ultralow (0+ with membrane staining) aBC. SG, targeting TROP2, is approved in HR+/HER2 negative [-; < 3+ by IHC] and triple negative BC (TNBC; HR-/HER2-). Given limitations in determining IHC 0-1+ status and lack of predictive biomarkers, biomarkers for sequencing these ADCs in those with HER2- aBC are needed. Recently, Thomas et al. reported the discovery of ADC TRS—a generalized model combining individual ADC target expression, proliferation, and adhesion to predict multi-ADC target/tumor type clinical benefit—as well as validation of SG and T-DXd TRS models (tuned by pan-tumor response rates) by a qRT-PCR based clinical trial assay (CTA; Strata Select ADC [SSA]) for predicting clinical benefit of first ADC (SG or T-DXd) in those with HER2- aBC (ASCO 2024 #3140; AACR 2025 #1014). Here, we evaluated ADC target expression and T-DXd/SG TRS status from SSA validation cohort HER2- BC patients stratified by clinical HR/HER2 IHC status. **Methods:** Adults with aBC from an observational trial (NCT03061305) with valid FFPE tumor tissue results from SSA validation cohort testing were included. aBC types were determined by HR/HER2 IHC results (by ASCO/CAP scoring), with those HER2 3+ or *HER2* amplified (by Strata Select testing) considered HER2+. ADC target component expression (*HER2* or *TROP2*; pan-tumor scaled absolute expression) and T-DXd and SG TRS statuses (+ associated with more clinical benefit) by SSA were compared by IHC defined aBC types. **Results:** 230 patients with aBC from SSA validation testing were included (median age 58 yrs, 40% self-reported non-European;180 with definitive aBC type [see Table for distribution]). *HER2* expression was significantly increased vs. *TROP2* in HER2+ and HR+/HER2 aBC, and did not significantly differ in those with TNBC (see Table). Across all patients, 42%, 30%, 27% and 0.4% were T-DXd/SG TRS +/+, -/-, +/- and -/+, respectively. Results were similar in those with HER2 IHC 0+ (n = 37, median *HER2* vs. *TROP2* = 2.2 vs. 2.3, p = 0.51; 8% and 3% T-DXd/SG TRS +/- and -/+, respectively. **Conclusions:** Pan-tumor optimized, validated ADC TRS models support sequencing T-DXd before SG in nearly all patients with advanced HER2- BC, including those with TNBC and HER2 0+ IHC. Prospective evaluation of the CTA is warranted. Research Sponsor: Strata Oncology.

ADC target expression (*HER2* or *TROP2*) and T-DXd | SG TRS status by SSA in BC patients.

					T-DXd/SG TRS Status			
BCa Type	**(n)**	**HER2^**	**TROP2^**	**p-value^**	**+/+**	**-/-**	**+/-**	**-/-**
HER2+	43	6.4	2.6	<0.0001	42%	7%	51%	0%
IHC NA*	50	2.6	2.7	0.31	44%	40%	16%	0%
HR+/HER2-	76	3.0	2.3	<0.0001	54%	20%	26%	0%
TNBC	61	2.3	2.3	0.7	25%	52%	21%	2%
Total	230	2.9	2.4	<0.0001	42%	30%	27%	0.4%

^Median, pan-tumor scaled *HER2* and *TROP2* target expression; Wilcoxon test.
*IHC not available; *HER2* not amplified.

Estrogen receptor (ER) expression on circulating tumor cells (CTCs) and cell free DNA (cfDNA) mutational landscape in the PACE randomized phase II study.

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Background: The PACE (NCT03147287) randomized phase II trial investigates CDK4/6 inhibition beyond progression in combination with endocrine treatment, with or without PD-L1 inhibition, in hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC) (Mayer et al 2024). We previously reported that cfDNA alterations and CTC number correlated with survival and treatment response (Jeselsohn et al 2024; Gerratana et al ASCO 2023). Here we investigated ER expression on CTCs in relation to the cfDNA mutational landscape. **Methods:** Samples were collected at baseline. CTC enumeration and ER protein expression on CTCs (by immunofluorescence) was evaluated with the CellSearch and the ACCEPT software. Samples were classified as CTC^{high} or CTC^{low} (cutoff $\geq$5 CTC/sample). CTC^{high} samples were defined ER+ if >15% CTCs/sample expressed ER to ensure good inter-group stratification. Concurrently, cfDNA was analyzed with the Guardant360 assay. Only pathogenic single nucleotide (snv) and copy number variations (cnv) with $\geq$3% prevalence were included and categorized into oncogenic pathways (Sanchez-Vega et al 2018). Differences in distribution across CTC groups were tested through Chi-squared and Fisher's test. **Results:** From 220 enrolled patients, 167 were evaluable for ER on CTCs. Of these, 91 were CTC^{low}, 30 were CTC^{high}/ER-, and 46 CTC^{high}/ER+. *ESR1* mutations were more common in CTC^{high} /ER+ samples, while CTC^{high}/ER- samples had higher incidence of alterations in *SMAD4*, *PIK3CA*, *BRAF* and *CDK4* compared to the other 2 groups (Table 1). CTC^{high}/ER- had also higher mutant allele frequency compared to CTC^{high} /ER+ and CTC^{low} (MAF > 3% in 73% vs 54% and 31%, respectively, $p < 0.001$). CTC^{low} samples had overall lower cfDNA alteration incidence. Similarly, alterations in the ER pathway were more frequent in samples with CTC^{high} /ER+, whereas alterations in PI3K, cell cycle and P53 pathways were more common in CTC^{high}/ER- samples. Alterations in the RTK/RAS/RAF pathway were more common in CTC^{high} samples (23% and 28% for ER- and ER+ vs 9.9% for CTC^{low}, p = 0.017). Similar results were observed with a 10% threshold. **Conclusions:** Distinct cfDNA alterations were identified based on ER expression in CTCs in HR+/HER2- MBC. Integrating CTC enumeration and cfDNA profiling may help elucidate resistance mechanisms, identify actionable targets, and predict benefit from continued CDK4/6 inhibition beyond progression. Research Sponsor: Pfizer; Merck KGaA; CrossRef Funder ID: 10.13039/100009945.

Incidence of cfDNA alterations across the 3 CTC-based groups.

cfDNA alterations	CTC^{low}[1]	CTC^{high}/ER-[1]	CTC^{high}/ER+[1]	P value
ESR1[2]	36 (40)	15 (50)	31 (67)	0.009
SMAD4[2]	0 (0)	3 (10)	2 (4.3)	0.009
PIK3CA[3]	2 (2)	4 (13)	0 (0)	0.012
BRAF[3]	1 (1)	1 (3.3)	5 (11)	0.022
CDK4[3]	1 (1)	3 (10)	2 (4.3)	0.035
ER pathway[2]	40 (44)	15 (50)	32 (70)	0.017
PI3K pathway[3]	2 (2.2)	4 (13)	0 (0)	0.012
Cell cycle pathway[3]	8 (8.8)	9 (30)	8 (17)	0.019
P53 pathway[2]	27 (30)	16 (53)	13 (28)	0.040

[1]n (%); [2]snv; [3]cnv.

Overall survival in patients with HR+/HER2- advanced or metastatic breast cancer treated with a cyclin-dependent kinase 4/6 inhibitor plus an aromatase inhibitor: A US Food and Drug Administration pooled analysis.

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Background: Cyclin-dependent kinase 4/6 inhibitors (CDKI) are FDA-approved for use in combination with aromatase inhibitors (AI) for the treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), advanced or metastatic breast cancer (MBC) as initial (1L) endocrine-based therapy. We have previously reported the pooled analyses of the benefit in progression-free survival of adding CDKI to AI, and here report the pooled overall survival (OS) results for adults treated with CDKI + AI for 1L HR+/HER2- MBC. **Methods:** We pooled individual patient data (N=2252) from 4 randomized trials (MONALEESA-2 & 7, MONARCH-3, PALOMA-2) of a CDKI (abemaciclib, palbociclib, ribociclib) or placebo + AI in adults with 1L HR+/HER2- MBC. OS was defined as time from randomization to death from any cause and was a key secondary endpoint in all 4 trials. Not all 4 trials reached OS statistical significance, but all OS hazard ratios of the individual trials were <1. The median OS was estimated using Kaplan-Meier methods, and hazard ratios with 95% confidence intervals (CI) were estimated using Cox regression models. Analyses were prespecified, with patients analyzed collectively and by various clinicopathological subgroups of interest. **Results:** Overall results in all patients and various clinicopathologic subgroups of interest are shown (Table). **Conclusions:** In this descriptive exploratory pooled analysis, the addition of a CDKI to AI suggested an association with an OS benefit for this class of drugs used as a component of 1L endocrine-based therapy for adults with HR+/HER2- MBC. Additional research is needed to determine which subgroup of patients may benefit more or less of the addition of a CDKI to AI. Research Sponsor: None.

	n	# Events CDKI/n (%)	# Events Placebo/n (%)	HR (95% CI)
All	2252	716/1320 (54)	550/932 (59)	0.81 (0.73, 0.91)
PR negative	273	84/155 (54)	89/118 (75)	0.51 (0.38, 0.70)
De Novo	752	233/450 (52)	173/302 (57)	0.82 (0.67, 1.00)
Lobular Histology	144	72/97 (74)	34/47 (72)	0.99 (0.66, 1.50)
Bone-Only	493	142/284 (50)	115/209 (55)	0.74 (0.58, 0.95)
Liver/Lung Mets	1111	365/639 (57)	291/472 (62)	0.81 (0.70, 0.95)
Age <40	193	40/106 (38)	44/87 (51)	0.78 (0.51, 1.21)
Age >70	403	159/247 (64)	106/156 (68)	0.86 (0.67, 1.09)
ECOG 1	851	305/499 (61)	239/352 (68)	0.78 (0.66, 0.93)
White	1594	529/919 (58)	407/675 (60)	0.88 (0.77, 1.00)
Asian	438	113/269 (42)	89/169 (53)	0.59 (0.45, 0.78)
Black or African American	43	14/25 (56)	11/18 (61)	0.80 (0.36, 1.76)

Additional clinicopathologic subgroup analyses conducted with results not shown.

Prospective cohort study of palbociclib in HR+/HER2- metastatic breast cancer in Japan.

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Background: The combination of palbociclib (PAL) with an aromatase inhibitor or fulvestrant has been shown to improve progression-free survival (PFS) in hormone receptor (HR)-positive and human epidermal growth factor receptor (HER2)-negative metastatic breast cancer. However, the addition of PAL to endocrine therapy increases toxicity and cost compared to endocrine therapy alone. In addition, PAL treatment may affect the efficacy of subsequent treatments, as its benefit in terms of overall survival (OS) has not yet been demonstrated. Therefore, it is crucial to prospectively evaluate whether PAL can improve clinical outcomes and quality of life (QoL) for patients in a real-world setting. **Methods:** A prospective observational study of PAL is planned in three cohorts (A, B, and C) categorized by line of endocrine treatment (1st, 2nd, or 3rd or later line) for postmenopausal metastatic or unresectable breast cancer. The primary endpoint is PFS in each line of treatment. For cohort B, PFS2 is defined as time from initiation of first-line therapy for metastatic disease. Based on the results of the PALOMA-2 and -3 studies, the planned sample size was set at 700 cases with confidence intervals: 340 in cohort A, 200 in cohort B and 130 in cohort C. Secondary endpoints include OS, clinical benefit rate, time to chemotherapy, adverse events (AEs), patient-reported outcomes and health-related quality of life, which will also be evaluated during follow-up. This study aims to determine whether the efficacy, safety and QoL outcomes of PAL treatment in daily clinical practice are comparable to those observed in clinical trials, and whether PAL affects the efficacy and safety of subsequent treatments. This report presents PFS results from each cohort. An exploratory analysis of OS rates from the start of 1st-line therapy for metastatic disease is also reported. **Results:** A total of 700 patients were enrolled from April 2019 to January 2023. After excluding cases with contraindications, the final cohort distribution was as follows: 246 in cohort A, 282 in cohort B, and 65 in cohort C. The median PFS was 25.8 months (95% CI: 21.4) for cohort A, 18.0 months (95% CI: 14.0-22.7) for cohort B, and 12.0 months (95% CI: 7.7-17.4) for cohort C. The median PFS2 for cohort B was 57.9 months (95% CI: 45.2-65.1). The 3-year OS rates for cohorts A and B from the start of 1st-line metastatic therapy were 76.3% and 93.1%, respectively. **Conclusions:** The PFS result for the 1st-line cohort (Cohort A) was nearly equivalent to the 24.8 months observed in PALOMA-2, while the 2nd-line cohort (Cohort B) showed markedly better results than the 9.5 months reported in PALOMA-3. Although the background of each cohort needs to be further investigated, the PFS2 result of Cohort B was excellent and the subsequent 3-year OS of this cohort was satisfactory. Based on these results, the use of PAL in the 2nd line setting may be clinically acceptable. Clinical trial information: UMIN000035863. Research Sponsor: Pfizer Inc.

Results of a phase 1 study of vosilasarm (EP0062), a first-in-class oral selective androgen receptor modulator (SARM) in patients with advanced or metastatic AR+/ ER+/HER-2- breast cancer.

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Background: Vosilasarm (EP0062) is an oral, nonsteroidal, Selective Androgen Receptor Modulator (SARM). Initially developed under the code RAD140, EP0062 has been reformulated with markedly improved bioavailability and pharmacokinetics. Preclinically, vosilasarm has been shown to act as a potent tissue-selective AR agonist, suppressing growth and proliferation of multiple AR+/ER+/HER-2- breast cancer cell lines and patient-derived xenograft models, as monotherapy or in combination with standard of care (SoC) regimens (Clin Can Res 2017 23(24); SABCS 2019 P5-05-01). Here we report results from the dose finding and optimization cohorts of an ongoing phase 1/2 study (NCT05573126) in patients (pts) with advanced AR+/ER+/ HER-2- breast cancer. **Methods:** The study recruited post-menopausal women with locally advanced or metastatic AR+/ ER+/HER-2- breast cancer, ≥ 18 years of age, with endocrine sensitive disease. AR+ defined as ≥ 10% AR nuclei staining by IHC. Primary objectives were to evaluate safety and determine the optimal dose for evaluation in future combination cohorts. Other endpoints included PK, ORR, DOR, CBR ≥6 months and genomic analysis (biopsy- or ctDNA-based NGS). **Results:** A total of 20 pts (Median age 59.5 y, PS 0/1 [70/30%]) were treated across 4 dose cohorts: 20mg QD (n = 2), 10mg BID (n = 10), 10mg QD (n = 5), 15mg BID (n = 3). The 10mg BID cohort was expanded for dose optimization. All pts received prior CDK4/6i and AI and/or SERD with a median of 4 prior lines (in any setting). CtDNA analysis showed genomic heterogeneity at baseline, with ESR1 mutations (8/19 pts) and TP53 mutations (9/19 pts) the most frequent. No DLTs were observed. 89% of all TEAEs were G1 or G2 with most common being increase in LFTs (55% of pts), nausea (40% of pts) and anemia (25% of pts). The LFT increases were transient, asymptomatic and generally occurred in cycle 1, with 2 pts requiring a dose interruption followed by reduction. Most common ≥ G3 TEAEs were ALT increase in 4 pts (20%). No treatment related deaths were observed. 19 pts were evaluable for efficacy. For 11/ 19 (58%) pts the best response was stable disease. 4/19 (21%) pts had clinical benefit with CBR ≥6 mo, corresponding with marked suppression of CA15-3 in 5/19 (26%) patients. Vosilasarm has a favorable PK profile with good bioavailability and no accumulation. Full data will be reported. 10 mg BID was selected as the optimal dose for Phase 2. **Conclusions:** Vosilasarm has promising clinical benefit, safety and tolerability in this heterogeneous, heavily pre-treated population. This confirms the potential of vosilasarm, a first in class SARM, as a new treatment strategy for AR+/ ER+/HER-2- breast cancer. The study is continuing with evaluation of vosilasarm in combination with SoC therapies including oral SERD, mTOR inhibitor and CDK4/6 inhibitors. Clinical trial information: NCT05573126. Research Sponsor: Ellipses Pharma.

Impact of BMI on CDK4/6 inhibitors efficacy and safety in advanced breast cancer: Results from a propensity score matched study—CAMELIA.

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Background: Body mass index (BMI) is strongly associated with the development and progression of breast cancer. Despite the widespread use of cyclin-dependent kinase (CDK) 4/6 inhibitors combined with endocrine therapy (ET) in hormone receptor (HR)-positive advanced breast cancer, the effect of BMI on therapeutic outcomes remains poorly understood. **Methods:** Patients aged ≥18 years with advanced HR-positive breast cancer who received CDK4/6 inhibitors at six hospitals in China were included. 588 patients admitted between December 2016 and December 2024 were evaluated. Patients were categorized into two groups based on BMI: Group 1 (BMI < 25.0 kg/m²) and Group 2 (BMI ≥ 25.0 kg/m²). Propensity score matching with a 3:1 ratio was performed, resulting in 452 patients included in the final analysis. The median follow-up duration was 21.53 months. Progression-free survival (PFS) and overall survival (OS) across BMI categories were compared using Kaplan-Meier (KM) curves and log-rank test. Univariate and multivariate cox regression analyses were performed to assess the impact of baseline clinical factors on PFS. **Results:** Of 452 patients, 339 (66.7%) were in Group 1, 113 (33.3%) were in Group 2 at baseline. The KM analysis revealed that patients with BMI ≥ 25 kg/m² had a significantly longer PFS compared to those with BMI < 25 kg/m². The median PFS was 16.77 months (95% CI: 12.86–20.67) in Group 1, versus 12.93 months (95% CI: 11.38–14.49) in Group 2 (p = 0.036, HR 0.737, 95% CI: 0.554–0.981). However, no significant difference in OS was observed between the two groups (Group 1: 55.6 months vs. Group 2: not reached, p = 0.949, HR 1.015, 95% CI: 0.637–1.618). Univariate and multivariate cox regression analyses identified BMI, lymph node, liver, bone, and brain metastasis are independent prognostic factors for the entire cohort. Subgroup analyses revealed that BMI ≥25 kg/m² was associated with improved survival in patients aged < 60 years, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 1, with lung metastases, received ≥ 1 line of chemotherapy, and received ≥2 lines of CDK4/6 inhibitors. While Group 1 demonstrated a higher overall response rate (ORR) (30.4% vs. 26.5%, p = 0.476), Group 2 had a higher disease control rate (DCR) (87.0% vs. 91.2%, p = 0.314), though neither reached statistical significance. No significant differences were found in the incidence of grade 3/4 hematologic adverse events (AEs) (36.9% vs. 31.5%, p = 0.460) or non-hematologic AEs (17.1% vs. 14.4%, p = 0.605). **Conclusions:** In this study, overweight patients (BMI ≥ 25 kg/m²) with metastatic breast cancer may benefit more from CDK4/6 inhibitors. Moreover, similar adverse events were observed across BMI groups. These findings suggest that BMI could serve as a key predictor of CDK4/6 inhibitors treatment response, providing valuable insights for personalized therapeutic strategies in metastatic breast cancer. Research Sponsor: None.

Characteristics of patients before and after matching according to BMI categories.

	Unmatched cohort				Matched cohort			
Characteristics	BMI<25kg/m² (n=448)	BMI≥25kg/m² (n=140)	*P*	SMD	BMI<25kg/m² (n=339)	BMI≥25kg/m² (n=113)	*P*	SMD
Age grope at study entry, No. (%)			0.134	0.152			0.694	0.036
< 60years	286 (63.8)	79 (56.4)			204 (60.1)	70 (61.9)		
≥60years	162 (36.2)	61 (43.6)			135 (39.8)	43 (38.1)		
ECOG PS			0.064	0.189			0.350	0.078
0	248 (56.4)	52 (37.1)			149 (43.7)	45 (39.8)		
≥1	240 (53.6)	88 (62.9)			191 (56.3)	68 (60.2)		
Stage at diagnosis			0.217	0.124			0.406	0.072
I-III	368 (82.1)	108 (77.1)			279 (82.3)	96 (84.7)		
IV	80 (17.9)	32 (22.9)			60 (17.7)	17 (15.0)		
Estrogen receptor status, No. (%)			0.131	0.226			0.434	0.070
1~10%	9 (2.0)	0 (0.0)			0 (0.0)	0 (0.0)		
10~50%	37 (8.3)	16 (11.4)			29 (8.6)	12 (10.6)		
> 50%	402 (89.7)	124 (88.6)			310 (91.4)	101 (89.4)		
Progesterone receptor status, No. (%)			0.328	0.150			0.940	0.030
Negative	65 (14.5)	21 (15.0)			55 (16.2)	19 (16.8)		
1~20%	121 (27.0)	29 (20.7)			75 (22.1)	26 (23.0)		
> 20%	262 (58.5)	90 (64.3)			209 (61.7)	68 (60.2)		
HER-2 status, No. (%)			0.052	0.204			0.812	0.053
Negative	418 (93.3)	124 (88.6)			311 (91.7)	104 (92.0)		
Positive	23 (5.1)	9 (6.4)			21 (6.2)	6 (5.3)		
Unknown	7 (1.6)	7 (5.0)			7 (2.1)	3 (2.7)		
Ki-67 status, No. (%)			0.138	0.184			0.475	0.097
< 20	166 (37.1)	46 (32.9)			120 (35.4)	36 (31.9)		
≥20	246 (54.9)	75 (53.6)			188 (55.5)	64 (56.6)		
Unknown	36 (8.0)	19 (13.5)			31 (9.1)	13 (11.5)		
Resistance to previous endocrine treatment, No. (%)			0.085	0.234			0.924	0.031
Primary resistance	80 (17.9)	27 (19.3)			61 (18.0)	20 (17.7)		
Secondary resistance	325 (72.5)	90 (64.3)			239 (70.5)	81 (71.7)		
ET naive	42 (9.4)	23 (16.4)			39 (11.5)	12 (10.6)		
non-sensitive	1 (0.2)	0 (0.0)			0 (0.0)	0 (0.0)		
Bone metastases			0.281	0.107			0.816	0.024
No	181 (40.4)	64 (45.7)			151 (44.5)	49 (44.1)		
Yes	267 (59.6)	76 (54.3)			188 (55.5)	64 (56.6)		
Visceral metastases			0.432	0.084			0.310	0.084
No	183 (40.8)	63 (45.0)			146 (43.1)	44 (40.5)		
Yes	265 (59.2)	77 (55.0)			193 (56.9)	69 (61.1)		
Previous endocrine therapy lines, No. (%)			0.136	0.198			0.673	0.068
0	206 (46.0)	77 (55.0)			170 (50.1)	59 (52.2)		
1	140 (31.2)	40 (28.6)			100 (29.5)	34 (30.1)		
≥2	102 (22.8)	23 (16.4)			69 (20.4)	20 (17.7)		
CDK4/6 inhibitors treatment lines, No. (%)			0.014	0.286			0.696	0.065
1	155 (34.6)	68 (48.6)			140 (41.3)	50 (44.2)		
2	90 (20.1)	22 (15.7)			60 (17.7)	20 (17.7)		
≥3	203 (45.3)	50 (35.7)			139 (41.0)	43 (38.1)		
Combination of CDK4/6 inhibitors therapy, No. (%)			0.644	0.070			0.943	0.028
Aromatase inhibitors	270 (60.3)	86 (61.4)			202 (59.6)	68 (60.2)		
Fulvestrant	172 (38.4)	51 (36.5)			132 (38.9)	43 (38.1)		
Others	6 (1.3)	3 (2.1)			5 (1.5)	2 (1.8)		
Disease-free survival, No. (%)			0.417	0.126			0.478	0.092
≤2years	75 (16.7)	23 (16.4)			54 (15.9)	21 (18.6)		
>2years	293 (65.4)	85 (60.7)			225 (66.4)	75 (66.4)		
De novo stage IV	80 (17.9)	32 (22.9)			60 (17.7)	17 (15.0)		

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; HER-2: human epidermal growth factor receptor 2; ET: endocrine treatment; CDK4/6: cyclin-dependent kinase 4/6.

Clinical utility of [^{18}F]fluoroestradiol (FES) PET/CT to guide second-line treatment decision in patients with ER-positive HER2-negative metastatic breast cancer progressing on first-line endocrine therapy.

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Background: Second line treatment options for patients with ER+/HER2- metastatic breast cancer (MBC) after progression on 1st line endocrine therapy (ET) continue to expand with novel endocrine agents (oral SERDs) and combination therapies (PIK3CA/AKTi, CDKi). However, short median PFS reported in clinical trials show that many patients do not benefit from 2nd line ET. Identifying endocrine-resistant MBC at time of progression on 1st line ET can help place patients on potentially more effective non-ET options (e.g., chemotherapy / antibody-drug conjugates). FES PET/CT has been approved for clinical use in the U.S. and allows whole-body evaluation of ER expression in MBC. Difference in FES uptake across lesions may reflect ER loss/downregulation, a mechanism of endocrine resistance. Goal of this clinical trial was to evaluate the impact of FES PET/CT results on 2nd line therapeutic management decisions. **Methods:** In this multicenter trial in the U.S. [NCT05068726], patients with progression of ER+/HER2- MBC on 1st line ET were prospectively enrolled to undergo FES PET/CT in addition to standard of care (SOC) imaging (CT + bone scan / FDG PET/CT). Treating oncologists completed questionnaires before and after FES PET/CT, detailing therapeutic management plans plus their confidence in the plans. FES PET/CT scans were compared with SOC imaging to assess FES uptake in MBC lesions. An FES uptake score (number of FES-positive lesions divided by total number of lesions per patient) was calculated to evaluate ER expression heterogeneity by central blinded image evaluation. **Results:** 45 patients underwent FES PET/CT. FES PET/CT results led to a change in therapeutic management in 17/45 patients (37.8%; 95% CI 23.8% - 53.5%). Revised management plan was ET in 5/17 and non-ET in 12/17 patients. FES uptake score was 1 (all lesions FES-positive) in 14/45 patients and $<$ 1 (with FES-negative lesions, indicating ER expression heterogeneity) in 31/45 patients. Of 14 patients with FES uptake score of 1, 11 received 2nd line ET. Of 31 patients with FES uptake score $<$ 1, 15 were treated with ET and 16 with non-ET, based on guidelines suggesting that an FES-negative lesion is predictive of lack of endocrine response. FES PET/CT results led to 25/45 patients avoiding additional tests (20 biopsies, 5 scans) and 7/45 patients receiving further testing (4 biopsies, 1 scan, 2 other). Treating oncologist's confidence in 2nd line treatment decision (measured in n = 45 on 10-point scale with 10 being fully confident) increased on average with 2 points from 6.6 (SD = 1.7) pre-FES PET/CT to 8.6 (SD = 1.8) post-FES PET/CT. **Conclusions:** FES PET/CT is a clinically useful tool in the post-first line ER+/HER2- MBC setting. FES PET/CT results led to a change in management in 37.8% of patients and increased oncologist's confidence in 2nd line treatment decision. Clinical trial information: NCT05068726. Research Sponsor: Zionexa SAS, a GE HealthCare Company.

Imlunestrant with or without abemaciclib in advanced breast cancer (ABC): Safety analyses from the phase III EMBER-3 trial.

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Background: Imlunestrant is a next-generation, brain-penetrant, oral SERD. The EMBER-3 trial (NCT04975308) in patients with ER+, HER2- ABC and disease progression on/after aromatase inhibitor therapy showed significant progression-free survival improvement with imlunestrant (imlu; 400 mg once daily [QD]) over standard therapy (SOC, fulvestrant or exemestane) among patients with *ESR1* mutations, as well as with imlunestrant+abemaciclib (imlu [400 mg QD] + abema [150 mg twice daily]) over imlu in all patients regardless of *ESR1* mutation status. Detailed safety analyses are presented. **Methods:** The safety population included all patients who received at least one dose of study treatment. Analyses included incidence, severity (CTCAE v 5.0), management, and outcomes of common treatment-emergent adverse events (TEAEs). **Results:** Safety analyses included 859 patients: imlu (n=327), SOC (n=324), and imlu+abema (n=208). Incidence of any (imlu: 83%; SOC: 84%; imlu+abema: 98%), ≥ grade 3 TEAEs (imlu: 17%; SOC: 21%; imlu+abema: 49%), and serious AEs (SAEs; imlu: 10%; SOC 12%; imlu+abema: 17%) were similar between imlu and SOC arms and higher in the combination arm. Most common any-grade AEs with imlu were diarrhea (21%), nausea (17%), and fatigue (23%) and with imlu+abema were diarrhea (86%), nausea (49%), and neutropenia (48%); majority were grade 1 AEs. Incidence of elevated transaminases (any%/≥G3%: 16/1 and 20/5), VTE (1/0 and 3/1), ILD (1/0 and 2/0), bradycardia (2/0 and 1/0), and photopsia (0/0 and 0/0) were relatively low or not observed with imlu and imlu+abema, respectively. Dose reduction rates were 2% with imlu and 39% with imlu+abema, and discontinuation rates due to AEs were low (4% and 6%, respectively). The table characterizes the most commonly observed AEs. Further details will be presented. **Conclusions:** Imlunestrant had a favorable safety profile, similar to SOC, with mostly grade 1 AEs. Safety of imlunestrant + abemaciclib was consistent with the known abemaciclib profile, without additive toxicity. AEs were manageable with supportive medications and/or dose adjustments, resulting in few discontinuations in all arms. Imlunestrant, as monotherapy or in combination with abemaciclib, provides a safe, tolerable, all-oral targeted therapy option for patients with ER+, HER2- ABC. Clinical trial information: NCT04975308. Research Sponsor: Eli Lilly and Company.

Characterization of commonly observed AEs.

	Diarrhea			Nausea		
	Imlu N=327	SOC N=324	Imlu+abema N=208	Imlu N=327	SOC N=324	Imlu+abema N=208
Grade 1 AE, %	18	9	50	14	8	31
Grade 2 AE, %	3	3	28	3	5	15
Grade ≥3 AE, %	0.3	0	8	0.3	0	2
Median time to onset (Q1–Q3), days	30 (15–129)	52 (17–132)	5 (2–17)	20 (4–56)	57 (10–147)	15 (3–48)
Median duration of Grade 2 AE (range), days	3 (1–28)	5 (1–55)	13 (1–87)	16 (4–89)	10 (1–90)	19 (2–266)
Median duration of Grade ≥3 AE (range), days	8 (8–8)	0	9 (1–47)	24 (24–24)	0	7 (6–13)
Dose reduction/discontinuation, %	0/0	0/0	18/1	0.3/0	0/0	5/0
Antidiarrheal medication/ Antiemetic, %	10	7	68	10	10	21

Giredestrant (G) with atezolizumab (ATEZO), and/or abemaciclib (ABEMA) in patients (pts) with ER+/HER2– locally advanced/metastatic breast cancer (LA/mBC): Interim analysis (IA) from the phase I/II MORPHEUS Breast Cancer study.

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Background: Endocrine therapy (ET) + a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) is a therapeutic mainstay for first-line treatment (tx) of ER+ mBC, but selection of effective ET combinations after progression remains a challenge. G is a highly potent, non-steroidal, oral (PO), selective ER antagonist and degrader shown to be well tolerated and to achieve robust ER occupancy. Immune checkpoint inhibition has shown a trend towards activity in a number of ER+ BC studies. Additionally, ABEMA (a CDK4/6i) has immunomodulatory activity, making its inclusion a compelling therapeutic approach. Here, we present a 24-week IA of the G + ATEZO ± ABEMA arms and a 22-week IA of the G + ABEMA arm from MORPHEUS BC (NCT04802759). **Methods:** Eligible pts had ER+, HER2– LA/mBC and had received prior tx with a CDK4/6i and 1–2 lines of ET. Pts were randomized to G (30 mg PO QD) alone (previously reported), G + ATEZO (840 mg IV Q2W), G + ATEZO + ABEMA (150 mg PO BID), or G + ABEMA until loss of clinical benefit/unacceptable toxicity. Investigational drug doses were identical across all arms. Primary endpoints were safety and objective response rate (ORR). Exploratory analyses included evaluation of circulating tumor DNA alterations and tumor gene expression using RNAseq. **Results:** As of Apr 24, 2024, 15 pts in the G + ATEZO arm, 30 in the G + ATEZO + ABEMA arm and, as of Jan 9, 2023, 15 in the G + ABEMA arm, were efficacy/safety evaluable. Many pts had prior fulvestrant (60%, 43%, and 27%, respectively) and prior CDK4/6i duration ≥12 mo (73%, 77%, and 53%). Safety data are shown in the Table. In the triplet arm, the most common grade ≥3 adverse event (AE) was neutropenia/neutrophil count decreased (20%). No grade 5 AEs were reported. Confirmed ORR (all partial responses) were 20%, 33%, and 7% in the G + ATEZO, G + ATEZO + ABEMA, and the G + ABEMA arms, respectively. 7/9 confirmed responses (in *ESR1*-evaluable pts) in the G + ATEZO + ABEMA arm were in pts with *ESR1*-mutated disease. Data with longer follow-up, including progression-free survival, detailed safety, and exploratory biomarker analyses, will be presented. **Conclusions:** The combinations of G + ATEZO, G + ATEZO + ABEMA, and G + ABEMA were tolerable, with no unexpected safety signals including no high-grade interstitial lung disease/pneumonitis and low rates of high-grade liver toxicity. Clinical activity was observed, with a trend towards improved ORR with G + ATEZO + ABEMA, particularly in tumors with *ESR1* mutations. Clinical trial information: NCT04802759. Research Sponsor: F. Hoffmann-La Roche Ltd.

n (%)	G + ATEZO (n = 15)	G + ATEZO + ABEMA (n = 30)	G + ABEMA (n = 15)
Any AE	14 (93)	30 (100)	15 (100)
AE: highest grade 3	8 (53)	15 (50)	8 (53)
AE: highest grade 4	0 (0)	0 (0)	1 (7)
Any-grade tx-related AE (TRAE)	12 (80)	30 (100)	13 (87)
TRAE leading to discontinuation of any tx	3 (20)	5 (17)	0 (0)

Phase Ib study of inavolisib (INAVO) + weekly paclitaxel (wP) in patients (pts) with locally advanced/metastatic (LA/m) incurable solid tumors: Safety, pharmacokinetics (PK), and preliminary antitumor activity.

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Background: wP is commonly used for treating solid tumors as a single agent or in combination with targeted agents. However, it has an unfavorable benefit–risk profile when given with pan-PI3K inhibitors or alpelisib. INAVO, a potent and selective PI3Kα inhibitor that also promotes mutated p110α degradation, was FDA approved in combination with palbociclib + fulvestrant for hormone receptor-positive, HER2-negative (HR+, HER2–), endocrine-resistant advanced breast cancer (BC) following recurrence on/after completing adjuvant endocrine therapy. We report data from INAVO + wP in pts with LA/m solid tumors from a Phase Ib study (CO42800; ISRCTN45319897). **Methods:** Eligible pts had progressed after standard systemic therapy. In part 1 (dose-escalation phase; 3+3 design), pts with LA/m incurable solid tumors received INAVO 6 mg/9 mg orally daily (PO QD) + wP (80 mg/m^2). In part 2 (dose-expansion phase), pts with LA/m incurable *PIK3CA*-mutated solid tumors (triple-negative BC [TNBC]; HR+, HER2– BC; others) received INAVO 9 mg PO QD (recommended dose from part 1) + wP. Primary endpoint: Safety/tolerability in parts 1 and 2. Secondary endpoints: Preliminary antitumor activity in part 2 (only TNBC and HR+, HER2– BC data are available); PK in parts 1 and 2. **Results:** Of 66 pts enrolled (parts 1 and 2), four received no treatment and eight were still on treatment at clinical cutoff (Oct 11, 2024). Reasons for study discontinuation were per protocol study completion (56.1%), death (16.7%), pt withdrawal (9.1%), loss to follow-up (1.5%), and other (4.5%). There were no dose-limiting toxicities. In safety-evaluable pts (n = 62), grade 3, 4, and 5 adverse events (AEs) occurred in 59.7%, 3.2%, and 0% of pts, respectively. One pt discontinued INAVO due to AEs; INAVO dose modifications (reduction/interruption) due to AEs occurred in 61.3% of pts. The most common AEs ($>$ 10% of pts) were diarrhea (61.3%), hyperglycemia (51.6%), and anemia (45.2%). Neutropenia (24.2%) and diarrhea (8.1%) were the most common grade 3–4 AEs. Serious AEs occurred in 30.6% of pts (mostly single AEs in individual pts, and unrelated to study treatment).In part 2, confirmed overall response rate in pts with TNBC (n = 20) was 50.0% and in pts with HR+, HER2– BC (n = 19) it was 36.8%. Median duration of confirmed response was 7.4 mo (95% confidence interval 5.2, 11.5) and 12.8 mo (3.7, not evaluable), respectively; median progression-free survival, 7.0 mo (3.5, 9.3) and 7.4 mo (6.2, 14.7). PK of INAVO and wP at Cycle 1, Day 15 were comparable to historic data. **Conclusions:** In CO42800, INAVO + wP was well tolerated in pts with LA/m solid tumors, including those with a *PIK3CA* mutation, with no new safety signals or drug–drug interactions observed. Encouraging preliminary antitumor activity shown in pts with HR+, HER2– BC or TNBC supports further investigation. Clinical trial information: ISRCTN45319897. Research Sponsor: Genentech, Inc.

PARPi effectiveness after CDK4/6i in *BRCA1*- and *BRCA2*-associated HR+/HER2- advanced breast cancer: Results from the multicenter real-world PAMBRACA study.

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Background: Poly(adenosine diphosphate–ribose) polymerase inhibitors (PARPi) are the paramount of personalized therapy for *BRCA1* and *BRCA2* pathogenic/likely pathogenic variant (P/LPV) carriers with hormone receptor-positive (HR+)/HER2-negative (HER2-) advanced breast cancer (aBC). Nevertheless, data on the efficacy of PARPi following cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) are limited. **Methods:** The PAMBRACA study is a multicenter, hospital-based, retrospective-prospective cohort study enrolling *BRCA1* and *BRCA2*-P/LPV carriers with HR+/HER2- aBC treated with ET+CDK4/6i and/or PARPi. In this analysis, the real-world Progression-Free Survivals (rwPFS) of ET+CDK4/6i and subsequent lines were evaluated through Kaplan-Meier method and compared with the log-rank test. Median follow-up was calculated using the reverse Kaplan-Meier method. Multivariate Cox regression model was used to adjust the association between treatment regimens and rwPFS for clinically relevant variables. **Results:** We included12 *BRCA1* and 57 *BRCA2*-P/LPV carriers who were diagnosed with HR+/HER2- aBC between January 1998 and December 2023 in six Italian Institutions. All the patients (pt) received CDK4/6i+ET for aBC (85.5% as first line, 7.2% as second line, 7.3% as third or subsequent line). At CDK4/6i starting, median age was 45 years (range 28-80); 52.2% of pts had visceral metastases and 17.4% had *de novo* aBC. Median follow-up was 39.5 months (mo). Among pts treated with CDK4/6i as first or second line, median rwPFS was 15.1 mo (95%CI 11.8-18.5) and 3.1 mo (95%CI 2.1-NA), respectively. Among the 49 patients who progressed to first or second-line CDK4/6i, 17 (34.7%) received a PARPi as first line post-CDK4/6i, 12 (24.5%) a monochemotherapy (monoCT), 8 (16.3%) an ET (+/- everolimus), 8 (16.3%) a polychemotherapy (polyCT) and 4 (8.2%) died without receiving a subsequent line. No significant differences in clinicopathological characteristics were observed among the treatment groups, except for the number of metastatic sites (<3 vs >3), which was higher for pts receiving mono/polyCT ($p = 0.053$). PARPi treatment was associated with significantly higher median rwPFS (13 mo vs 4.5 mo for monoCT vs 3 mo for ET vs 6 mo for polyCT, $p < 0.001$), also after adjusting for the number of metastatic sites [for PARPi vs other lines, adjusted hazard ratio (aHR) 0.20, 95%CI 0.09-0.49, $p < 0.001$]. 17 pts received PARPi as later treatment lines, which were independently associated with lower median rwPFS vs PARPi as first post-CDK4/6i line (6 vs 13 mo, aHR 2.81, 95%CI 1.15-6.90, $p = 0.024$). **Conclusions:** AfterCDK4/6i+ET, PARPi were independently associated with longer rwPFS compared to other systemic therapies in *BRCA1* and *BRCA2*-P/LPV carriers with HR+/HER2- aBC. Earlier PARPi use after CDK4/6i was associated with greater clinical benefit. Research Sponsor: None.

A phase I/IIa study to evaluate the tolerability, safety, pharmacokinetics and efficacy of eciruciclib (BPI-1178) alone in advanced solid tumors and in combination with endocrine therapy for advanced or recurrent HR+/HER2- breast cancer.

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Background: Eciruciclib (BPI-1178) is a new cyclin-dependent kinases (CDKs) 2/4/6 inhibitor, which has shown strong inhibition on the expression of CDK2/4/6 in pre-clinical studies. This first-in-human phase I/IIa study aimed to assess the preliminary efficacy, safety and tolerability of eciruciclib monotherapy for advanced solid tumors or in combination with endocrine therapy (ET) for HR+/HER2- advanced breast cancer (ABC). **Methods:** Patients with advanced solid tumors included in phase I received eciruciclib alone at doses of 25~500 mg in a 3+3 dose-escalation or expansion manner. Phase IIa consisted of two cohorts, A and B. Cohort A included patients with HR+/HER2- ABC who had progressed after ET receiving eciruciclib in combination with fulvestrant, and treatment-naive patients with HR+/HER2- ABC in cohort B were treated with eciruciclib in combination with letrozole. All patients administered eciruciclib with either intermittent (21 days on, 7 days off) or continuous (28 days on) dosing schedule in a 28-day cycle until disease progression, unacceptable toxicity, etc. Safety was assessed as per CTCAE 5.0. Efficacy endpoints included confirmed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), etc. assessed by investigators per RECIST 1.1. **Results:** As of August 9, 2024, a total of 129 patients have been enrolled. And 33 patients were enrolled in Phase l study. No DLT was observed. In Phase IIa Cohort A, 70 patients were enrolled and in which 64 patients were evaluable for efficacy. 26 patients were enrolled into cohort B with 25 efficacy-evaluable patients. In Cohort A, the top three treatment related adverse events (TRAEs) of grade ≥ 3 were neutrophil count decreased (35.7%), white blood cell count decreased (14.3%), and hypertriglyceridemia (14.3%) while in Cohort B those were neutrophil count decreased (23.3%), hypertriglyceridemia (16.7%), alanine aminotransferase increased (10.0%), and white blood cell count decreased (10.0%). No TRAE leading to permanent discontinuation or death occurred in this trial. **Conclusions:** Eciruciclib in combination with ET demonstrated promising efficacy and manageable safety profile in patients with HR+/HER2- ABC. Clinical trial information: NCT04282031. Research Sponsor: Beta Pharma (Suzhou) Co., Ltd.

	Cohort A (n = 64)				Cohort B (n = 25)	
	400 mg [a] (n = 20)	300 mg [a] (n = 16)	300 mg [b] (n = 20)	200 mg [b] (n = 8)	400 mg [a] (n = 19)	300 mg [a] (n = 6)
ORR, n (%)	9 (45.0)	7 (43.8)	11 (55.0)	0 15 (78.9)	5 (83.3)	
DCR, n (%)	17 (85.0)	13 (81.3)	20 (100.0)	8 (100.0)	18 (94.7)	6 (100.0)
Median PFS, months (95% CI)	18.3 (7.2, NR)	7.3 (2.4, NR)	NR (12.8, NR)	NR	NR (16.7, NR)	NR

[a]intermittent dosing schedule;
[b]continuous dosing schedule; NR, not reached.

Quantifying the clinical impact of tissue reflex testing for liquid biopsy *ESR1* mutation–negative cases with low ctDNA tumor fraction (TF) in HR(+)HER2(-) breast cancer.

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Background: *ESR1* mutations (*ESR1*mut) commonly drive acquired resistance to estrogen deprivation by aromatase inhibitors, a first-line standard of care for HR(+)HER2(-) metastatic breast cancer (MBC). We previously published that approximately 63% of patients with HR(+) HER2(-) MBC at progression have a liquid biopsy (LBx) negative for *ESR1*mut. The absence of an *ESR1*mut may either accurately reflect the tumor genotype (true negative) or represent a false negative due to insufficient ctDNA shedding, with the risk of missing an actionable mutation. Among these patients, 40% exhibit a high ctDNA TF ≥1% (informative negative), while 60% have a low ctDNA TF < 1% (indeterminate negative). This suggests that up to 38% of all patients with HR(+)HER2(-) MBC in this context could potentially benefit from reflex tissue biopsy (TBx) for *ESR1*mut in cases deemed indeterminate negative by LBx due to low ctDNA shedding. The goal of this study is to determine the rate of *ESR1*mut detection in a new TBx after an indeterminate negative result from FoundationOne Liquid CDx (F1LCDx). **Methods:** This study included a cohort of patients with BC who underwent tissue and liquid Foundation Medicine comprehensive genomic profiling (CGP) within an interval of up to 90 days during routine clinical care. Clinical data of a subset of patients with confirmed HR(+)HER2(-) MBC was obtained from the US-wide deidentified Flatiron Health-Foundation Medicine MBC clinico-genomic database (CGDB). The data originated from ~280 cancer clinics (~800 sites of care) between 01/2014-09/2024. False negative rate (FNR) and positive percent agreement (PPA) for *ESR1*mut detection were calculated with tissue CGP as reference. **Results:** A total of 522 BC patients underwent TBx and LBx. Among these, 229 (43.9%) had ctDNA TF < 1%. Without accounting for TF, the overall FNR for *ESR1*mut was 6.3% and the PPA was 67.1%. In LBx with TF ≥1%, the FNR for *ESR1*mut was 0.9% and PPA was 96.0%. In contrast, for TF < 1% samples, the FNR was 12.0% and the PPA 25.7%. 101 patients were included in the CGDB and had a confirmed HR(+)HER2(-) MBC, in which 56 (55.4%) had LBx with ctDNA TF < 1%. The overall FNR for *ESR1*mut in this subset of patients was 9.5% and the PPA was 61.9%. In LBx with TF ≥1%, the FNR was 0% and PPA was 100%. And for TF < 1%, the FNR was 15.1% and PPA 20.0%. **Conclusions:** BC patients with informative negative *ESR1*mut (defined as LBx *ESR1*mut negative with TF ≥1%) are unlikely to have *ESR1*mut detected on tissue CGP testing. However, patients with indeterminate negative *ESR1*mut (defined as LBx *ESR1*mut negative with TF < 1%), 12-15% were found to be false negatives. This suggests that approximately 5% of all HR(+)HER2(-) MBC patients with *ESR1*mut could be missed without reflex testing with a TBx. ctDNA TF levels offer critical guidance in deciding when a reflex to tissue is warranted, ensuring accurate treatment. Research Sponsor: None.

Thymidine kinase activity (TKa) as independent predictor of outcome in metastatic breast cancer (MBC) patients in the GEICAM/2013-02 PEARL trial.

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Background: TKa is a proliferation biomarker measurable in blood via the DiviTum™ TKa assay. Levels of TKa before and during treatment can provide prognostic, predictive and monitoring information in MBC. The PEARL trial (NCT02028507) was a phase III, multicenter, open-label, randomized study that compared endocrine therapy (ET) + CDK4/6 inhibitor Palbociclib (Palbo) vs. Capecitabine (Cape) in aromatase inhibitor-resistant HR+/HER2- MBC patients (pts). ET + Palbo did not improve median progression-free survival (mPFS 17.8 vs. 17.3 months (m.), p = 0.9) or overall survival (mOS 31.1 vs. 32.8 m., p = 0.5) over Cape. We explored whether TKa levels could predict better response to ET + Palbo vs Cape. **Methods:** Plasma from 555 pts (92%) was collected at baseline (BL) and on treatment (C1D15, C2D15). 1129 samples were analyzed using the DiviTum TKa assay (FDA approved/CE labelled, Biovica, Sweden). Cutoffs: 250/400 DiviTum units of Activity (DuA) for BL, 50 DuA or fold change (C1,C2/BL) $>$ 2 for on-treatment. The Kaplan-Meier method estimated median PFS and OS. Adjusted hazard ratio (HR) with 95% confidence interval (CI) were calculated using Cox proportional hazards regression model, considering relevant prognostic clinical variables. **Results:** BL TKa $\leq$ 250 DuA predicted better mPFS (11.4 vs. 4.04 m., aHR 2.1; 95% CI 1.7-2.6, p $<$ 0.0001) and mOS (38.47 vs. 17.31 m., aHR 3.2; 95% CI 2.45-4.19, p $<$ 0.0001) regardless of therapy. After starting therapy, Cape and ET + Palbo elicited distinct TKa responses due to their different mechanisms. At C1, C2, pts on Cape had higher mTKa vs ET + Palbo (448 vs. 28 DuA, p $<$ 0.0001). In the CT arm, an increase of TKa at C1 or C2 greater than 2-fold from BL predicted for better mPFS (13.04. vs. 6.34 m., aHR 0.59; 95% CI 0.43-0.81, p = 0.0013) and mOS (39.26 vs. 23.23 m., aHR 0.31; 95% CI 0.2-0.5, p $<$ 0.0001). In the ET + Palbo arm, a TKa at C1 or C2 $>$ 50 DuA predicted a shorter mPFS (3.68 v 11.27 m, aHR 2.81; 95% CI 2.08-3.8, p $<$ 0.0001) and mOS (18.73 vs. 45.11 m., aHR 3.44; 95%CI 2.34-5.06, p $<$ 0.0001). Similar results are observed regardless of BL TKa value. Exploring a BL TKa $>$ 400 DuA demonstrated a better response to Cape compared to ET+ Palbo, despite overall very poor outcomes: mPFS 4.04 m on Cape vs 2.01 on ET + Palbo, (aHR 1.72; 95% CI 1.14-2.59, p $<$ 0.0096), and showed a similar trend in mOS, 15.4 m on Cape vs 14.6m on ET+Palbo, (aHR 1.29 95% CI 0.84-1.99, p = 0.24). **Conclusions:** These data demonstrate that CT vs a CDK4/6 inhibitor influence TKa response differently, and the direction and magnitude of the TKa response can predict for benefit to a specific therapy. The original PEARL study analysis showed no outcome differences between Cape vs ET + Palbo in HR+/HER2- MBC pts, however assessment of TKa before and during therapy identified which patients had the highest probability of responding. Utilization of TKa as a predictive biomarker may allow for better personalized treatment selection. Clinical trial information: NCT02028507. Research Sponsor: None.

Prognostic role of estrogen receptor (ER) expression in breast cancer (BC) metastases and its dynamics from primary to metastatic disease: Results from a large multicentric cohort of patients with phenotypically stable ER+(≥10%)/HER2- BC.

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Background: ER expression is one of the main determinants of prognosis in patients (pts) with BC. Phenotypic conversion from ER+ (ER>=10%)/HER2- primary BC towards ER<10%/HER2- advanced BC has a well-known negative impact on outcome. However, in the specific context of phenotypically stable ER+/HER2- BC, the prognostic impact of ER expression in metastases or ER dynamics during disease evolution, remains largely understudied. **Methods:** We enrolled pts with advanced BC undergoing biopsy of a metastatic site. ER+ was defined as ER>=10%. ER expression was evaluated both as continuous and categorical variable (categories: 10-30%, 30-50%, 50-100%). Overall survival (OS) was the primary study endpoint. Cox multivariable models included covariates associated with OS in univariate analysis. **Results:** Among 1114 pts, 410 had ER+/HER2- phenotype in both primary and metastatic tumor specimens. In this subgroup, ER expression (both continuous and categoric) in metastases had significant prognostic value: for each 10% lower ER expression, the risk of death increased by 6.7% (p=0.011). Pts with ER 10-30% had significantly worse OS than those with ER 50-100% (HR 0.62, p=0.023), and numerically shorter than ER 30-50% (HR 0.51, p=0.063). The table shows the evolution of ER categories from primary BC to metastases. ER expression dynamics also had prognostic impact. Regarding continuous ER expression changes in paired primary vs. metastatic BC, each 10% ER increase corresponded to 5.9% decrease in the risk of death (p=0.008). Pts whose tumors showed an increased ER expression from 10-30% to 50-100% had the most favorable outcome overall, with better OS compared to pts with persistently low ER levels (HR 6.73, p=0.002), or to pts with decreased ER expression in metastases - particularly pts whose ER levels dropped from 50-100% to 10-30% (HR 2.89, p=014). These pts also had superior OS when compared to pts with persistently high ER levels (HR 2.08, p=0.043). The prognostic impact was preserved at the multivariate analysis (including age, grade, visceral/non-visceral disease, biopsy site). **Conclusions:** Intratumor ER expression and dynamics may in part explain the prognostic heterogeneity of pts with ER+/HER2- stable phenotype from primary to advanced BC. Pts with lower ER levels in metastases are prognostically disadvantaged. Dynamic changes in ER expression provide additional insights beyond those captured by single-point assessment. Interestingly, pts whose tumors shifted from ER 10–30% to ER 50–100% showed the most favorable prognosis, even outperforming those with consistently high ER levels. Research Sponsor: None.

	Metastases, ER							
	10-30%		30-50%		50-100%		Total	
Primary BC, ER	n	%	n	%	n	%	n	%
10-30%	5	1.2	0	0	18	4.4	23	5.6
30-50%	7	1.7	4	1.0	11	2.7	22	5.4
50-100%	24	5.9	21	5.1	320	78.0	364	89
Total	36	8.8	25	6.1	349	85.1	410	100

SIM0270 in combination with palbociclib in patients with ER+/ HER2- advanced breast cancer: The phase Ib study.

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Background: SIM0270 is a highly potent oral selective estrogen receptor degrader (SERD) which has shown ER degradation and robust antitumor activity across variety of preclinical models. Here, we present results of SIM0270 combined with palbociclib cohort(dose escalation and dose expansion) from Phase I study in patients with ER+/HER2- advanced breast cancer (NCT05293964). **Methods:** Patients with ER+/HER2- advanced breast cancer were enrolled. The key inclusion criteria for dose escalation and dose expansion were the same as follows: ≥ 1 prior endocrine therapy (ET) with disease recurrence/ progression while being treated with adjuvant ET for ≥ 24 months and/or first line ET for ≥ 6 months in advanced setting; ≤2 prior chemotherapies in advanced setting; and prior fulvestrant was allowed. A Bayesian Optimal Interval design (BOIN) was adopted for dose escalation. The key endpoint of dose escalation was dose limiting toxicities (DLT), and the key endpoints of dose expansion included safety and tolerability, pharmacokinetics (PK) and efficacy. **Results:** As of December 26, 2024, 44 patients were enrolled including 12 from dose escalation and 32 from dose expansion, with a median follow up of 11.8 months. No DLT was reported in dose escalation. In total, 38 patients (86.4%) had visceral disease, and 8 patients (18.2%) had ESR1 mutation at baseline. 22 patients (50%) received prior endocrine therapy in the advanced setting, of which, 15 patients (34.1%) had aromatase inhibitor (AI), 12 patients (27.3%) had fulvestrant. 13 patients (29.5%) received prior chemotherapy in the advanced setting.The most common treatment emerged adverse events (TEAEs) were white blood cell count decreased (95.5%) and neutropenia (95.5%). Sinus bradycardia was reported in 77.3% (34/44) of the patients, 85.3% (29/34) were grade 1 (asymptomatic) requiring no dose modification. Grade 3/4 treatment-related AEs (TRAEs) occurred in 77.3% of the patients with most commonly reported events including neutropenia (70.5%) and white blood cell count decreased (40.9%). No fatal AEs were reported. TRAEs led to dose reduction were reported in 38.6% for palbociclib and 9.1% for SIM0270. No TRAEs led to treatment discontinuation. And 24 patients remain on study treatment. In the response evaluable patients, confirmed overall response rate (ORR) was 41.5% (17/41) and clinical benefit rate (CBR, defined as complete response, partial response or stable disease ≥ 24 weeks) was 82.5% (33/40). Median progression free survival (PFS) was not reached (NR). In patients with ESR1 mutation at baseline, ORR and CBR were 87.5% (7/8) and 100% (8/8), respectively. **Conclusions:** SIM0270 in combination with palbociclib showed acceptable safety and tolerability, promising clinical activity in patients with ER+/HER2- advanced breast cancer. Clinical trial information: NCT05293964. Research Sponsor: Simcere Zaiming Pharmaceutical Co., Ltd.

First-line (1L) ribociclib (RIB) + endocrine therapy (ET) vs combination chemotherapy (combo CT) in clinically aggressive hormone receptor (HR)+/HER2− advanced breast cancer (ABC): A subgroup analysis of patients (pts) with or without liver metastases (mets) from RIGHT Choice.

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Background: The phase II RIGHT Choice trial reported a statistically significant progression-free survival (PFS) benefit at the primary prespecified analysis and a 9-month (mo) benefit at the final analysis with 1L RIB + ET over combo CT in pts with clinically aggressive HR+/HER2− ABC. As liver mets in ABC indicate a worse prognosis, an analysis by liver mets status was performed (data cutoff: May 10th, 2023). **Methods:** Pre- and perimenopausal women (N = 222) with no prior systemic therapy for clinically aggressive HR+/HER2− ABC were randomized 1:1 to receive RIB + letrozole or anastrozole + goserelin or physician's choice of combo CT. Enrolled pts had ABC for which combo CT was clinically indicated by physician's judgment. **Results:** In total, 107 (RIB + ET, n = 54; combo CT, n = 53) and 115 (RIB + ET, n = 58; combo CT, n = 57) pts presented with or without liver mets, respectively. Pts with liver mets had PFS of 18.3 vs 12.7 mo and median time to treatment failure (mTTF) of 13.2 vs 8.3 mo with RIB + ET vs combo CT, respectively (Table). A clinical benefit rate (CBR) of 77.8% vs 67.9%, overall response rate (ORR) of 64.8% vs 60.4%, and median time to response (mTTR) of 6.4 vs 3.0 mo were seen in the RIB vs CT arm, respectively. Pts without liver mets had PFS of 25.2 vs 15.4 mo and mTTF of 24.0 vs 10.1 mo in the RIB vs CT arm, respectively, and similar CBR, ORR, and TTR regardless of treatment (tx). No new safety signals were observed in pts with liver mets. A numerically longer median time to deterioration (mTTD) in FACT-B total score was seen with RIB + ET vs combo CT in pts with and without liver mets. **Conclusions:** This analysis from RIGHT Choice showed similar clinically meaningful efficacy and quality-of-life benefits and no new safety signals for RIB + ET vs combo CT between pts with and without liver mets. These results support the 1L use of RIB + ET in pts with clinically aggressive HR+/HER2− ABC even in the presence of liver mets. Clinical trial information: NCT03839823. Research Sponsor: Novartis Pharmaceuticals Corporation.

Liver mets	Tx arm	n	mPFS, mo (95% CI)	HR (95% CI)	mTTF, mo (95% CI)	HR (95% CI)	CBR[a], % (95% CI)	ORR[a], % (95% CI)	mTTR[a], mo (95% CI)	HR (95% CI)	mTTD (FACT-B total score)[b], mo	HR (95% CI)
Yes	RIB + ET	54	18.3 (10.3-24.0)	0.68 (0.42-1.11)	13.2 (10.2-21.2)	0.60 (0.39-0.92)	77.8 (64.4-88.0)	64.8 (50.6-77.3)	6.4 (4.6-23.9)	0.68 (0.42-1.10)	37.7	0.68 (0.34-1.34)
	Combo CT[c]	53	12.7 (7.5-21.0)		8.3 (5.3-12.8)		67.9 (53.7-80.1)	60.4 (46.0-73.5)	3.0 (2.6-6.7)		18.4	
No	RIB + ET	58	25.2 (18.6-NE)	0.57 (0.34-0.93)	24.0 (16.4-32.2)	0.44 (0.29-0.69)	84.5 (72.6-92.7)	67.2 (53.7-79.0)	4.6 (2.8-10.2)	0.81 (0.52-1.28)	NE	0.59 (0.29-1.21)
	Combo CT[c]	57	15.4 (8.8-20.0)		10.1 (7.8-13.6)		80.7 (68.1-90.0)	63.2 (49.3-75.6)	4.5 (1.4-8.2)		37.1	

NE, not evaluable.
[a]Without confirmation;
[b]≥7 point decrease;
[c]docetaxel + capecitabine, paclitaxel + gemcitabine, or capecitabine + vinorelbine.

Elacestrant (Ela) combinations with ribociclib (Ribo) and everolimus (Eve) in patients (pts) with ER+/HER2- locally advanced or metastatic breast cancer (mBC): Update from ELEVATE, a phase (Ph) 1b/2, open-label, umbrella study.

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Background: Progression of ER+/HER2- mBC on 1L endocrine therapy (ET) + CDK4/6i is associated with several mechanisms of resistance that impact efficacy and subsequent therapy. Treatment options include endocrine monotherapy, continuing ET+CDK4/6i, or PI3K/AKT/mTOR pathway–ET combination regimens. Acquired *ESR1* mutations emerge in up to 50% of patients and continuing SOC ET is limited by resistance to ET due to these mutations. Several trials have shown improved mPFS with the addition of Eve: 3.6-6.8 mo (Cook 2021, Vasseur 2024) or switch in CDK4/6i: 5.3 mo (Kalinsky 2023). In the Ph 3 EMERALD trial, single-agent Ela significantly improved PFS vs SOC ET (*ESR1*-mut tumors HR 0.55; 95% CI 0.39-0.77; P=0.0005; all pts HR 0.70; 95% CI 0.55-0.88; P=0.0018) with manageable safety in pts with ER+/HER2- mBC who had prior ET+CDK4/6i (Bidard 2022). This analysis reports updated safety and preliminary efficacy for Ela in combination with Ribo or Eve. **Methods:** ELEVATE evaluates Ela in combination with everolimus (Eve), alpelisib (Alp), capivasertib (Capi), ribociclib (Ribo), palbociclib (Palbo), or abemaciclib (Abema) to address different resistance mechanisms. Pts with ER+/HER2- mBC and 1-2L of prior ET are eligible regardless of *ESR1*-mut status. Objectives are to identify the RP2D (Ph 1b) and evaluate PFS (Ph 2) with each combination. **Results:** Elacestrant combinations with Ribo or Eve showed safety consistent with the known profiles of each drug + SOC ET. The most common AEs (≥30%) with Ela + Ribo (n=32) from Ph 1b were neutropenia (38%; 25% ≥Gr3) and nausea (31%; 0 ≥Gr3). The most common AEs for Ela + Eve (n=72) from Ph 1b + Ph 2 were nausea (54%; 6% ≥Gr3), diarrhea (43%; 7% ≥Gr3), stomatitis (38%; 3% ≥Gr3), and fatigue (32%; 6% ≥Gr3). Median PFS for Ela + Ribo was 7.2 months, while for Ela + Eve was 8.5 months. Table 1 summarizes mPFS from Ph 1b in efficacy-evaluable pts who received prior ET+CDK4/6i, as of Dec 2024. Updated data will be presented. **Conclusions:** Elacestrant plus Ribo or Eve demonstrates promising Ph 1b efficacy in pts with ER+/HER2- mBC with progressive disease after ET+CDK4/6i in all patients. Ela 345 mg + Ribo 400 mg QD was determined as the RP2D. Previously, Ela 345 mg + Eve 7.5 mg was identified as the RP2D. Elacestrant has the potential to become an ET backbone for various targeted agents, offering an all-oral treatment regimen in pts with ER+/HER2- mBC, delaying chemo or ADC-based regimens. Clinical trial information: NCT05563220. Research Sponsor: None.

Ph 1b mPFS in prior ET+CDK4/6i, efficacy-evaluable population.

	N	Ela (86-345 mg) + Ribo (400-600 mg)	N	Ela (258-345 mg) + Eve (5-10 mg)
mPFS, mo (95% CI)	32	7.2 (3.52 - 12.78)	22	8.5 (7.23 - 16.07)

Differential genomic landscape of estrogen receptor (ER)-low versus ER-positive (ER+) and ER-negative (ER-) metastatic breast cancer (MBC).

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Background: Guidelines define ER+ breast cancer (BC) as ≥1% tumor nuclei staining positive by IHC. Data on managing ER-low tumors (1–10% ER staining) is limited, with mixed evidence suggesting outcomes similar to ER- but a higher risk of death with adjuvant endocrine therapy (ET) omission. We aimed to examine the genomic landscape of ER-low MBC compared to ER+ and ER-. **Methods:** This retrospective study included consecutive patients (pts) with MBC who consented to clinicopathologic data collection and genomic profiling (OncoPanel) on tumor samples with matched ER IHC through the EMBRACE (Ending Metastatic Breast Cancer for Everyone) program. For multiple sequencing timepoints, the first was analyzed. SNVs, CNVs and TMB were compared among ER groups. Genes altered in > 3% of pts were analyzed for ER status association, with Benjamini-Hochberg adjusted $p < 0.2$ subjected to Holm-corrected pairwise testing. **Results:** Between 10/2000-12/2020, 1199 pts were identified:48 ER-low, 797 ER+, and 354 ER-. Median age at diagnosis was 63.8 (34.8-86.8), 64.4 (30.8-96.3), and 62.6 (30.3-92.7) years for ER-low, ER+, and ER- groups, respectively. De novo stage IV disease was observed in 8.3% (4/48) of ER-low, 27.0% (215/797) of ER+, and 17.2% (61/354) of ER- cases. Overall, 801/1199 (66.8%) had metastatic and 398/1199 (33.2%) had primary samples sequenced. 27/48 ER-low (56.3%), 451/797 ER+ (56.6%), and 73/354 ER- (20.6%) pts received ET before sequencing. CDK4/6i were administered in 8/48 ER-low (16.7%), 107/797 ER+ (13.4%), and 5/354 ER- (1.4%) pts prior to sequencing. The most clinically relevant genomic alterations are shown in the Table. *TP53* mutations (mts) were more frequent in ER-low vs ER+ BC, and not significantly different between ER-low and ER- tumors. *PIK3CA* and *CDH1* alterations were more frequent in ER-low than ER- BC, with no significant difference compared to ER+. *AKT1* and *RB1* alterations were significantly higher in ER-low vs ER+ BC. *ESR1* mts were not significantly different between ER+ and ER-low BC. Median TMB was higher in ER-low vs ER+ cases, without significant differences between ER-low and ER- cases. **Conclusions:** ER-low BC has a distinct genomic profile, with high *TP53* mts (similar to ER-) and frequent PI3K pathway alterations (typical of ER+). Ongoing analyses of clinicopathologic features and survival across ER-low, ER+, and ER- cohorts will be presented. Research Sponsor: Terri Brodeur Breast Cancer Foundation; The Benderson Family Fund; NIH/NCI grant; 1P50CA168504.

Characteristic	ER+ (N = 797)	ER-low (N = 48)	ER- (N = 354)	ER-low vs ER+ (p value)	ER-low vs ER- (p value)	ER+ vs ER- (p value)
TP53	24%	79%	83%	**1.45 x 10^-14**	0.689	**1.85 x 10^-79**
PIK3CA	39%	31%	13%	0.291	**0.00292**	**1.96 x 10^-21**
CDH1	19%	17%	3%	0.85	**0.00193**	**6.66x10^-14**
AKT1	2%	15%	4%	**0.0155**	**0.0155**	0.635
RB1	1%	12%	9%	**0.00354**	0.35	**0.000116**
PTEN	9%	10%	14%	0.828	0.828	0.828
ESR1	11%	6%	0%	0.612	**0.00322**	**3.06x10^12**
CCND1 **(CNV)**	17%	12%	3%	0.551	**0.0258**	**2.83 x 10^-11**
TMB, median (IQR)	6.844 (4.562)	8.365 (6.917)	7.604 (4.562)	**0.018**	0.212	**0.001**

Molecular and prognostic convergence of HR+/HER2− metastatic breast cancer (MBC) to a TNBC-like profile: Insights from circulating tumor DNA (ctDNA)-based genomic analysis across treatment lines.

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Background: While the transition to a triple negative (TNBC)-like profile represents a recognized mechanism of treatment resistance for hormone receptor-positive, HER2-negative (HR+/HER2-) MBC, the molecular mechanisms of this phenomenon remain largely unknown. This analysis investigated the genomic and prognostic differences between HR+/HER2− and TNBC across treatment lines through ctDNA profiling analysis **Methods:** This retrospective study analyzed a multi-institutional cohort of 1071 patients (pts) with HER2 negative MBC and ctDNA testing with the Guardant360 NGS panel within a large academic consortium (PMAC). HR and HER2 status were defined based on the most recent biopsy, pts with ER-low profile (ER < 10% regardless of PR status) were excluded. Associations across single nucleotide and copy number variations (SNVs and CNVs), HR+/HER2− and TNBC subtypes across treatment lines were tested by multinomial logistic regression (MLR) in terms of Relative Risk Ratio (RRR). The impact of prognosis was evaluated through Cox regression for overall survival (OS), defined from time of baseline ctDNA collection. **Results:** There were 827 pts with HR+/HER2- MBC (77.2%) and 244 pts with TNBC (22.8%). Multivariable MLR, designed with first line HR+/HER2- as the reference, investigated genomic alterations across treatment lines. In second line, *ESR1* SNVs (RRR 7.34, $p < 0.001$) and *EGFR* CNVs (RRR 0.15, $p = 0.01$) were significantly associated with HR+/HER2-, while *TP53* SNVs had a higher prevalence in TNBC (RRR 2.71, $p = 0.009$). In third line, *ESR1* SNVs were significantly enriched in HR+/HER2- (RRR 5.44, $p < 0.001$), while *TP53* SNVs emerged for TNBC (RRR 5.26, $p < 0.001$). From fourth line onward (≥ 4L), *ESR1* SNVs (RRR 8.09, $p < 0.001$), *TP53* SNVs (RRR 1.81, $p = 0.022$) and *PIK3CA* CNVs (RRR 5.93, $p = 0.003$) showed higher prevalence in HR+/HER2- relative to first line HR+/HER2-, while *TP53* SNVs were also associated with TNBC (RRR 10.43, $p < 0.001$). Compared to TNBC, HR+/HER2− had a favorable prognostic impact in terms of OS in first (HR 0.32, $p < 0.001$), second (HR 0.35, $p < 0.001$) and third line (HR 0.37, $p < 0.001$). However, in ≥ 4L, no significant differences emerged (HR 0.79, $p = 0.282$), with similar results observed with respect to TNBC across all lines (HR 1.01, $p = 0.929$). *MYC* CNVs had an unfavorable prognostic role for both HR+/HER2− ≥4L (HR 2.41, $p = 0.004$) and TNBC in all lines (HR 2.14, $p = 0.014$). **Conclusions:** Our study suggests a dynamic molecular evolution of HR+/HER2− MBC, with a progressive acquisition of molecular and prognostic features compatible with a TNBC-like profile and loss of endocrine sensitivity. These findings highlight the need for comprehensive biological characterization of this subtype across treatment lines to better understand its evolution under therapeutic pressure and consequently adapt treatments. Research Sponsor: None.

Ultrasensitive ctDNA monitoring during CDK4/6 inhibitor therapy for metastatic breast cancer.

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Background: The combination of CDK4/6 inhibitor (CDK4/6i) and endocrine therapy (ET) is the standard first-line treatment for patients with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). However, it exhibits highly variable efficacy, with some cancers progressing within 3–6 months while many others achieve durable and potentially indefinite complete responses (CRs). While pharmacologic strategies to escalate or deescalate this therapy exist, diagnostic tools to identify the patients who would benefit from each approach are needed. Ultrasenstive ctDNA offers the potential to assess disease burden dynamically and with more precision. In this study, we evaluate the validity of an ultrasensitive assay capable of detecting ctDNA levels in the parts per million range for monitoring patients with HR+/HER2- MBC. **Methods:** Patients from the MSK-LINC prospective ctDNA monitoring study, who received CDK4/6i+ET for HR+/HER2- MBC were included in the study. MRD monitoring was performed using personalized tumor-informed panels designed from whole genome sequencing (WGS) of matched tumor and normal specimens to identify up to 2,000 somatic alterations for each patient using the Precise MRD assay (Myriad Genetics). Results were reported as an overall ctDNA detection status and a quantitative tumor fraction. **Results:** 29 patients with HR+/HER2- MBC (8 *de novo*, 21 recurrent) were included in this ongoing study. The median progression-free survival (PFS) was 48.8 months (range 2.6 – 78.5) with 17/29 of patients experiencing disease progression. ctDNA panels were successfully designed for all cases, and 140/146 (95.9%) plasma samples passed QC. All pre-treatment samples had detectable ctDNA with a median tumor fraction of 1.4% (range 0.00093%, 14.0%). An early decrease in ctDNA levels, $>$ 50% reduction from baseline or levels $<$ 0.01% in the second sample collected within 3 months, was significantly associated with longer PFS ($p < 0.001$). We focused on 7 patients who achieved radiographic CR all with PFS $>$ 3y. Notably, 3 patients had continued to have ultra low levels of ctDNA (median: 0.0086%, range 0.00032%, 0.11%), indicating stable viable micrometastatic disease below the threshold of imaging, effectively controlled by treatment. In contrast, 4 patients also achieved molecular CR (mCR) defined as sustained undetectable ctDNA suggesting that metastatic disease was either eradicated or rendered dormant without significant cell turnover. **Conclusions:** Ultrasensitive ctDNA monitoring is a promising tool for monitoring disease burden and treatment response. Our results highlight the ability of ctDNA to distinguish between stable molecular disease vs. mCR, highlighting the potential of ctDNA as a biomarker for tailoring treatment strategies in patients who achieve outstanding clinical responses. Research Sponsor: Myriad Genetics, Inc.; Susan G. Komen.

Effectiveness comparison of palbociclib, ribociclib and abemaciclib in patients with HR+/HER2- aBC: Updated results from the real-world, Italian study PALMARES-2.

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Background: The Cyclin Dependent Kinase 4/6 inhibitors (CDK4/6i) Palbociclib (P), Ribociclib (R) and Abemaciclib (A) combined with Endocrine Therapy (ET) are the standard 1st line therapy for patients (pts) with Hormone Receptor positive, Human Epidermal growth factor Receptor 2-negative, advanced Breast Cancer (HR+/HER2- aBC). However, based on conflicting results of large real-world (RW) studies (Vernieri C et al. Abstr 1014, ASCO 2024; Rugo H et al. PS2-03, SABCS 2024), it remains unclear whether P, R and A are similarly effective. **Methods:** PALMARES-2 is a multicenter, observational Italian RW study comparing the effectiveness of 1st line P, R or A in female pts with HR+/HER2- aBC. The primary endpoint is overall survival (OS); RW progression-free survival (rwPFS) and time to chemotherapy (TTC) are secondary endpoints. rwPFS, TTC and OS were defined as the time between 1st line ET+CDK4/6i initiation and disease progression/death, initiation of 1st chemotherapy line/death, or patient death, respectively. We used Inverse Probability of Treatment Weighting (IPTW) to balance 14 prognostic covariates related to patients (age, ECOG PS, menopausal status), tumor biology (ER, PgR, HER2, Ki67, grading, histology, endocrine sensitivity/resistance/*de novo* metastatic) and metastatic sites (liver, bone, lung, serosal) in P, R and A cohorts. Effectiveness comparisons were reported as adjusted Hazard Ratio (aHR) and 95% confidence interval (CI). **Results:** With a cutoff date of Jan 10th, 2025, we enrolled 3598 pts, of whom 1392 (38.7%), 1408 (39.1%) or 798 (22.2%) received P, R or A, respectively. Pts receiving A were more likely to have endocrine-resistant disease, liver metastases and lower PgR expression, and less likely to have *de novo* metastatic disease ($p < 0.001$). Median follow-up was shorter in R/A cohorts (31.8/29.6 months) than in the P cohort (52.4 months). Median rwPFS, TTC and OS in the whole population were 26.1, 39.4 and 67.1 months, respectively. After IPTW adjustment, R and A were associated with better rwPFS and TTC when compared to P, while only R was associated with better OS (Table). R and A did not show significant rwPTS, TTC or OS differences (Table). **Conclusions:** The three CDK4/6i have different effectiveness in HR+/HER2- aBC pts. Longer follow-up of PALMARES-2 study and more pts/events in the A cohort are needed to perform definitive OS comparisons between P, R and A. Research Sponsor: None.

	P (N = 1392) N° events (%)	R (N = 1408) N° events (%)	A (N = 798) N° events (%)
rwPFS	992 (71.2%)	711 (50.5%)	418 (52.4%)
TTC	845 (60.7%)	516 (36.6%)	332 (41.6%)
OS	586 (42.1%)	270 (19.2%)	189 (23.7%)
	R vs P: aHR (95% CI; *P*)	**A vs P: aHR (95% CI; *P*)**	**A vs R: aHR (95% CI; *P*)**
rwPFS	0.88 (0.80-0.97; 0.02)	0.88 (0.77-0.99; 0.04)	0.99 (0.87-1.13; 0.91)
TTC	0.83 (0.74-0.94; <0.01)	0.86 (0.75-0.99; 0.04)	1.04 (0.89-1.20; 0.65)
OS	0.75 (0.64-0.87; <0.01)	0.91 (0.76-1.09; 0.3)	1.21 (0.99-1.49; 0.06)

Use of baseline plasma circulating tumor DNA (ctDNA) to predict duration of endocrine therapy (ET) and CDK4/6 inhibitor (CDK4/6i) therapy (tx) and to analyze intrinsic vs acquired endocrine resistance.

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Background: ET + CDK4/6i is standard-of-care for patients (pts) with hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC). We aimed to identify predictors ET + CDK4/6i tx duration and to compare genomic profiles in pts with intrinsic vs acquired resistance. **Methods:** Plasma samples were collected from pts with HR+/HER2- MBC enrolled in the EMBRACE cohort study who had plasma collection within 3 months (mo) prior to CDK4/6i initiation to 14 days after initiation. The primary outcome was duration of ET+CDK4/6i tx, defined as time from tx initiation to end of tx. Intrinsic resistance was defined as pts with tx duration $<$ 180 days. Plasma samples were analyzed using the Guardant360 assay, which includes genotyping of $>$ 700 genes and tumor fraction (TF) score. TF was estimated by normalizing cancer-specific differentially methylated regions with matched control regions in each sample. The predictive value of baseline TF (0 vs $>$ 0) was tested using a Cox regression model including age, line of tx, and liver metastases. For comparison of pts with intrinsic vs acquired resistance, analysis was limited to samples with TF $>$1% to minimize the impact of variation in tumor shed. Gene frequency between intrinsic and acquired resistance samples were compared using q-tests($q < 0.25$). **Results:** A total of 188 pts were included. Median age at MBC diagnosis was 57.5 yrs. ET+CDK4/6i was given in the first-line (1L) in 115 pts, second-line (2L) in 37 pts, and $>$ 2L in 36 pts. Of 167 pts, TF was undetectable (TF = 0) in 19 (11%) and detectable (TF $>$ 0) in 148 (89%). In Cox regression, baseline TF ($p = 0.001$), line of tx ($n = 0.002$), and presence of liver metastasis ($p = 0.014$), but not age, were predictors of duration of tx. Median duration of tx was 44.6 mo in pts with baseline TF = 0 vs. 5.8 mo in pts with baseline TF $>$ 0 (HR 0.28, 95% CI 0.14-0.56). Similar results were found when restricting the analysis to those receiving tx in the 1L or 2L. There were notable differences in the frequency of ESR1 (63% vs 48%), CDH1 (38% vs 18%), PTEN (21% vs 9%), RB1 (32% vs 20%), and CDKN2A (20% vs 5%) alterations in pts with intrinsic vs acquired resistance, though these did not reach statistical significance in the setting of small sample size. ESR1 fusions were seen in 14% (8/56) pts with intrinsic resistance vs 7% (3/44) pts with acquired resistance. Among pts with intrinsic resistance, ERBB2 copy number loss was present in 7(13%) (6 het loss, 1 homozygous deletion), RB1 copy number loss in 10 (18%) (all het loss), and CDKN2A copy number loss in 9(16%) (7 het loss, 2 homozygous deletions). **Conclusions:** Baseline TF in ctDNA is highly predictive of time on ET+CDK4/6i tx in pts with HR+/HER2- MBC. Baseline genomic profiles differ qualitatively between pts with intrinsic vs acquired resistance. If validated, baseline plasma may provide a valuable tool in tx selection. Research Sponsor: Guardant Health; Breast Cancer Research Foundation; Saverin Breast Cancer Research Fund; Pan Mass Challenge; NCCN-Pfizer Collaborative Grant.

Comparing clinical benefit of trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in a large cohort of HER2-negative metastatic breast cancer (MBC).

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Background: T-DXd and SG are antibody-drug conjugates (ADCs) increasingly used in HER2-negative BC, however, there are insufficient data to guide ADC sequencing and use in tumors of various HER2 expression levels. **Methods:** A total of 4033 HER2 negative MBC treated with SG or T-DXd that underwent tumor profiling at Caris Life Sciences (Phoenix, AZ) were studied. HER2 low (Her2-L), ultra low (Her2-UL) and null (Her2-N) were tested by IHC and CISH. Hormone receptor status (HR+/-) was tested by ER and PR IHC. Real-world clinical data were obtained from insurance claims. Time on treatment (TOT) was determined as the interval from start to end of the ADCs. Cox proportional hazards model was used for hazard ratio (HR) and log-rank for p values. **Results:** Overall, 1444 (36%) were treated with T-DXd but not SG (T-only) while 1808 (45%) with SG but not T-DXd (S-only). HR+ cases comprise 64% of T-only and 24% of S-only cohorts; 75% and 68% of T-only and S-only tumors were taken from metastatic sites. As expected, HER2-L, HER2-UL and HER2-N cohorts treated with T-DXd had decreased TOT (4.8 months (m), 4.1m and 3.5m, p< .001) while HER2 status had no impact on SG TOT (3.0m, 2.8m and 3.4m). Interestingly, even in HER2-N group, T-only showed a borderline better TOT than S-only (Table, p=.053); this effect was significant in HR+ HER2-N subset but not significant in HR-HER2-N. Similarly, in HER2-UL and L, T-DXd TOT was significantly longer than SG TOT; when further stratified by HR status, the effect was highly significant in HR+ and not seen in HR- cohorts. In cohorts crossed over from one ADC to another, patients treated with T-DXd first (N=420) or SG first (N=361) showed no TOT difference (10.4m vs. 10.8m, p= .4); although the HER2-N subset had moderate preference of SG first (11.5m vs. 8.5m, HR=0.66 [0.52-0.84], p< .001, while TOT were similar in HER2-UL (HR=0.93, p=.7) and HER2-L (HR=1.04, p=.7) groups. **Conclusions:** We report outcome from a large real world dataset and demonstrate that T-DXd shows statically significant improved outcome in HR+ tumors across HER2 subgroups while in TNBC, both agents exhibit comparable benefit. In patients treated with both ADC's, SG first showed preferred outcome in HER2-N group but not in HER2-UL or L. We provide important insight on clinical benefit of the two widely used ADCs in breast cancer and warrants further validation in independent cohorts. Research Sponsor: None.

T-DXd (T-only) TOT and SG TOT (S-only) in cohorts stratified by HER2 and HR status.

	All				HR+				HR-			
	TOT (T;S, months)	N (T;S)	HR [95% CI]	p	TOT	N	HR	p	TOT	N	HR	p
HER2-N	4.7; 3.4	262; 1116	1.1 [1-1.3]	0.053	4.8; 3.0	209; 277	1.5 [1.2-1.8]	**<0.001***	4.6; 3.5	48; 822	1.1 [0.8-1.4]	0.6
HER2-UL	4.8; 3.0	295; 289	1.4 [1.2-1.7]	**<0.001***	5.1; 2.5	245; 99	1.8 [1.4-2.2]	**<0.001***	3.2; 3.0	46; 188	1.1 [0.8-1.6]	0.4
HER2-L	4.9; 3.5	707; 244	1.2 [1-1.4]	**0.011***	5.1; 3.1	595; 77	1.5 [1.2-1.9]	**<0.001***	4.2; 3.9	100, 164	1.1 [0.8-1.3]	0.7

*:Significant.

Steroid receptor expression and overall survival in breast cancer patients with ER+ bone metastasis: A retrospective review.

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Background: Endocrine therapy (ET) resistance is common in estrogen receptor-positive (ER+) metastatic breast cancer (BC), where bone metastases (BMET) are usually the first sign of spread. ER signaling and ET effects can depend on other steroid hormones receptors (SHRs), such as progesterone receptors (PR) and androgen receptors (AR). However, the roles of these receptors in ER+ BC BMET are underexplored. To address this gap, PR and AR protein expression in HER2-/ER+ BMET and associations with overall survival (OS) were examined. **Methods:** In a retrospective analysis on BC BMET samples analyzed at Caris Life Sciences, n = 2038 HER2- BMETS were identified by immunohistochemistry (IHC) (≤1+intensity or ≤10% staining, or 2+ & > 10% with CISH-null reflex test). HER2- ER+ (by IHC, ≥1+ & ≥1%) BMETs ("ER+ BMET" n = 1700; 84.5% of total) were then examined for prevalence of IHC+ SHR expression (PR: ≥1+ & ≥1%; AR: ≥1+ & ≥10%) and associated pathogenic/likely pathogenic *ESR1* or *PIK3CA*gene mutations (mut). Associations of SHR status with clinical outcomes were tested by inferring OS from biopsy collection or start of therapy to last contact. **Results:** Most ER+ BMET expressed PR (59.3%) or AR (87.1%). Only 9.4% of PR+/ER+ BMET were AR-null, while 38.2% of AR+/ER+ BMET were PR-null. Overall, "triple positive" (AR+/PR+/ER+) BMET comprised the largest group (53.7%), followed by PR-null AR+/ER+ BMET (33.2%). AR-null ER+ BMET with (5.6%) or without PR (7.3%) were less common. AR+ status was associated with better outcomes for ER+ BMET patients (pts) with longest OS for "triple positive", while "loss" of PR was associated with shorter OS (Cox proportional hazards ratio (HR) = 1.37, $p < 0.0001$). AR-null status was associated with worse OS compared to "triple positive" regardless of PR status (AR-/PR- HR = 1.66, $p < 0.001$; AR-/PR+ HR = 1.85, $p < 0.0001$). In ER+ BMET with *ESR1mut* (16.3%), OS for triple positive tumors, which were more prevalent (74.0%) due to increased PR expression, was reduced (HR = 1.92, $p < 0.0001$ vs *ESR1wt*). For *PIK3CA*, "loss" of PR abrogates benefits associated with AR+ status only in *PIK3CAmut* pts (48.7%) with patterns between SHR groups otherwise maintained. Among ER+ BMET pts who received aromatase inhibitors or fulvestrant, AR+ status was associated with the best OS, regardless of PR status, where treatment was associated with significantly longer OS (vs no treatment) across SHR groups, except in PR+/AR-null. For ER+ BMET pts treated with CDK4/6 inhibitors, OS was highest in the "triple positive" cohort, with onlyAR+ SHR groups demonstrating improved OS with treatment. **Conclusions:** Based on this analysis, AR expression is more prognostic of OS than PR, regardless of treatment, in pts with ER+ BC BMETs, with "triple positive" BMETs generally associated with the best OS. Research on SHRs as mediators vs biomarkers of risk in ER+ BC BMETs is needed to provide direction for possible therapeutic targeting. Research Sponsor: None.

Evaluating accuracy and concordance of pathologists and the utility of AI assistance software for digital HER2 IHC assessment in breast cancer including HER2-ultralow scoring: An international multicenter observational study.

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Background: The emergence of novel therapeutic agents demonstrating improved progression-free survival (PFS) and overall survival (OS) in breast cancer patients with low HER2 expression underscores the need for accurate and reproducible HER2 status assessment. However, challenges such as subjective interpretation of immunohistochemistry (IHC) staining and variability in assay quality hinder diagnostic consistency. AI-based decision support software could enhance diagnostic accuracy and reproducibility. To date, systematic evaluation of pathologist performance in scoring low HER2 expression, as well as the role of AI assistance, remains limited in real-world, multicenter settings. **Methods:** Six academic centers from different countries provided digital HER2 IHC-stained breast cancer images (n = 728) generated with five whole-slide scanner models and one microscope camera. In a two-arm observational study, consensus ground truth (GT) scores were established by two expert pathologists per center without AI assistance. Subsequently, two additional pathologists (scorers) evaluated each case both without and with AI support. Scoring followed ASCO/CAP 2023 HER2 interpretation guidelines, with an additional subclassification of IHC 0 cases into "null" (IHC 0 with no staining) and "ultralow" (IHC 0 with membrane staining). **Results:** For the HER2-low decision range, AI software alone achieved 91.0% accuracy in distinguishing HER2 0 from 1+/2+/3+ scores against GT. Across the four categories, AI achieved 80.3% accuracy compared to 77.6% for scorers alone and 81.4% with AI assistance. AI support improved inter-reader agreement from 73.5% to 86.4%. When the HER2 ultralow category was included, AI assistance increased scorers' average accuracy across all classes from 70.4% to 74.7% and boosted inter-reader agreement from 65.6% to 80.6%. For differentiating HER2 null from HER2 ultralow, AI improved scorers' accuracy from 68.6% to 77.9%, resulting in 40% more cases being classified as HER2 ultralow and 65% reduction in the number of incorrectly scored HER2 null cases. **Conclusions:** This first international multicenter study on HER2 IHC diagnosis, including HER2 ultralow scoring highlights the challenges faced by pathologists and the significant benefits of AI decision-support systems in real-world settings. AI assistance improved pathologist concordance and accuracy, particularly at the HER2 null vs. ultralow boundary, reducing diagnostic errors. Incorporating AI into routine clinical diagnostics has the potential to optimize treatment selection for breast cancer patients. Research Sponsor: AstraZeneca.

Elacestrant combinations in patients (pts) with ER+/HER2- locally advanced or metastatic breast cancer (mBC): Safety update from ELEVATE, a phase (Ph) 1b/2, open-label, umbrella study.

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Background: Tumors develop resistance following 1L endocrine therapy (ET) + CDK4/6i in ER+/HER2- mBC. Elacestrant (Ela) significantly improved PFS vs standard-of-care (SOC) ET (*ESR1*-mut tumors HR 0.55; 95% CI 0.39-0.77; P=0.0005; all pts HR 0.70; 95% CI 0.55-0.88; P=0.0018) with a manageable safety profile for pts with ER+/HER2- mBC and prior ET+CDK4/6i (Bidard 2022). ELEVATE (NCT05563220) evaluates Ela in combination with everolimus (Eve), alpelisib (Alp), capivasertib (Capi), ribociclib (Ribo), palbociclib (Palbo), or abemaciclib (Abema) to address different resistance mechanisms. Prior analyses have demonstrated safety consistent with the known profiles of each agent in combination with SOC ET. Ph 1b safety and efficacy evaluations reported the RP2D and antitumor activity with the following combinations: Ela + Eve (RP2D: Ela 345 mg QD + Eve 7.5 mg QD) and Ela + Abema (RP2D: Ela 345 mg QD + Abema 150 mg BID)(Ciruelos ESMO 2024, Rugo ESMO 2024). Ela 345 mg + Palbo 125 mg was determined as the RP2D (Rugo SABCS 2024). Herein, we report updated safety that includes additional pts/dose levels, and longer observation time for Ela in different combinations. **Methods:** Eligible pts have ER+/HER2- mBC and 1-2L of prior ET regardless of *ESR1*-mut status. Objectives are to determine the RP2D (Ph 1b) and evaluate PFS (Ph 2) with each combination. **Results:** Table 1 reports the most common all-grade AEs from Ph 1b (Ribo, Alp, Capi combinations) and Ph 1b + Ph 2 (Eve combination) as of Dec 2024. Ela 345 mg + Ribo 400 mg QD was identified as the RP2D. Updated data will be presented. **Conclusions:** Elacestrant combinations continue to demonstrate safety consistent with the known profiles of each drug + SOC ET without increased risk of associated AEs. Elacestrant has the potential to become an ET backbone for multiple targeted agents, providing an all-oral treatment option in pts with ER+/HER2- mBC, delaying chemo or ADC-based regimens. Clinical trial information: NCT05563220. Research Sponsor: None.

Treatment-emergent AEs (≥30%).

	Ph 1B Ela (86-345 mg) + Ribo (400-600 mg) (n=32)	Ph 1B + Ph 2 Ela (258-345 mg) + Eve (5-10 mg) (n=72)	Ph 1B Ela (258 mg) + Alp (150-250 mg) (n=11)	Ph 1B Ela (258-345 mg) + Capi (320 mg) (n=9)
All grades, n (%)	Neutropenia* 12 (38) Nausea 10 (31)	Nausea 39 (54) Diarrhea 31 (43) Stomatitis 27 (38) Fatigue 23 (32)	Nausea 8 (73) Vomiting 6 (55) Rash† 4 (36)	Nausea 6 (67) Fatigue 5 (56) Diarrhea 5 (56) Vomiting 3 (33)
Grade ≥3, n (%)	Neutropenia* 8 (25)	Diarrhea 5 (7) Nausea 4 (6) Fatigue 4 (6) Stomatitis 2 (3)	Rash† 2 (18) Nausea 1 (9)	0

*Combined terms;
†Maculopapular rash.

Enhancing precision oncology for Haitian breast cancer patients through deep learning-enabled computational pathology tools.

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Background: While early-stage breast cancer is often curable in high-resource settings, mortality-to-incidence ratios remain unacceptably high for women in lower- and middle-income countries (LMIC). This disparity is due to an inability within LMICs for patients to access basic cancer diagnostics (e.g., IHC). Consequently, there is a major need to develop innovative approaches for the cancer diagnostic-therapeutic pipeline to deliver high-quality care for LMIC patients. To this end, deep learning (DL) has shown considerable promise in identifying clinically relevant biology within histopathology (H&E). Therefore, we have curated an unprecedented dataset of H&E whole slide images (WSIs) and tissue-matched estrogen receptor (ER) status for 5500 breast cancer slides from Zanmi Lasante (Haiti). **Methods:** Using The Cancer Genome Atlas (TCGA) breast cancer and Haitian datasets, we trained a DL-enabled tool, using H&E WSIs, to predict ER status for each patient. As the TCGA dataset predominantly comprises patients of European ancestry, we assessed whether a TCGA-trained model would generalize to Haitian patients. After WSI processing and feature extraction, attention-based weakly supervised multiple instance learning was used to train a classification model. To assess performance, both the TCGA and Zanmi Lasante datasets were split into training (70%), validation (15%), and testing (15%) sets, and the results were compared across both patient populations. **Results:** Using the TCGA dataset (2100 H&E WSIs), we trained an ER classification model. This model demonstrated a performance of an area under receiver operating characteristic (AUROC) of 0.92 on the "held-out" TCGA test set, but only an AUROC of 0.71 on the Haitian "held-out" test set for ER status prediction. This drop in model performance, or domain shift, is consistent with known biological differences between breast cancers enriched in Black women compared to those in Caucasian women. Notably, pre-training our model on the TCGA dataset and then fine-tuning on a portion of the Haitian training set (2800 WSIs) substantially improved predictive performance to an AUROC of 0.85 on the Haiti test set. **Conclusions:** This study illustrates the potential of DL to advance precision oncology in low-resource settings and highlights the need for adequate training data from LMIC patients. We anticipate tools from this work will be deployed for use in Haitian breast cancer patients to inform precision-based use of endocrine therapies. Research Sponsor: None.

Cell-free circulating chromatin profiling for epigenomic characterization of mechanisms of response and resistance to sacituzumab govitecan in breast cancer.

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Background: The efficacy of sacituzumab govitecan (SG), a TROP2-directed antibody-drug conjugate (ADC), in hormone receptor-positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC) has been demonstrated, yet biomarkers predicting response and resistance remain an unmet clinical need. We applied a novel multimodal epigenomic liquid biopsy assay to characterize tumor-specific transcriptional activation of relevant genes of interest and resistance mechanisms in the phase 2 SACI-IO HR+ trial (NCT04448886). **Methods:** Baseline plasma samples were collected from patients (pts) with HR+/HER2- mBC enrolled in SACI-IO HR+, which compared SG alone to SG combined with pembrolizumab (SG-pembro). Genome-wide signals from promoters, enhancers and DNA methylation were profiled from 1 mL of plasma from 95 pts, of which 80 met the assay quality control thresholds and ctDNA metrics required for downstream analysis (ctDNA $\geq$ 0.5%, N_{SG}= 42, $N_{SG-pembro}$= 38). We used epigenomic and RNA-seq datasets from 23 breast cancer cell lines to train a model to predict *TROP2* expression ($r = 0.66$, $P < 0.01$) and tested for association with progression free survival (PFS). We used Gene Set Variation Analysis to score samples for HALLMARK gene set activities using gene-proximal epigenomic signals and tested for independent association of those activities with PFS via CoxPH models, with baseline ctDNA fraction included as a known prognostic covariate. Statistical significance was determined based on improved model fit compared to ctDNA alone. **Results:** Compared to healthy donors, plasma from trial pts was enriched for breast cancer specific signatures such as estrogen response and hedgehog signaling (FDR $<$ 0.05), highlighting the ability of the liquid biopsy platform to extract tumor specific signal. Baseline ctDNA fraction was prognostic in both treatment arms (Hazard Ratio $[HR]_{SG}$= 0.38, $P <$ 0.01; $HR_{SG-pembro}$= 0.28, $P < 0.01$). Conversely, predicted *TROP2* expression was not associated with PFS in either treatment arm. In the SG arm, higher activity of pathways such as epithelial to mesenchymal transition and Wnt signaling were associated with shorter PFS (FDR $<$ 0.1), highlighting potential mechanisms of resistance. Gene signatures related to cell cycle such as mitotic spindle and E2F targets were associated with longer PFS (FDR $<$ 0.1). The above pathway associations with PFS were not statistically significant in the SG-pembro arm. **Conclusions:** This study demonstrates the feasibility of a multimodal epigenomic liquid biopsy platform for non-invasive characterization of therapeutic response and resistance to SG with or without pembrolizumab in HR+/HER2- mBC. By providing real-time insight into transcriptional regulation, this approach may improve patient stratification and guide ADC treatment strategies. Clinical trial information: NCT04448886. Research Sponsor: Gilead Sciences; Merck; Komen; METAvivor; Gateway for Cancer Research; Mehlman Family Fund.

Treatment patterns in HR+/HER2- metastatic breast cancer (MBC) with co-occurring *PIK3CA* and *ESR1* mutations.

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Background: *PIK3CA* and *ESR1* mutations co-occur in 12-15% of patients with HR+/HER2- MBC. While FDA-approved PI3K inhibitors (PI3Ki) and selective estrogen receptor degraders (SERDs) have advanced care for patients with biomarkers, treatment outcomes and optimal sequencing in those with co-occurring mutations remain unclear. **Methods:** We conducted a retrospective analysis of patients with HR+/HER2- MBC and co-occurring *PIK3CA* and *ESR1* mutations treated at Memorial Sloan Kettering (MSK) between 2010 and 2024. Mutations were identified via MSK-IMPACT (tumor tissue) and MSK-ACCESS (ctDNA), with additional genomic data integrated from Guardant and Foundation One. Clinical and treatment data, including PI3Ki (alpelisib, inavolisib or investigational agents) and/or SERDs (fulvestrant or oral agents) were abstracted. Median progression-free survival (mPFS) was assessed in patients with mutations identified prior to therapy initiation. **Results:** 3,166 patients with HR+/HER2- MBC were identified, including 1,444 (46%) with *PIK3CA* mutations, 664 (21%) with *ESR1* mutations and 243 (8%) with co-occurring mutations. After excluding 26 patients with incomplete records or concurrent malignancies, the final cohort included 217 patients (7%), with 206 having MSK-IMPACT, 58 MSK-ACCESS, 49 Guardant, and 3 FoundationOne data. Of 217 patients, 77 (36%) received a PI3Ki after a median of 4 prior lines (range: 1–16), with 68 (88%) having prior CDK 4/6i. Single-agent SERD was administered to 46 patients (21%) after a median of 3 prior lines (range: 2–18), including 34 (74%) with prior CDK 4/6i. 8 patients received PI3Ki followed by SERD, and 7 received SERD followed by PI3Ki, either consecutively or with intervening treatments. The mPFS was 7.1 m with PI3Ki (95% CI: 4.6–9.3) and 4.0 m with single-agent SERD (95% CI: 3.4–9.8). In the SERD cohort, earlier line of treatment (1–2 vs. 3+; HR 0.29, 95% CI 0.09–0.90) and liver metastasis (HR 3.42, 95% CI 1.10–10.6) were independently associated with PFS. CDK 4/6i duration ≥12 m in the SERD cohort was associated with improved mPFS in stratified analysis (9.8 vs. 2.7 m; log-rank p = 0.002). For patients treated with PI3Ki followed by SERD (n = 8), mPFS1 was 8.9 m (95% CI: 5.6, NE) and mPFS2 was 6.0 m (95% CI: 2.3, NE). SERD to PI3Ki (n = 7) yielded a mPFS1 of 3.4 m (95% CI: 1.8, NE) and mPFS2 of 10.0 m (95% CI: 1.6, NE). **Conclusions:** Prior CDK4/6i ≥ 12 m in patients with co-occurring mutations treated with a SERD was associated with significantly improved PFS, potentially reflecting a conditioning effect of prior therapy. The total PFS (PFS1 + PFS2) in patients treated with sequential targeted therapies was similar; however, small sample sizes and potential confounders in this retrospective cohort limit definitive interpretations. Larger prospective studies are needed to determine optimal sequencing strategies. Research Sponsor: None.

Targeting PARP-1 in ER-positive endocrine-resistant breast cancer.

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Background: Resistance to endocrine therapy (ET) in breast cancer (BC) patients is frequently associated with acquired ESR1 gene mutations like the Y537S, which triggers a constitutive estrogen receptor (ERα) activation. Therefore, the identification of novel therapeutic strategies is crucial for the management of ER-positive, ET-resistant BC. In this context, PARP1 poly(-ADP-ribose) polymerase 1 (PARP-1) has emerged as a promising therapeutic target, based on its involvement in the regulation of oxidative DNA damage in BC cells. **Methods:** Data from the METABRIC dataset were used to assess the clinical relevance of PARP-1 in ER-positive BC patients. As experimental models, MCF7 and T47D BC cell lines expressing ERα wild type (wt) or Y537S mutation were used. PARP-1 regulation was investigated by western blotting, immunofluorescence, and chromatin immunoprecipitation (ChIP) assays. Gene expression, promoter assays, and chromatin immunoprecipitation sequencing (ChIP-seq) studies allowed us to analyze the transcriptional activity mediated by ERα. Cell cycle, proliferation and colony formation experiments as well as *in vivo* studies were performed to evaluate the biological effects of the PARP-1 inhibitor niraparib. **Results:** We observed that the up-regulation of PARP-1 upon exposure to 17β-estradiol (E_2) occurs through ERα in BC cells expressing either ERα wt or Y537S mutation. Moreover, we assessed that the transcriptional activity of ERα relies on PARP-1, as demonstrated by the ability of nirabarib to prevent the transactivation of ERα and the regulation of ERα target genes. In addition, niraparib halted the proliferation and cycle progression of BC cells expressing either ERα wt or Y537S mutation. Of note, niraparib suppressed primary tumor growth in xenograft tumors derived from ERα Y537S mutated MCF7 cells. **Conclusions:** Our data suggest that crosstalk between PARP-1 and ERα is involved in the proliferative responses of ERα wt or Y537S mutated BC cells. Therefore, targeting PARP-1 could provide a promising strategy to overcome the ET resistance of BC cells. Research Sponsor: None.

Racial and ethnic differences in biomarker testing for targetable alterations among patients with HR+ HER2- metastatic breast cancer (mBC).

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Background: In recent years novel therapies have been approved for patients (pts) with mBC and *ESR1*, *AKT1*, *PTEN*, *PIK3CA*, and *gBRCA* alterations. Given limited evidence on which patients are receiving standard of care, this study assessed racial and ethnic inequities in biomarker testing and the role of social determinants of health (SDOH) in explaining potential inequities. **Methods:** This study leveraged the US nationwide Flatiron Health electronic health record (EHR)-derived, deidentified database of > 750 000 pts with BC. Adult female pts diagnosed (dx) with HR+ HER2- mBC between 1/1/2011, and 4/30/2024, with a geocodeable address were included. Testing rates for alterations in *ESR1*, *PIK3CA*, *AKT1*, *PTEN*, and *gBRCA* were measured over time from mBC dx using variables extracted from unstructured clinician documentation in the EHR using machine learning. Fine and Grey models accounting for competing risks were used to estimate subdistribution hazard ratios (HR) and 95% confidence intervals (CI) for biomarker access. Models were adjusted for covariates including age, stage, ECOG status, and dx year, followed by practice setting and area-level SDOH factors (ie, English language proficiency, residential segregation, vehicle ownership, urbanicity, and residence in medically underserved areas). **Results:** The cohort included 36 316 pts (61.5% non-Latinx [NL]-White, 6.1% Latinx, 9.7% NL-Black, 1.9% NL-Asian, and 20.8% NL-Other/Unknown). Overall, Asian, Black, and Latinx pts were less likely than White pts to undergo biomarker testing (adjusted HR [95% CI]: Latinx, 0.88 [0.82-0.95]; NL-Black, 0.87 [0.82-0.93]; NL-Asian, 0.87 [0.76-0.98]). Racial/ethnic inequities in overall biomarker testing were partially explained by SDOH factors. Specifically, the White-Latinx inequity in testing was mediated by residential segregation ie, association attenuated towards the null (mediated HR [95% CI], 0.94 [0.87-1.02]), limited English proficiency (0.92 [0.85-1.00]), and lack of vehicle ownership (0.91 [0.84-0.98]). Compared with White pts, NL-Black pts were less likely to be tested for *ESR1* (HR [95% CI], 0.86 [0.77-0.95]) and *PIK3CA* (0.86 [0.80-0.92]). Latinx pts were less likely to be tested for *PIK3CA* (0.87 [0.80-0.95]) and this inequity was mediated by residential segregation (0.96 [0.87-1.05]) and limited English proficiency (0.92 [0.84-1.00]). **Conclusions:** Asian, Black, and Latinx pts were generally less likely than their White counterparts to receive biomarker testing after a mBC dx, especially for *PIK3CA* and *ESR1*. SDOH factors explained some of these biomarker testing inequities. Equitable access to biomarker testing should be prioritized to ensure patients have access to the most effective therapies. Future research should examine whether racial/ethnic inequities in biomarker testing are associated with inequities in treatment and outcomes. Research Sponsor: Flatiron Health.

Therapeutic impact of novel agents in patients with stage IV de novo HR+ve/Her2-ve breast cancer: Results from a real world dataset.

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Background: The objective of this retrospective analysis was to look at the therapeutic impact of CDK4/6i and novel agents among pts with stage IV Denovo HR+ve/HER2-ve breast cancer (BC). **Methods:** We utilized a federated network of de-identified health data representing approximately 165 million pt lives available through the TriNetX Research Network. We identified 41,843 pts with HR+ve/HER2-ve stage IV Denovo BC treated diagnosed between Jan 2005 - Jan 2025. Propensity score matching analysis by age and site of metastases was carried out. OS was computed using the Kaplan Meier product limit method. The index event is the date of diagnosis. **Results:** 8,541(20.4%) received a CDK4/6i. Among pts treated with CDK4/6i 1,396(16.3%), 6,169 (72.2%) and 2,157 (25.2%) pts received Ribo, Palbo and Abema respectively. Over time there has been a significant decrease in use of palbocilcib with significant increase in use of abema and ribo. Median OS was similar between Ribo and Abema(HR 0.88; 95%CI (0.75,1.04) p=0.14). Compared to pts receiving palbo median OS was signficantly better among pts receiving abema (HR 0.77; 95%CI (0.69,0.85) p<0.0001) or ribociclib (HR 0.69; 95% CI (0.60,0.81) p<0.0001).628 pts received more than one CDK4/6i. (152 palbo + ribo, 118 ribo + abema, 368 abema+ palbo). 5-year OS was 63.9% and 70.4%(HR 1.37; 95%CI 1.06,1.77) respectively among pts who received 1 vs >1 CDK4/6i. Among patients treated with CDK4/6i, OS was significantly longer among pts who received elacestrant vs those who did not (HR 0.401; 95%CI (0.215,0.745). 228 pts treated with a CDK4/6i received an antibody drug conjugate (ADC). Median time to use of an ADC was 45m. 5yr OS was 75.8% vs 58.7% among those who did and did not receive an ADC respectively (HR 0.45, 95%0.30,0.67). 5yr OS was 76.2% vs 52.7% among those who did and did not receive Trastuzumab deruxtecan respectively (HR 0.37, 95% 0.19,0.70). 5yr OS was 76.2% vs 60.4% among those who did and did not receive Sacituzumab govetican respectively (HR 0.40, 95%0.25,0.65). **Conclusions:** Among pts with stage IV Denovo HR+ve/HER2-ve BC treated with a CDK4/6i using a CDK4/6i beyond progression is an option. Novel agents such as oral SERDS and ADCs are also associated with improved prognostic outcome in the real world setting. Research Sponsor: None.

Updated efficacy of mutant-selective PI3Kα inhibitor RLY-2608 in combination with fulvestrant in patients with *PIK3CA*-mutant HR+HER2- advanced breast cancer: ReDiscover trial.

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Background: Oncogenic *PIK3CA* mutations constitutively activate PI3Kα and drive approximately 40% of HR+HER2- breast cancer (BC); however, the toxicity (hyperglycemia, rash, diarrhea, stomatitis) of non-selective inhibitors (i) limits their tolerability and efficacy. RLY-2608 is the first oral, pan-mutant-selective, allosteric PI3Kαi designed to overcome these limitations. We report efficacy and safety of RLY-2608 + standard-dose fulvestrant (F) in pts with *PIK3CA*-mutant, HR+HER2- BC treated in the FIH study, ReDiscover (NCT05216432). **Methods:** Previously treated adult pts with advanced HR+HER2- BC and *PIK3CA* mutation per local assessment were eligible. Pts were eligible to enroll with measurable or non-measurable disease. Key objectives were investigator-assessed efficacy per RECIST 1.1 and adverse events (AEs) per CTCAE v5.0. **Results:** As of 4NOV24, safety was assessed in 118 pts treated across RLY-2608 doses 100-1000 mg BID, and efficacy in the 52 pts without detectable *PTEN/AKT* co-alterations treated at the RP2D (600 mg BID). All pts received prior endocrine therapy and CDK4/6i with 48% having ≥ 2 prior systemic therapies for advanced disease including 56% with prior F/SERD and 25% with prior chemotherapy or antibody-drug conjugate. Median follow-up was approximately 9.5 months. The RP2D provided exposure in the target therapeutic range and rapid clearance of mutant *PIK3CA* ctDNA. 31/52 pts had measurable disease with 26/31 (83.9%) achieving disease control, 23/31 (74.2%) experiencing radiographic tumor reduction and 12/31 achieving an objective response (38.7%, 95% CI 21.8-57.8) with median time-to-response 8 weeks. mPFS was 9.2 months (95% CI 5.8,18.4) across all 52 RP2D pts, and 11.4 months (95% CI 7.2-NR) in 32 pts receiving RLY-2608 at the RP2D as 2L treatment. Treatment-related AEs (TRAEs) were generally low-grade, manageable and reversible, most commonly hyperglycemia (42.4% any grade; 2.5% Gr 3), nausea (41.5%; 0.8% Gr 3), fatigue (40.7%; 8.5% Gr 3), creatinine increased (34.7%; 0.8% Gr 3), and diarrhea (30.5%; 1.7% Gr 3). There were no grade 4/5 TRAE; and severe, off-target stomatitis and rash were absent or rare. **Conclusions:** RLY-2608 demonstrates favorable safety/tolerability along with highly encouraging PFS observed across *PIK3CA* genotypes in pts with advanced *PIK3CA*-mutant HR+HER2- BC previously exposed to CDK4/6i. These data validate RLY-2608 as the first allosteric pan-mutant selective PI3Kαi and support advancing RLY-2608 + F to pivotal testing, which is planned for later this year. Clinical trial information: NCT05216432. Research Sponsor: Relay Therapeutics.

Impact of body weight and body composition on survival and toxicities in patients receiving CDK4/6 inhibitors for ER+/HER2- metastatic breast cancer.

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Background: Body composition influences treatment outcomes and adverse events in many oncologic conditions including metastatic breast cancer (mBC). The objective of our study was to evaluate the impact of body composition measures on progression-free survival (PFS) and adverse events in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors for estrogen receptor-positive (ER+)/HER2- mBC. **Methods:** A single institution retrospective analysis of 207 patients treated with CDK4/6 inhibitors was conducted. Baseline body weight and body composition measures (total fat, visceral fat, subcutaneous fat, skeletal muscle area, skeletal muscle density and muscular adiposity) were analyzed. PFS was evaluated using Cox proportional hazard models, and logistic regression was used to evaluate the relationship between these variables and adverse events. Early changes in body composition were defined as variations in muscle or fat compartments within 3 months. Low muscle quality was defined as muscle power index value of 1 to 2 Standard Deviations below the normal range. **Results:** The median age of our cohort was 61 years, with 77% of patients being postmenopausal and 46% identifying themselves as Black. Most patients received palbociclib (76%), followed by abemaciclib (14%) and ribociclib (10%) as part of their treatment. Median BMI was 27.97 kg/m2, with 36% being classified as obese. Sarcopenia was present in 18% of our patients, and 71% had low muscle quality. Higher BMI (HR, 0.96; 95% CI, 0.93-0.99; p 0.01), obesity (HR, 0.60; 95% CI, 0.42-0.86; p = 0.01) and weight (HR, 0.99; 95% CI, 0.98-0.99; p = 0.01) were significantly associated with improved PFS. Modest but statistically significant associations with PFS were observed for total fat (HR 0.99; 95% CI 0.98-0.99; p = 0.01) and subcutaneous fat (HR, 0.99; 95% CI, 0.98-0.99; p = 0.01); however, this was not the case for visceral fat and muscle adiposity. There was no significant association between body muscle compartment distribution (including sarcopenia) and PFS. Early changes in skeletal muscle density were associated with improved PFS (HR, 0.95; 95% CI, 0.91-0.99; p = 0.01), while sarcopenia and low muscle quality were not significant predictors. Grade 3/4 hematologic toxicities were associated with lower muscle area (p = 0.02), but no significant association between fat compartments and adverse events was found. **Conclusions:** Obesity is associated with improved survival outcomes in patients receiving CKD4/6 inhibitors for ER+/HER2- mBC; furthermore, this effect is driven by subcutaneous fat. Early changes in skeletal density during CDK4/6 inhibitors treatment is a potential predictor of improved outcomes. Muscle area is a potential predictor of treatment toxicities. Our findings suggest that body composition plays an important role in outcomes and adverse events in this group of patients. Research Sponsor: None.

Phase 1 trial of exercise as first-line therapy for hormone receptor (HR)–positive advanced breast cancer (TBCRC 054).

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Background: Observational studies show post-diagnosis exercise is associated with reduced risk of cancer death in patients with HR-positive breast cancer. We conducted a phase 1a dose-finding trial of exercise therapy as first-line treatment for HR-positive advanced breast cancer (TBCRC 054). **Methods:** This multicenter trial was conducted using a patient-centric, decentralized platform (NCT03988595). Non-exercising patients receiving first line endocrine plus CDK4/6 inhibitor therapy were allocated using an adaptive continual reassessment design to one of four escalated exercise therapy dose levels (range: 90 to 300 min/week) of individualized, moderate-intensity treadmill walking for 6 consecutive months. The trial was later amended to add a fifth dose level of 375 min/week and to allow dose cohort backfilling. Exercise therapy sessions were conducted remotely in patient's homes with real-time monitoring. The primary objective was to identify the recommended phase 2 dose (RP2D) as determined by feasibility and preliminary clinical efficacy. Feasibility was evaluated by relative exercise dose intensity (REDI). A dose level was considered feasible if ≥70% of patients achieved a REDI ≥75%. One-year progression free survival (PFS) rates were assessed by the Kaplan-Meier method. **Results:** Fifty-four women (median age 53 [46 to 63] years) were enrolled between August 2019 and April 2024; 23 (43%) had visceral metastases, 43 (80%) received an aromatase inhibitor, 11 (20%) received fulvestrant, and 53 (98%) received a CDK4/6 inhibitor. The proportion of patients with REDI ≥75% in each dose level was: 90 min/week (n = 10): 80%, 150 min/week (n = 10): 60%, 225 min/week (n = 11): 82%, 300 min/week (n = 13): 62%, and 375 min/week (n = 10): 40%. Among the two feasible dose levels (90, 225 min/week), 1-year PFS rate was 70% (95% CI, 47% to 100%) in the 90 min/week dose level and 91% (95% CI 75% to 100%) in the 225 min/week dose level. No serious adverse events were observed. Overall, 225 min/week (~ 45 minutes per treatment at 5 times weekly) was selected as the RP2D. **Conclusions:** This multicenter phase 1 trial showed that exercise therapy doses of 90 and 225 min/week are feasible and safe in patients receiving first line endocrine-based therapy. These data also support the rationale for a phase 2 trial testing the preliminary clinical efficacy of exercise at the RP2D of 225 min/week in HR-positive advanced breast cancer. Clinical trial information: NCT03988595. Research Sponsor: National Cancer Institute; R01CA235711.

Pulmonary toxicities in patients (pts) with metastatic breast cancer (mBC) treated with trastuzumab deruxtecan (T-DXd): The Mayo Clinic Enterprise Experience, updated.

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Background: T-DXd has become an important treatment option in mBC and other malignancies. Interstitial lung disease/pneumonitis (ILD) occurred in 10-14% of pts in the DESTINY-Breast trials (0-2% G5 ILD), and with potential lower incidence/severity in earlier line settings (Krop et al, ASCO 2023). We previously reported the Mayo Clinic Rochester, MN experience with T-DXd related ILD in mBC (Hoppenworth et al, ASCO 2024). Here, we expand the data to include patients treated at all locations of the Mayo Clinic Enterprise. **Methods:** We retrospectively identified pts with mBC who received ≥1 dose of T-DXd across the Mayo Clinic enterprise (Rochester, MN; Mayo Clinic Health System locations in MN/WI; Scottsdale, AZ; and Jacksonville, FL) between July 2022-December 2023. Demographic, mBC characteristics, and pulmonary clinical variables were abstracted from the clinical records. Data were summarized using descriptive statistics. Diagnosis of ILD was determined by treating clinicians, and severity was approximated to CTCAE V5 based on clinical documentation. **Results:** 252 pts with mBC received T-DXd during the study period. The majority were Caucasian (86%) and female (99%) with a median age of 63. 91 pts (36%) were current/formers smokers and 97 (39%) had prior pulmonary comorbidities. The majority had HER2 low (155, 62%) and HR positive (164, 65%) mBC. 35 (14%) developed any grade ILD [G1: 6 (17%), G2: 13 (37%), G3: 3 (8.6%), G4: 3 (8.6%), G5: 10 (29%)], with 15 (43%) presenting with ≥G3. 29 (83%) presented with at least 1 symptom (cough or SOB). Among those with previous pulmonary toxicity, 4 (33%) had previous pneumonitis in the ILD cohort. The median prior lines of all therapies (including endocrine therapy) were 5, with a median of 3 prior lines of chemotherapy in both the ILD (range 1-13) and non-ILD cohorts (range 1-13). Median onset to any grade ILD was 7 cycles. 20 pts (57%) received steroids for ILD. 14 (40%) had a bronchoscopy, all had a CT chest, 16 (46%) were hospitalized, 7 (20%) were intubated and 1 (3%) had a lung biopsy. Pts with G5 ILD had a median of 3 lines of chemo and a median of 8 cycles prior to onset of ILD, compared to 3 lines of chemo and a median of 7 cycles for those with G1-4 ILD. G5 pts were all Caucasian females, 5 were former smokers, 5 were non-smokers, 1 had a history of pneumonitis. T-DXd was rechallenged in 4 pts (G1-2 ILD) without ILD recurrence. **Conclusions:** In this retrospective case series,14% of pts treated with T-DXd experienced any grade ILD (4% G5) which is in alignment with the rate observed in the pivotal DESTINY-Breast trials, though with higher rates of G5 toxicity. Among those with ILD, increased lines of therapy were not associated with increased risk. Further research is needed to correlate risk. Research Sponsor: None.

Preliminary efficacy and safety of TQB2102 in patients with HER2 low-expressing recurrent/metastatic breast cancer: Results from a phase 1b study.

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Background: TQB2102 is a novel antibody-drug conjugate (ADC) comprised of a recombinant humanized anti-HER2 bispecific antibody that simultaneously binds to two distinct HER2 epitopes (ECD4 and ECD2), an enzyme-cleavable linker, and a DNA topoisomerase I inhibitor payload. This study aims to evaluate the efficacy and safety of TQB2102 for patients (pts) with HER2-expressing relapsed/metastatic breast cancer. **Methods:** This 1b phase, open-label, multicenter, randomized trial was divided into two cohorts: Pts in cohort 1 were HER2 low-expressing breast cancer and in cohort 2 were HER2 positive BC, all pts were refractory or intolerant to standard therapy. In cohort 1, HER2 low-expressing pts were randomly assigned to receive TQB2102 monotherapy at a dose of 6.0 mg/kg (Q3W, IV) or 7.5 mg/kg (Q3W, IV). The primary endpoint was ORR per RECIST v1.1, and the secondary endpoints were PFS, DCR and safety etc. **Results:** 73 HER2 low-expressing female pts were randomized to receive at least one dose of TQB2102 6mg/kg (n = 37) or 7.5mg/kg (n = 36), the median age was 53. All pts had received chemotherapy in the metastatic setting, and hormone receptor positive pts (n = 50) also had received prior CDK4/6 inhibitors. In cohort 1, pts had undergone a median of 4 prior treatment lines (range: 1-10) in the metastatic setting, the median prior lines of chemotherapy therapies were 2 (range: 1-5), and 12.3% (n = 9) pts had received prior ADCs. As of data cutoff on Nov 1, 2024, median follow-up time was 7.16 months. ORR was 53.4% (39/73) in cohort 1, and the ORR of 7.5mg/kg (58.3%) was better relative to 6.0mg/kg (48.7%). Objective responses were observed in subgroups with HR positive pts (27/50, ORR 54.0%), HR negative pts (12/23, ORR 52.2%); of which the ORR of 7.5mg/kg with HR+ and HR- was 66.7% (14/21) and 46.7% (7/15), respectively. For HER2 low-expressing pts who received prior ADC therapies, the ORR was 44.4% (4/9). In cohort 1, DCR was 86.3% (63/73, among 6 pts was not available), and median PFS was not yet mature. TRAEs were reported in 71 (97.3%) HER2 low-expressing pts. Grade≥3 TRAEs and serious TRAEs were reported in 30 (41.1%), 13 (17.8%) pts, respectively. The main TRAEs were neutropenia, leukopenia, anemia, nausea, vomiting. The common TRAEs and grade ≥3 TRAEs occurred similarly at both doses, with hematologic toxicities such as anemia were slightly higher at 7.5mg/kg than at 6.0mgkg, but all were tolerable. No Interstitial lung disease was reported in cohort 1 pts. **Conclusions:** TQB2102 was well-tolerated and showed promising antitumor activity in heavily pretreated HER2 low-expressing recurrent/metastatic breast cancer pts. The recommended phase 3 dose of TQB2102 in HER2 low-expressing r/m BC was 7.5 mg/kg Q3W. A phase III trial to evaluate the efficacy and safety of TQB2102 versus investigator-selected chemotherapy in HER2 low-expressing r/m BC is currently ongoing (NCT06561607). Clinical trial information: NCT06115902. Research Sponsor: None.

Standard-dose vs fixed-dose capecitabine in patients with advanced gastrointestinal and metastatic breast cancer.

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Background: Capecitabine at the FDA-approved standard dose (SD) of 1250 mg/m^2 twice daily for 14 days with a 7-day break, has significant toxicities. We conducted a randomized trial comparing SD and fixed dose (FD) Capecitabine 1500 mg twice daily, 7 days on, 7 days off in patients with metastatic breast cancer (MBC) and advanced gastrointestinal (GI) cancers. We previously reported that in MBC cohort progression-free survival and overall survival were similar, and FD had significantly lower toxicities. We now present time to treatment failure (TTF) and toxicity in MBC and GI cohorts. **Methods:** Patients with MBC or advanced GI cancers (colorectal, small bowel, gastroesophageal, pancreatic and bile duct) with any prior lines of therapy were randomized 1:1 to either FD-7/7 or SD-14/7. Post hoc analysis was performed to determine TTF, and landmark analysis was performed for Freedom from Treatment Failure (FFTF). Capecitabine-related toxicities [diarrhea, hand foot syndrome (HFS) and stomatitis] were solicited and graded at each visit. **Results:** 182 patients were enrolled (N=93 FD, N=89 SD) of which 153 had MBC and 29 had an advanced GI cancer. Median TTF was 4.92 months (3.02, 5.93) in FD arm, and 3.11 months (2.49, 3.90) in SD arm (log rank p=0.0111). Landmark analysis of FFTF is shown in Table 1. At 24 months, the FFTF in the FD arm was 15.6%, while in the SD arm it was 2.5% (p=0.0054). Grade 2 and higher toxicities were more common in SD compared to FD, including HFS, diarrhea, and stomatitis (Table 1) **Conclusions:** Fixed-dose capecitabine at 1500 mg twice daily for 7 days on and 7 days off demonstrates a longer time to treatment failure compared to the standard FDA-approved dosing in patients with MBC and advanced GI cancers and is associated with significantly lower toxicities. Clinical trial information: NCT02595320. Research Sponsor: None.

Landmark freedom from treatment failure at 12, 24 and 36 months; solicited adverse events.

Time	FD-7/7, N=93 Survival Probability Estimate	SD-14/7, N=89 Survival Probability Estimate	P-value
3-month	61.3%	51.4%	0.1917
6-month	39.6%	30.6%	0.2224
12-month	23.8%	14.1%	0.1188
24-month	15.6%	2.5%	0.0054
Adverse Event		Number (proportion)	
Diarrhea			
Any Grade	51 (54.8%)	59 (66.3%)	0.1142
Grade 2-4	8 (8.6%)	35 (39.3%)	<0.0001
Grade ≥ 3	3 (3.2%)	20 (22.5%)	<0.0001
HFS			
Any Grade	46 (49.5%)	61 (68.5%)	0.0090
Grade 2-4	13 (14.0%)	40 (44.9%)	<0.0001
Grade ≥ 3	1 (1.08%)	15 (16.9%)	0.0002
Stomatitis			
Any Grade	24 (25.8%)	48 (53.4%)	0.0001
Grade 2-4	2 (2.2%)	13 (14.6%)	0.0023
Grade ≥ 3	0 (0.0%)	6 (6.7%)	0.0125*

*Fisher's exact test.

Limited changes in the CNS immune microenvironment in patients with breast cancer metastasis and capturing these changes using machine learning.

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Background: Metastasis of breast cancer to the central nervous system (CNS) is common, especially in triple negative and HER2-positive tumors. The CNS is considered immune specialized and likely the brain and brain-border immune microenvironment creates a sanctuary site for breast cancer CNS metastasis. A better understanding of the immune microenvironment may allow for better utilization of immunotherapy to treat CNS metastasis. Toward this goal, we evaluated the cellular transcriptomic profile of cerebrospinal fluid (CSF) cells and compared between patients with documented metastatic tumor by cell-free DNA (cfDNA) testing of the CSF fluid (cfCSF-Pos) and patients without evidence of cfDNA metastasis (cfCSF-Neg) (Charifa et al., https://doi.org/10.1016/j.jlb.2024.100281). **Methods:** RNA was extracted from the CSF cells of 63 cfCSF-Pos patients and 93 cfCSF-Neg patients. The RNA was sequenced and quantified using a targeted RNA panel of 1600 genes by next generation sequencing (NGS). We used two thirds of the samples for training a machine learning (ML) system and one third for testing. The ML system uses Bayesian statistics with k-fold cross-validation (with k = 12) to first rank the top biomarkers distinguishing CSF-Pos from CSF-Neg samples. Then Random Forest was used to distinguish between the two classes using the top ranked biomarkers. **Results:** cfCSF-Neg contains mainly T-cells with median CD2:CD22 RNA ratio of 70.07 (range 0.01-14820). This was not significantly different (p = 0.19) from cfCSF-Pos cases (median: 41.31, range: 0.4-10172). The ratio of CD4:CD8A in cfCSF-Neg (median: 4.89, range: 0.47-2522) was also not significantly different (p = 0.31) from that in cfCSF-Pos cases (median: 5.0, range: 0.29-48). While significant variation in the levels of T- and B-cells is noted within each group, there was no significant difference in the individual cell population (T-cells, B-cells, plasma cells, natural killer cells, neutrophils, monocytes, or dendritic cells) overall after adjusting for multiple testing. Despite this lack of difference in cell populations, the testing set showed that cfCSF-Pos patients can be readily distinguished from cfCSF-Neg patients with AUC of 0.886 (CI: 0.797-0.976) using 30 top genes selected by ML. Except for KRT8 and KRT19, the majority of the top genes selected by the ML algorithm suggests modulation of T-cell activation including but not limited to TBX21, CD3D, CD5, IKZF3, NFATC2, and INPP5D. **Conclusions:** The data suggest the CNS remains immunologically specialized with modulating the adaptive immune response in the setting of breast cancer metastasis. Significant modulation in the CSF T-cells suggests selective targeting with immunotherapy may prove beneficial with the potential for active monitoring using this combination CSF cellular and cfDNA approach. Research Sponsor: None.

A phase II study to evaluate the safety and efficacy of BB-1701 in subjects with HER2 expression locally advanced/metastatic breast cancer previously treated with HER2-ADC containing TOP-I inhibitor.

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Background: BB-1701 is an HER2-targeting antibody-drug conjugate (ADC) containing eribulin. In phase I study, BB-1701 had shown promising antitumor activity in breast cancer (BC) patients with HER2 high/low expression and manageable safety profile. Currently, there are no approved treatment options for metastatic BC patients with high/low expression who have received HER2-ADC containing TOP-I inhibitor, especially for trastuzumab deruxtecan. We report the preliminary efficacy and safety results from the ongoing phase 2 study of BB-1701 in advanced or metastatic breast cancer patients with HER2 expression previously treated with HER2-ADC containing TOP-I inhibitor. **Methods:** Patients enrolled were ≥18 years of age; had confirmed locally advanced/metastatic HER2 expressing breast cancer; disease progression after previous HER2-targeting ADC (containing TOP-I inhibitor) therapy; an ECOG PS < 2; and measurable lesion(s) (per RECIST v1.1). HER2 expression was confirmed by IHC before patient enrollment. BB-1701 is administered at 1.6 mg/kg Q3W. **Results:** As of 28 January 2025, 23 patients with HER2 high/low-expressing breast cancer have been enrolled and treated. Median age is 51 years, all patients are female, and 26.1%/73.9% patients have ECOG PS 0/1. The median number of prior systemic therapy lines was 4.0, 21.7%/78.3% HER2 status are high expression/low expression. All patients experienced at least one treatment-emergent adverse events (TEAEs). The most common (≥10%) all grade TEAES are neutrophil count decreased, platelet count decreased, Aspartate aminotransferase increased, and white blood cell count decreased. One grade 3 TEAEs is peripheral neuropathy, and another grade 3 TEAE is neutrophil count decreased. There has been no grade 4 or grade 5 events as of data cut-off date. One treatment emergent serious adverse event is peripheral neuropathy. Of the 23 patients, 14 were evaluable for efficacy. Among 14 evaluated patients, 4 patients achieved partial response (PR) and 9 patients had stable disease (SD), with disease control rate (DCR) of 92.8%. Among 3 HER2 high-expressing patients who were previously treated with trastuzumab deruxtecan, 1 patient achieved PR and 2 patients had SD with DCR of 100.0%. Among 8 HER2 low-expressioning (IHC 1+) patients, 3 patients achieved PR (2 patients received prior trastuzumab deruxtecan and 1 patient received prior SHR-A1811) and 4 patients had SD with DCR of 87.5%. More data will be presented at the ASCO meeting. **Conclusions:** BB-1701 shows promising antitumor activity and a manageable safety profile in HER2 expressing breast cancer patients who had previously been treated with HER2-ADC (containing TOP-I inhibitor). Clinical trial information: CTR20241422.
Research Sponsor: None.

Results of a phase I study of alpelisib and sacituzumab govitecan (SG) in patients with HER2-negative metastatic breast cancer (MBC).

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Background: Sacituzumab govitecan (TROP2-directed antibody drug conjugate, ADC) is effective in treatment of pretreated HER2-negative MBC. PI3K is the most frequently altered pathway in breast cancer. This phase I trial investigated the combination of SG plus alpelisib (oral α-specific PI3K inhibitor) in HER2-negative MBC. **Methods:** Eligible patients had HER2-negative MBC and had received $\geq$1 prior line of chemotherapy in the advanced or neo/adjuvant setting and had not received prior PI3K/AKT inhibitor. The study was 3+3 dose escalation design: dose level 1: alpelisib 250 mg+SG 8 mg/kg; dose level 2: alpelisib 250 mg+SG 10 mg/kg; dose level 3: alpelisib 300 mg+SG 10 mg/kg. Alpelisib was dosed PO daily and SG IV, D1 and 8 every 21 days. Antidiarrheal prophylaxis was utilized for the first two cycles. Primary endpoint was recommended phase 2 dose (RP2D). Additional endpoints included adverse events (AEs), objective response rate (ORR), progression-free survival (PFS), and pharmacokinetics. **Results:** 12 patients were enrolled between 2022-2024 (dose level 1: N = 3, dose level 2: N = 6, dose level 3: N = 3). 7/12 (58%) had triple-negative breast cancer (TNBC), and 5/12 (42%) had hormone receptor (HR)-positive disease. All patients had visceral disease. 8/12 (67%) had $\geq$1 prior metastatic chemotherapy; 4/12 (33%) had prior immunotherapy; 3/12 (25%) had prior ADC. One dose-limiting toxicity (hyperbilirubinemia) was observed at dose level 2. RP2D was alpelisib 300 mg + SG 10 mg/kg. The most frequent grade $\geq$3 treatment-related AEs were electrolyte imbalance (G3 17%, G4 17%), neutropenia (G3 33%, G4 0%), diarrhea (G3 17%, G4 0%), and hyperglycemia (G3 8%, G4 8%). There were no G5 AEs. Pharmacokinetics of SG and its metabolites were consistent with previous reports. Among 11 patients evaluable for response, ORR was 36% (4/11) (complete response [CR] = 1, partial response [PR] = 3) and clinical benefit rate (CR + PR + stable disease $>$ 24 weeks) was 64% (7/11). ORR in TNBC was 50% and in HR-positive disease was 20%. Among patients with prior ADC, ORR was 33% and clinical benefit rate was 67%. Three of four patients with ORR had response lasting $>$ 6 months, with median duration of response of 14.9 (range 3.2 to 28.1) months. Median PFS was 5.7 months. Tumor and serial ctDNA analysis are ongoing. **Conclusions:** Combination of SG + alpelisib was feasible, with manageable side effects. The toxicity profile of the combination was consistent with the known safety profiles of the two agents. This combination demonstrated encouraging efficacy in HER2-negative MBC, with prolonged duration of responses, and warrants further evaluation in larger studies. Clinical trial information: NCT05143229. Research Sponsor: Novartis; Gilead Sciences.

Assessing the impact of scalp cooling in patients receiving trastuzumab deruxtecan for metastatic breast cancer.

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Background: Outcomes for patients (pts) with metastatic breast cancer (MBC) have improved with novel antibody drug conjugates like trastuzumab deruxtecan (T-DXd). While T-DXd has been associated with increased risk of alopecia, there are limited data describing the efficacy of scalp cooling in preventing alopecia and improving quality of life among pts receiving T-DXd. **Methods:** This prospective, phase II study enrolled pts with MBC without alopecia at baseline who were initiating treatment with T-DXd; pts elected to participate in a scalp cooling (SC) arm with the Paxman scalp cooling system or a non-SC arm. The primary endpoint was hair loss, defined as locally assessed CTCAE v5.0 grade ≥1 alopecia occurring at C3D1, C5D1, or end of treatment (EOT), whichever occurred first. The impact of SC on quality of life (QOL) was assessed using the Chemotherapy-Induced Alopecia Distress Scale (CADS) and body image scale (BIS) at baseline, C3D1, C5D1, and EOT. The study aimed to enroll 20 pts per arm to provide at least 80% power to detect a 28% decrease in hair loss rate between the SC vs non-SC arms (8% vs 36%) using a difference in proportions test (one-sided type I error 10%). **Results:** A total of 40 evaluable pts were enrolled: 20 in SC arm and 20 in non-SC arm. Median age was 61 (33-77); 2 (5%) were Black, 2 (5%) were Hispanic. Twenty-eight (70%) pts had hormone receptor positive disease, 11 (27.5%) HER2+, 2 (5.0%) triple-negative. Thirty-five (87.5%) had prior chemotherapy for MBC; median prior lines was 1 [range: 0-5]. 27 (67.5%) had prior endocrine therapy, 28 (70.0%) had prior CDK4/6 inhibition; 7 (17.5%) had prior use of SC. Thirty-three (82.5%) pts (18 [90%] in SC arm, 15 [75%] in non-SC arm) experienced >grade 1 alopecia, with similar rates observed in both arms (p = 0.41). Grade 2 alopecia was the main reason (45%) for SC discontinuation. Median time to G2 alopecia was 2.76 months (95% CI: 1.64-NA) in SC arm and 4.60 months (95% CI: 2.53, NA) in non-SC arm (p = 0.8). Median CADS scores trended upward from baseline to EOT (Baseline: 3.50; C3: 7.22; C5: 9.00; EOT: 11.5) in the SC arm and were more variable in the non-SC arm (baseline: 3.00; C3: 5.00; C5: 2.56; EOT: 6.50); median BIS scores trended upward in both the SC (baseline: 3.00; C3: 8.00; C5: 9.00; EOT: 11.5) and non-SC arms (baseline: 3.00; C3: 5.00; C5: 5.00; EOT: 9.00), with no statistically significant difference. **Conclusions:** In this prospective phase II trial, the use of SC with T-DXd did not show a benefit in hair preservation vs no SC. QOL analysis was not significantly different for those receiving SC vs no SC. Small sample size and lack of randomization may limit interpretation of results. Further work is planned to investigate strategies to improve efficacy of SC with ADCs. Clinical trial information: NCT04986579. Research Sponsor: AstraZeneca and Daiichi Sankyo; Paxman Scalp Cooling; Friends of Dana-Farber.

CTCAE v5 alopecia.

CTCAE v5 Alopecia	All N=40	SC Arm N=20	Non-SC Arm N=20	P-value
No alopecia	7(17.5%)	2(10.0%)	5(25.0%)	0.41
Grade 1	11(27.5%)	7(35.0%)	4(20.0%)	
Grade 2	22(55.0%)	11(55.0%)	11(55.0%)	

Bria-IMT + checkpoint inhibitor: Phase I/II survival results compared to benchmark trials in metastatic breast cancer.

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Background: Bria-IMT is a combination immunotherapy consisting of allogeneic whole cell cancer vaccine (SV-BR-1-GM) administered w/ immune checkpoint inhibitor (CPI). SV-BR-1-GM breast cancer cells are engineered to directly stimulate anti tumor immunity via expression of tumor associated antigens and secretion of GM-CSF to enhance dendritic cell activation. Addition of CPI potentiates SV-BR-1-GM to overcome the immune suppressive tumor microenvironment. **Methods:** This Ph I/randomized Ph II study evaluated the Bria-IMT regimen in pts w/ metastatic breast cancer; CTX (300 mg/m^2) on day -2/-3, SV-BR-1-GM and CPI on Day 0, w/ low dose peg interferon α at inoculation sites on day 2 ($\pm$1) . Phase II pts were randomized 1:1 to receive CPI at cycle 1 or cycle 2. Two SV-BR-1-GM formulations (w/ vs w/o IFNγ incubation) were evaluated. Biomarkers included cancer-associated macrophage-like cells, circulating tumor cells, PD-L1 scores, and delayed-type hypersensitivity skin tests. **Results:** 54 pts (22 Ph I, 32 Ph II) enrolled; 11 received pembrolizumab, 44 retifanlimab (1 crossover). 33 (61%) pts were ER+/PR+/HER2-, 18 (33%) TNBC, 3 (6%) HER2+. Median OS, PFS, ORR, and CBR were evaluated against two pivotal Ph 3 trials, ASCENT[1] (SG in TNBC) and TROPiCS-02[2] (SG in HR+/HER2- MBC) (see Table 1). In randomized pts, C1 vs C2 CPI had PFS (3.7 vs 3.2 mos, P=0.09) and OS (11.4 vs 7.4 mos, P=0.19). Pts receiving Ph 3 formulation (w/o IFNγ; N=37) had greater PFS (3.6 vs 2.6 mos, P=0.01) and OS (13.4 vs 6.9 mos, P=0.01). Bria-IMT was well tolerated w/ no Tx related D/Cs. **Conclusions:** The Bria-IMT Ph 3 formulation cohort OS was comparable to ASCENT and TROPiCS-02 (13.43 vs 11.8, 14.4 mos), exceeding TPC arms (6.9, 11.2 mos). CBR (61%) compared favorably to ASCENT (40%) and TROPiCS-02 (34%); ORR (14%) matched or exceeded TPC arms (4%, 14%). These outcomes were observed in a more heavily pretreated population, demonstrating Bria-IMT's clinical activity. Randomized Ph 2 results suggest efficacy and safety in heavily pretreated MBC, w/ no significant OS difference between C1 and C2 CPI initiation and 22% of pts still in active survival follow up. Superior outcomes w/ the Ph 3 formulation support its continued evaluation. A randomized Ph 3 trial is ongoing, comparing Bria-IMT vs treatment of physician's choice (NCT06072612). Clinical trial information: NCT03328026. Research Sponsor: BriaCell Therapeutics Corp.

Trial (Cohort)	Age (Median, Range)	Prior Therapies (Median)	OS (Median, mos)	PFS (Median, mos)	ORR (%)	CBR (%)
Bria-IMT (Overall Cohort)	61 (38-81)	6 (2-13)	9.9 (1.8-30.3)	3.6	10%	55%
Bria-IMT (Ph 3 Formulation)	62 (44-80)	6 (2-13)	13.43 (1.8-30.3)	3.6 (1.8-16.5)	14%	61%
ASCENT (SG)	54 (27-82)	4 (2-17)	11.8	4.8	31%	40%
ASCENT (TPC)	53 (27-81)	4 (2-14)	6.9	1.7	4%	8%
TROPiCS-02 (SG)	57 (49-65)	3	14.4	5.5	21%	34%
TROPiCS-02 (TPC)	55 (48-63)	3	11.2	4	14%	22%

References:
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First-line durvalumab plus chemotherapy with or without oleclumab for locally advanced or metastatic triple-negative breast cancer: SYNERGY overall survival and circulating tumor DNA analysis.

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Background: SYNERGY (NCT03616886) is a randomized, investigator-initiated, phase I/II trial testing if targeting the immunosuppressive adenosine pathway with the anti-CD73 antibody oleclumab, plus the anti-PD-L1 durvalumab and chemotherapy, enhances antitumor activity in untreated locally advanced or metastatic triple-negative breast cancer (TNBC). Here, we report the overall survival (OS) and circulating tumor DNA (ctDNA) analysis. **Methods:** 133 patients received weekly carboplatin and paclitaxel x12 plus durvalumab, with (arm A) or without (arm B) oleclumab (6 in phase I, 63 in arm A, 64 in arm B). Maintenance with durvalumab +/- oleclumab was continued until disease progression or unacceptable toxicity. The primary endpoint was clinical benefit rate at week 24 (previously reported, Nat Commun. 2023;14(1): 7018). Secondary endpoints included OS and progression-free survival (PFS). Exploratory endpoint included ctDNA analysis. Circulating cell free DNA (cfDNA) was extracted from 343 plasma samples collected at baseline (n = 128), week 3 (n = 122), and week 13 (n = 93). For ctDNA detection, we performed low-coverage genome-wide sequencing of cfDNA from the above-mentioned samples and from 55 plasma samples from healthy donors to correct a possible batch effect. **Results:** Data cut-off was September 13, 2024, with a median follow-up of 21.7 months. Median OS was not significantly different between arms: 25.1 vs. 20.9 months in arm A vs. B, respectively; HR 0.97 (95%CI 0.63-1.50, p = 0.90). The updated median PFS showed similar PFS: 4.8 vs. 5.4 months in arm A vs. B, respectively; HR 1.22, (95%CI 0.84-1.78, p = 0.29). Among the 343 plasma samples analyzed, ctDNA detection declined from 77% at baseline to 46% at week 3, to 18% at week 13. At any timepoint, CtDNA detection was significantly associated with worse PFS and OS (Table). Twelve patients across both arms exhibited exceptional long responses, without progressive disease and still receiving the study treatment at data cutoff; all exceptional responders evaluable for ctDNA analysis had ctDNA clearance. **Conclusions:** Theaddition of oleclumab to chemo-immunotherapy did not improve PFS or OS in advanced TNBC. However, a subgroup of patients experienced exceptional long-lasting response, indicating potential benefit in selected cases. CtDNA detection was strongly associated with poorer outcomes at all timepoints, underscoring its potential as a biomarker in this disease/setting. Clinical trial information: NCT03616886. Research Sponsor: AstraZeneca.

Timepoint	ctDNA detection	mPFS (95% CI)*	P value	mOS (95% CI)*	P value
Baseline	Yes	4.6 (4.2-5.4)	0.002	19.3 (16.6-25.9)	0.007
	No	9.2 (5.7-16.4)		37.5 (22.5-NE)	
Week 3	Yes	3.9 (2.7-4.7)	<.001	18.1 (12.8-26.5)	0.003
	No	5.7 (4.6-9.3)		25.7 (19.0-NE)	
Week 13	Yes	0.7 (0.4-2.4)	<.001	8.4 (7.3-24.2)	<.001
	No	3.7 (3.4-6.2)		25.6 (22.1-34.5)	

*PFS and OS for Week 3 and 13 estimated from this time point.

Multiomic profiling of LRRC15 in triple negative breast cancer (TNBC).

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Background: Leucine-rich repeat-containing protein 15 (*LRRC15)* has emerged as a potential biomarker and therapeutic target for various cancers due to its high expression in cancer-associated fibroblasts (CAFs) and role in tumor progression. High LRRC15 expression is associated with poor prognosis in TNBC. This study aims to define the multiomic profile of *LRRC15* in TNBC. **Methods:** 3,038 TNBC samples were analyzed via Next-Generation Sequencing (592, NextSeq; Whole Exome Sequencing, NovaSeq) and Whole Transcriptome Sequencing (NovaSeq; Caris Life Sciences, AZ). Immune cell fractions were estimated using WTS deconvolution (Quantiseq). Stromal cell abundance in the tumor microenvironment (TME) was estimated from RNA expression profiles using MCP Counter. *LRRC15*-high (H) and -low (L) tumors were classified by RNA expression above or below the 25th percentile. Real-world overall survival (OS) and treatment-related survival were derived from insurance claims and calculated from tissue collection or treatment initiation to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U tests with multiple comparison adjustments ($q < .05$). **Results:** *LRRC15*-H TNBC tumors had higher frequency of *PIK3CA* (25.9% vs 16.8), PIK3R1 (6.2% vs 1.6%), PTEN (11.3% vs 5.8%), but lower frequency of *RB1* (7.8% vs 12.1%) and *KMT2D* (2% vs 4.4%) compared to *LRRC15*-L, all $q < 0.05$. *LRRC15*-H had higher PD-L1 positivity (32.3% vs 24.5%, $q < 0.05$). Analysis of immune cells showed *LRRC15*-H TNBC had higher infiltration of B cells (4.2% vs 3.5%), M1 macrophages (4.3% vs 2%), M2 macrophages (4% vs 2.5%), Tregs (1.9% vs 1.1%), neutrophils (4.9% vs 3.9%), $CD8^+$ T cells (0.4% vs 0.1%), but lower dendritic cells (2.5% vs 3%), all $q < 0.05$. *LRRC15*-H tumors had greater abundance of CAFs (575.6 vs 93.78, 6.14 fold change (FC)) and endothelial cells (7.3 vs 3.7, 1.97 FC), all $q < 0.05$. *LRRC15*-H had higher T-cell inflamed score (71.5 vs -77) and *IFNg* score (-0.14 vs -1.72), all $q < 0.05$. *LRRC15*-H tumors had higher expression of immune checkpoint genes (*CD274, PDCD1, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, TNFSF14, TIGIT, BTLA, CEACAM1, CD47, CD80, CD86, CD160, CD274*; FC 1.2-2.5, $q < 0.05$). *LRRC15*-H was associated with better OS (mOS: 24.7 vs 13.6 months; HR 0.61, 95% CI 0.53-0.7, $p < 0.001$). Post-pembrolizumab survival was longer for *LRRC15*-H patients (mOS: 27.2 vs 19.4 months; HR 0.61, 95% CI 0.42-0.89, $p = 0.01$). **Conclusions:** *LRRC15*-H TNBC exhibited better outcomes with pembrolizumab, likely due to higher immune cell fractions and increased CAFs. These findings highlight TNBC heterogeneity and position *LRRC15* as a potential biomarker for tumor stratification, a possible adverse prognostic biomarker and a positive predictive biomarker. Ongoing phase I trials targeting LRRC15 show promise. Combining *LRRC15*-targeted therapies with immunotherapy may improve TNBC outcomes, warranting further validation in breast cancer models. Research Sponsor: None.

Acute circulating tumor DNA dynamics during and after infusional therapy initiation.

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Background: For patients with advanced breast cancer, the proportion of tumor-derived DNA in circulation ('tumor fraction'/TF) has been shown to be prognostic. There is evidence that early change in TF may correlate with response to therapy, potentially providing a rapid, minimally-invasive predictive biomarker. However, there is little known regarding TF dynamics during and in the hours immediately after infusion of targeted or cytotoxic therapies, including whether there is a 'surge' in ctDNA corresponding to acute cell death. We hypothesized that tracking TF change peri-infusion would provide insight regarding acute ctDNA dynamics. **Methods:** Banked plasma samples were derived from a phase 1b trial of HSP90 inhibitor onalespib with paclitaxel in patients with advanced triple negative breast cancer. Plasma was collected during the first cycle of therapy on study pre-infusion, end-of-infusion (EOI), then 0.5/1/2/4/6/8/24 hours post-infusion for 1) onalespib alone (day -7); 2) paclitaxel alone 7 days later (day 1); 3) onalespib+paclitaxel 7 days later (day 8) for a total of maximum 26 time points per patient. 317 samples from 14 patients underwent shallow whole genome sequencing (sWGS) and TF determination. The objective was to evaluate change in TF from pre-infusion to 6-hours and 24-hours post-infusion. Exploratory objectives included association of TF dynamics with progression-free survival (PFS) and overall survival (OS). **Results:** 313/317 (98.7%) of available plasma samples completed sWGS. Of these, 104/313 (33.2%) were collected on onalespib alone, 114/313 on paclitaxel alone (36.4%), and 95/313 (30.4%) on onalespib+paclitaxel. For the co-primary objectives, there was a significant decline in TF from pre-infusion to 6 hours for paclitaxel alone (Wilcoxon signed rank $p = 0.03$) but no significant change for onalespib alone/onalespib+paclitaxel or from pre-infusion to 24 hours for any treatment group (all Wilcoxon signed rank $p > 0.05$). There was a significant decline in TF from pre-infusion day -7 (median TF 16%) to 24 hours after C1D8 (median TF 6.5%, Wilcoxon signed rank $p = 0.004$). Baseline TF≥20% was associated with significantly worse PFS (log-rank $p = 0.002$) with a trend toward worse OS (log-rank $p = 0.067$) but categorization of TF change using ctDNA-RECIST was not associated with significant differences in PFS or OS. **Conclusions:** In this study of > 300 plasma timepoints during the first cycle of treatment on a phase Ib clinical trial, there was no significant 'surge' in ctDNA TF within minutes to 24 hours of infusion of onalespib, paclitaxel or both in combination. However, there was a significant decline in TF over the first full cycle of therapy. This suggests that despite ctDNA half-life of minutes-to-hours, consistent change in TF may not be detectable for days or weeks, providing important insight in the design of studies evaluating ctDNA change as a minimally-invasive biomarker. Research Sponsor: None.

A phase 1b study of Plk1 inhibitor onvansertib in combination with paclitaxel in metastatic triple-negative breast cancer (mTNBC) patients.

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Background: TNBC represents 15-20% of all breast cancer and is characterized by a more aggressive clinical course compared to other subtypes with response rate $< 10\%$ after 2-3 lines of chemotherapy. Onvansertib is an oral polo-like kinase 1 (PLK1) ATP-competitive inhibitor with preclinical data showing synergy when combined with paclitaxel (P) in TNBC models. Here, we report safety and outcome data for subjects enrolled in a phase 1b clinical trial of onvansertib and P for patients (pts) with mTNBC. **Methods:** Eligible pts received escalating doses of onvansertib, studied using a Bayesian Optimal Interval (BOIN) design, with a fixed dose of P to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) of onvansertib. The primary objective was the characterization of dose-limiting toxicity (DLT). Onvansertib was tested at 9, 12, and 18 mg/m^2 dose levels (DL). Onvansertib was administered orally, once daily for 21 consecutive days, followed by 7 days off; P was administered intravenously at 80 mg/m^2 once on days 1, 8, and 15 of every 28-day cycle. Exploratory objectives included pharmacokinetic (PK) and circulating tumor DNA analyses. **Results:** 17 pts enrolled from September 2022 to August 2024. Median line of chemotherapy for mTNBC was 3 (range 1-11), 14/17 pts received prior taxane, 7/17 immunotherapy (IO), and 13/17 a prior antibody drug conjugate (ADC). There were 3 pts enrolled at DL0 (9 mg/m^2), 4 at DL1 (12 mg/m^2), and 10 at DL2 (18 mg/m^2). One pt in DL2 remains on treatment, and 16 are off study (11 pts discontinued due to disease progression (PD) per RECIST 1.1; 3 due to clinical PD; 1 due to unacceptable toxicity; 1 death unrelated to the study drug). DLTs were observed in 0/3 pts at DL0, 1/4 (25%) at DL1, and 3/10 (30%) at DL2. Common adverse events were anemia (47% $\geq$ Grade 2, 12% Grade 3), decreased neutrophil count (47% $\geq$ Grade 2, 24% Grade 3-4), and fatigue (24% $\geq$ Grade 2, 6% Grade 3). Best responses included 24% partial response (PR, 2/4 confirmed) and 24% stable disease (2/4 SD $\geq$ 12 weeks) (Table 1). All 4 responders were treated in DL2 (18mg/m^2), 3/4 pts received prior P (2/4 in mTNBC setting) and IO (all in mTNBC), 2/4 received an ADC. The RP2D of onvansertib in combination with P is 18 mg/m^2. PKs and other biomarkers will be presented. **Conclusions:** The combination of onvansertib and P demonstrated a safe toxicity profile and promising clinical activity in pretreated mTNBC pts and warrant further exploration of the combination at the RP2D. Clinical trial information: NCT05383196. Research Sponsor: METAVIVOR; Cardiff Oncology.

Best response per RECIST 1.1 among different DL.

Response	All Pts (N=17)	DL0 (N=3)	DL1 (N=4)	DL2 (N=10)
PR	4 (23.5%)	0 (0.0%)	0 (0.0%)	4 (40.0%)
Confirmed PR	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (20.0%)
Unconfirmed PR	2 (11.8%)	0 (0.0%)	0 (0.0%)	2 (20.0%)
SD	4 (23.5%)	2 (66.7%)	2 (50.0%)	0 (0.0%)
SD > 12 wks	2 (11.8%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
SD < 12 wks	2 (11.8%)	0 (0.0%)	2 (50.0%)	0 (0.0%)
PD	9 (52.9%)	1 (33.3%)	2 (50.0%)	6 (60.0%)
By RECIST 1.1	8 (47.1%)	1 (33.3%)	1 (25.0%)	6 (60.0%)
Clinical PD	1 (5.9%)	0 (0.0%)	1 (25.0%)	0 (0.0%)

Camrelizumab plus nab-paclitaxel and cisplatin as first-line treatment for metastatic triple-negative breast cancer: A prospective, single-arm, open-label phase II trial.

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Background: Platinum-based chemotherapy plays an important role in the treatment of TNBC. Our previous research has demonstrated the superiority of nab-paclitaxel/cisplatin (AP) regimen as the initial treatment for metastatic TNBC(mTNBC; *Xichun Hu, 2020ESMO)*. Camrelizumab is a humanized monoclonal antibody against PD-1. Herein, we conducted this prospective, single arm, open-label phase II study to evaluate the efficacy and safety of camrelizumab in combination with AP regimen as the first-line treatment of mTNBC (NCT04537286). **Methods:** Patients with untreated mTNBC received camrelizumab (200 mg D1), nab-paclitaxel (125 mg/m^2 D1,D8) and cisplatin (75 mg/m^2 D1) intravenously every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR),overall survival (OS) and safety. Exploratory analyses included immunohistochemistry and RNA sequencing of archival tumour samples. **Results:** A total of 90 patients were enrolled. Overall, median age was 51 years; 46.7% of patients had three or more metastatic sites; 78.9% of patients had visceral involvement; 82.2% of patients had taxanes exposure. As of data cutoff (July 10th 2024), median duration of follow-up was 18.1 months. Median PFS was 11.8 (95%CI 10.1-13.6) months and median OS was 27.1 (95%CI 22.1-33.6) months. ORR was 71.1% and DCR was 86.7%. Median time to response was 1.5 months. TRAEs were reported in all patients while grade 3-4 TRAE occurred in 55.6% patients, including neutropenia (34.4%), leukemia (24.4%), and anemia (10.0%). irAEs were reported in 57.8% patients, including RCCEP (45.5%), rash (11.1%), pneumonitis (10.0%), while grade 3-4 irAEs only occurred in 4.4% patients. Three-months landmark analyses showed that patients with irAE have significantly longer OS than those without (29.3 vs. 22.1 months, P = 0.018). Exploratory analyses demonstrated that patients with PDL1 CPS ≥10 had significantly longer PFS (13.7 vs 11.4 months, P = 0.039). Patients with high TILs had significantly longer OS (23.1 vs.10.3 months, P = 0.003). The proportion of PDL1 positive (CPS ≥1) patients was 81.8% in basal compared to 0% in non-basal subtype (P = 0.023). Hallmark pathway analysis showed that the activation of DNA repair pathway (HR,11.6, 95%CI 2.4-55.7, P = 0.002) and MYC target pathway (HR,7.4,95%CI 1.9-28.2, P = 0.004) was significantly associated with shorter PFS, while the activation of KRAS signaling (HR,3.2, 95%CI 1.1-9.7, P = 0.035) was significantly associated with worse OS. **Conclusions:** Camrelizumab plus AP as first-line treatment in patients with mTNBC demonstrated satisfying efficacy with manageable toxicity. Randomized controlled trial is warranted in the future. Clinical trial information: NCT04537286. Research Sponsor: None.

Safety and efficacy of the anti-TROP2 antibody-drug conjugate (ADC) IBI130 in patients (pts) with advanced triple-negative breast cancer (TNBC) and other solid tumors: Results from the phase 1 study.

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Background: TROP2 is a promising therapeutic target in various solid tumors. IBI130 is composed of an anti-TROP2 antibody conjugated to the camptothecin derivative NT1. Herein, we report the multi-regional, first-in-human, phase 1 study of IBI130. **Methods:** Eligible pts with unresectable locally advanced or metastatic solid tumors who failed or intolerant to standard treatment were enrolled. The study included dose escalation and dose expansion. IBI130 was intravenously administered at 1/2/4/6/8/10/12 mg/kg Q3W during dose escalation, which was guided by modified continuous reassessment method (mCRM) according to Bayesian logistic regression model (BLRM) and escalation with overdose control (EWOC) principle. Primary endpoint was safety. Secondary endpoint was efficacy assessed by investigator per RECIST v1.1 including objective response rate (ORR), disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS). **Results:** As of Dec 15, 2024, 71 pts were enrolled from China and Australia (median age: 60 years [range: 30-81], female: 85.9%, Caucasian: 16.9%, ECOG PS 1: 48.6%; prior lines of anticancer treatment≥2: 63.8%). Median follow-up of the study was 4.6 months (range: 0.8-9.7). No dose-limiting toxicity (DLT) was observed across all dose levels during dose escalation (n = 18). Median treatment duration was 18 weeks (range: 3-45) with 40 (56.3%) pts still on treatment. Treatment-emergent adverse events (TEAEs) occurred in 68 (95.8%, with 90.1% treatment-related adverse events [TRAEs]) pts including grade 3 (G3) events in 17 (23.9%, with 15.5% TRAEs) pts. No grade 4-5 events occurred. Common TEAEs (≥30%) were stomatitis (52.1%, with 9.9% G3), nausea (31.0%, with 2.8% G3) and rash (31.0%, with 1.4% G3). Interstitial lung disease occurred in 1 pt (1.4%, G1). Only 1 pt (1.4%) had G3 lymphocyte count decreased. Other ≥G3 hematological toxicities were not observed. TRAEs led to dose reduction in 5 (7.0%) pts and treatment discontinuation in 1 (1.4%) pts. Efficacy of IBI130 was evaluable in 30 pts with TNBC treated at 4/6/8/10 mg/kg (all stage IV, and 96.7% had failed or were intolerant to taxanes). The overall ORR was 50.0% (95% CI: 31.3-68.7) and DCR was 83.3% (95% CI: 65.3-94.4). As for different dose levels, ORR and DCR were 40.0% (95% CI: 5.3-85.3) and 60.0% (95% CI: 14.7-94.7) for 4 mg/kg (n = 5), 40.0% (95% CI: 5.3-85.3) and 80.0% (95% CI: 28.4-99.5) for 6 mg/kg (n = 5), 50.0% (95% CI: 18.7-81.3) and 100% (95% CI: 69.2-100.0) for 8 mg/kg (n = 10), 60.0% (95% CI: 26.2-87.8) and 80.0% (95% CI: 44.4-97.5) for 10 mg/kg (n = 10). DoR and PFS data were not mature as of the cutoff date. **Conclusions:** IBI130 was well tolerated featured by superiority of hematological safety, and encouraging efficacy of IBI130 was observed in advanced TNBC, supporting its potential as a best-in-class TROP2 ADC. Clinical trial information: NCT05923008. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

SHR-A1811 plus adebrelimab in unresectable or metastatic triple-negative breast cancer: Results from a phase 1b/2 expansion cohort.

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Background: SHR-A1811 is a novel HER2-directed antibody-drug conjugate with promising antitumor activity in breast cancer (BC), yielding a confirmed objective response rate (ORR) of 79.4% in HER2 positive BC, 60.9% in HER2 low-expressing BC, and 52.0% in triple-negative BC (TNBC) as monotherapy. We evaluated SHR-A1811 in combination with adebrelimab (anti-PD-L1 antibody), pyrotinib (irreversible, pan-HER receptor tyrosine kinase inhibitor), pertuzumab, or albumin-bound paclitaxel in unresectable or metastatic breast cancer in an open-label, dose-finding and efficacy expansion phase 1b/2 study. Here, we report the safety and efficacy results of the SHR-A1811 plus adebrelimab cohort. **Methods:** Patients (pts) with unresectable or metastatic TNBC and ≥1 line of prior treatment received intravenous SHR-A1811 at an escalating dose of 4.8 mg/kg and 5.6 mg/kg Q3W, in combination with adebrelimab (1200 mg Q3W) in phase 1b part. In phase 2 part, TNBC pts with no systematic antitumor therapy in the recurrent or metastatic setting were treated with SHR-A1811 at 4.8 mg/kg Q3W plus adebrelimab. Primary endpoints were safety and ORR. The data cutoff date was Nov 30, 2024. **Results:** Fifty TNBC pts were enrolled in total. In phase 1b, 8 pts were enrolled and treated. No DLT was observed. The confirmed ORR was 66.7% (2/3) and 60.0% (3/5) in the 4.8 mg/kg and 5.6 mg/kg dose group, respectively. In phase 2, 42 treatment naive TNBC pts were enrolled. 13 (31.0%) pts had ≥3 metastases sites, 22 (52.4%) pts were HER2-low (IHC 2+/ISH- or IHC 1+)/ultra-low (IHC 0-1), 20 (47.6%) pts were HER2-nul (IHC 0), and 30 (71.4%) pts were PD-L1-positive (CPS ≥1). At the time of data cutoff, the median follow-up time was 4.6 mo (range, 0.2-10.4). Among efficacy evaluable TNBC pts, the overall ORR was 66.7% (26/39) (Table). ORR was 77.8% (21/27) in the PD-L1-positive subgroup. The 6-month PFS rate was 86.2%. SHR-A1811 plus adebrelimab was well tolerated with no new safety concerns identified. Treatment-emergent adverse events of grade ≥3 occurred in 26 (61.9%) out of 42 pts in phase 2, with decreased neutrophil count (45.2%), decreased white blood cell count (33.3%), and decreased lymphocyte count (9.5%) being the most common. **Conclusions:** SHR-A1811 plus adebrelimab had a good safety and tolerability profile. The combination showed encouraging antitumor activity in unresectable or metastatic TNBC, irrespective of HER2 or PD-L1 expression status. Clinical trial information: NCT05353361. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Phase 2 preliminary efficacy summary[1].

	SHR-A1811 4.8 mg/kg + adebrelimab		
	CPS ≥1 (N = 30)	CPS <1 (N = 12)	Total (N = 42)
ORR, Overall[2]	21/27 (77.8)	5/12 (41.7)	26/39 (66.7)
HER2-low/-ultralow	11/13 (84.6)	4/9 (44.4)	15/22 (68.2)
HER2-nul	10/14 (71.4)	1/3 (33.3)	11/17 (64.7)
6-mo PFS rate, % (95% CI)	88.9 (43.3, 98.4)	78.8 (38.1, 94.3)	86.2 (60.7, 95.7)

[1]HER2 and PD-L1 results were based on central lab assessment.
[2]Data are n/N1(%) with N1 = the number of efficacy evaluable patients.

ETER901: A randomized, open-label, phase III trial of anlotinib in combination with anti-PD-L1 antibody benmelstobart (TQB2450) versus nab-paclitaxel in first-line treatment of recurrent or metastatic triple-negative breast cancer.

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Background: Recurrent or metastatic triple-negative breast cancer (TNBC) represents an aggressive malignancy with unfavorable prognoses. Benmelstobart (TQB2450) is a humanized monoclonal antibody targeting PD-L1, and anlotinib (ALTN) is an anti-angiogenic oral multi-target tyrosine kinase inhibitor. Herein, we present the findings of a randomized, open-label, phase 3 study comparing the combination of benmelstobart plus ALTN with nab-paclitaxel as first-line treatments for patients (pts) with recurrent or metastatic TNBC. **Methods:** In this phase 3 trial, patients with previously untreated stage IV or recurrent/metastatic TNBC were randomly allocated in a 1:1 ratio. One group received 1200 mg of intravenous benmelstobart on day 1, along with 12 mg of oral ALTN from days 1 to 14, following a 3-week cycle. The other group was administered 100 mg/m^2 of intravenous nab-paclitaxel on days 1, 8, and 15 within a 4-week cycle. Randomization was stratified based on whether patients had received neoadjuvant or adjuvant taxane therapy and the presence or absence of liver or brain metastases at baseline. The primary endpoint was progression-free survival (PFS), evaluated by the blinded independent central review by RECIST version 1.1. **Results:** The initial plan was to enroll 332 pts in this trial. However, due to the COVID-19 pandemic, the enrollment process was delayed, and recruitment was terminated in January 2023. Eventually, 147 pts were randomized (with a median follow-up of 14 months), among whom 75 were assigned to the benmelstobart plus ALTN group and 72 to the nab-paclitaxel group. In the intention-to-treat analysis, as assessed by the investigators, the median PFS was 7.85 months for the benmelstobart plus ALTN combination, in contrast to 5.55 months for nab-paclitaxel (hazard ratio, 0.70; 95% confidence interval, 0.46 to 1.06; P = 0.1687). The median overall survival was 35.81 months for study group and 21.03 months for control group (hazard ratio, 0.78; 95% confidence interval, 0.49 to 1.24; P = 0.2625). Grade ≥3 drug-related adverse events occurred in 56.5% of the patients in the study group and 36.6% in the control group. The most prevalent grade ≥3 adverse events in the study group were hypertension (28.0%) and hypertriglyceridemia (13.3%). **Conclusions:** The combination of benmelstobart plus ALNT might extend both progression-free survival and overall survival in the first-line treatment of patients with recurrent or metastatic TNBC. The adverse events were in line with the previously established safety profiles of each individual agent. (Funded by Chia Tai Tianqing Pharmaceutical Group Co., Ltd. ClinicalTrials.gov number, NCT04405505). Clinical trial information: NCT04405505. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Clinical, sociodemographic, and facility-related determinants of immunotherapy use in metastatic triple-negative breast cancer.

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Background: Immunotherapy has emerged as a promising treatment option for metastatic triple-negative breast cancer (mTNBC), yet the factors influencing its adoption remain poorly understood. This study investigates the clinical, sociodemographic, and facility-related determinants of immunotherapy use in patients with mTNBC from 2015 to 2020, utilizing data from the National Cancer Database (NCDB). **Methods:** We conducted a retrospective cohort study of mTNBC patients from the NCDB between 2015 and 2020, categorizing them into two groups: those who received immunotherapy and those who did not. Patients were excluded if they had missing data on key variables such as immunotherapy receipt and clinical characteristics (e.g., tumor stage, subtype). Univariable and multivariable logistic regression analyses were performed to identify factors influencing immunotherapy adoption. The impact of immunotherapy on overall survival was assessed using Cox proportional hazards regression analysis. Overall survival between the two groups was compared using the log-rank test. **Results:** A total of 1,887 mTNBC patients were included in the study: 1,656 (87.8%) did not receive immunotherapy, and 232 (12.2%) received immunotherapy. Multivariable logistic regression identified several factors associated with immunotherapy use. Later year of diagnosis (2018–2020: OR 5.35, $p < 0.001$) and academic facilities (OR 1.43, $p = 0.044$) were positively associated with immunotherapy use. In contrast, older age (71+: OR 0.49, $p = 0.019$), facilities in rural areas (OR 0.43, $p = 0.042$), Black race (OR 0.73, $p = 0.039$), Hispanic ethnicity (OR 0.53, $p = 0.026$), and higher Charlson comorbidity scores (OR 0.31, $p = 0.035$ for scores ≥ 2) were associated with a lower likelihood of receiving immunotherapy. Insurance status did not significantly influence immunotherapy use. Log-rank test showed that patients receiving immunotherapy had significantly improved survival compared to those who did not (Figure 1). The median survival for patients receiving immunotherapy was 2.21 years (95% CI: 1.80–2.96), compared to 1.01 years (95% CI: 0.93–1.11) for those not receiving immunotherapy (log-rank $p < 0.001$). Cox regression analysis showed that immunotherapy use was associated with a significantly reduced risk of death (HR 0.59, 95% CI: 0.46–0.77, $p < 0.001$). **Conclusions:** Immunotherapy use in mTNBC has increased in recent years, with clinical, sociodemographic, and facility-related factors influencing its adoption. Patients receiving immunotherapy had significantly better survival outcomes. Our findings highlight the importance of addressing disparities in access to immunotherapy, particularly related to race, age, ethnicity, and comorbidity burden, to ensure equitable treatment and outcomes for all mTNBC patients. Research Sponsor: None.

Chemokines as predictive biomarkers for immune checkpoint inhibitor (ICI) efficacy in triple negative breast cancer (TNBC).

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Background: TNBC, although an aggressive breast cancer (BC) subtype, is highly immunogenic and the only BC subtype where the ICI pembrolizumab is approved. However, predictive biomarkers for pembrolizumab benefit are limited. The chemokines *CXCL9* and *CXCL10* attract $CD8^+$ T cells into the tumor microenvironment (TME) and are associated with chemotherapy benefit, but little is known about their role in prediciting pembrolizumab benefit in TNBC. We investigated the association of *CXCL9*, *CXCL10* and their cognate receptor *CXCR3* with TME and ICI efficacy. **Methods:** 3,038 TNBC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ). Tumor mutational burden (TMB) totaled somatic mutations per tumor (high > 10 mt/MB). Immune cell fractions were estimated using WTS deconvolution (Quantiseq). *CXCL9/CXCL10/CXCR3*-high (H) and -low (L) tumors were classified by RNA expression above or below the 50th percentile. Real-world overall survival (OS) was derived from insurance claims and calculated from start of pembrolizumab to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U with multiple comparison adjustments ($q < .05$). **Results:** TNBC expressed higher levels of *CXCL9* and *CXCL10* (median (TPM): 5.3 and 14.7) compared to N = 1,082 HER2+ (4.8 and 10.3, $p < 0.05$) and N = 4,918 HR+HER2- (2.7 and 7, $q < .05$) BC. *CXCR3* expression was higher in TNBC compared to HR+HER2- (1.9 vs 1.7, $q < .05$), but no difference when compared to HER2+ (1.9 vs 2, $q = 0.97$) BC. *CXCL9/CXCL10/CXCR3*-H TNBC had higher median OS post pembrolizumab [*CXCL9*-H vs -L: 26.5 vs 15.7 months (mo), HR: 0.65 (95% CI 0.5-0.84); *CXCL10*-H vs -L: 26.0 vs 20.6 mo, HR 0.74 (0.57-0.95); *CXCR3*-H vs -L: 32.6 vs 18.3 mo, HR 0.68 (0.52-0.88), all $p < 0.05$]. *CXCL9*-H, *CXCL10*-H and *CXCR3*-H had higher PD-L1 positivity (22C3), TMB high, higher T cell inflamed score, *TP53* mutations, elevated B and $CD8^+$T cells infiltration, but not neutrophils, and higher expression of immune checkpoint genes (Table). **Conclusions:** High *CXCL9/CXCL10/CXCR3* expression is associated with longer survival in patients with TNBC post pembrolizumab, and characterized by an immune-enriched TME. Further investigation is needed to evaluate this chemokine axis in TNBC and its potential as a therapeutic target to enhance ICI efficacy. Research Sponsor: NIH (NCATS, NCI); K08CA279766-01A1.

TME characteristics by *CXCL9, CXCL10* and *CXCR3* expression.

	CXCL9			*CXCL10*			*CXCR3*		
	High	Low	q-value	High	Low	q-value	High	Low	q-value
PD-L1 %	54	14	<.05	54	14.7	<.05	49	19	<.05
TMB high %	14.3	8	<.05	12.6	9.7	<.05	12.4	9.8	<.05
B cell (median %)	4.4	3.5	<.05	4.3	3.6	<.05	5	3.4	<.05
CD8+T cell (median %)	1.2	0	<.05	1	0	<.05	1.3	0	<.05
Neutrophil (median %)	4.2	4.5	<.05	4.2	4.4	<.05	4.2	4.3	0.2
T cell inflamed score	100	-84	<.05	98	-84	<.05	108	-100	<.05
***CTLA4* (median TPM)**	3.2	0.7	<.05	3	0.8	<.05	3.4	0.7	<.05
***LAG3* (median TPM)**	6.6	2.1	<.05	6.9	2	<.05	6.8	2	<.05
***TP53* mutation %**	88	81	<.05	90.5	78.6	<.05	86	83	0.08

Comprehensive molecular and immune characterization of adrenergic stress-signaling receptor *ADRB2* in triple negative breast cancer (TNBC).

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Background: Chronic stress-mediated β2-adrenergic receptor (β2-AR) signaling promotes tumor growth via immunosuppression in the tumor microenvironment (TME) in preclinical models. Blockade of β2-AR has shown higher survival benefit in patients with TNBC in observational studies compared to other breast cancer (BC) subtypes. However, the molecular and immunological features associated with *ADRB2* (gene for β2-AR) gene expression in TNBC are unknown, prompting this investigation. **Methods:** 3,038 TNBC samples were analyzed via NGS (592-gene panel, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences, Phoenix, AZ). Immune cell fractions were calculated by deconvolution of WTS: Quantiseq. TNBC *ADRB2*-high(H) and *ADRB2*-low(L) RNA expression were classified as above or below the 50th percentile, respectively. Real-world overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Statistical significance was assessed using chi-square and Mann-Whitney U tests with multiple comparison adjustments ($q < 0.05$). **Results:** *ADRB2* gene expression was lowest in TNBC (median (TPM: 1.6) compared to N = 453 HR-HER2+ (1.9), N = 629 HR+HER2+ (2.0) and N = 4,918 HR+HER2- (2.2) BC (all $q < 0.05$). African American or Black patients (N = 670) had lower expression of *ADRB2* compared to European American or White (N = 1,412) TNBC patients (1.3 vs 1.7, $q < 0.05$). *ADRB2*-H TNBC had higher mutation frequency of *PIK3CA* (21% vs 15.4%), *CDH1* (7% vs 3.5%), *NF1* (8% vs 4%), *AKT1* (3.5% vs 2.1%), but lower frequency of *TP53* (81.6% vs 87.5%), *NOTCH1* (2.5% vs 4.5%) and *NOTCH3* (4.4% vs 11.7%) compared to *ADRB2*-L, all $q < 0.05$. *ADRB2*-H had greater PD-L1 (22C3) positivity (39.1% vs 30.2%, $q < 0.05$), higher % of B cells (4.5 vs 3.4), M1 Mφ (3.4 vs 2.8), M2 Mφ (3.9 vs 2.2), Tregs (2.2 vs 1.3), NK cells (3.1 vs 2.6), DC (3.1 vs 2.9), CD8$^+$ T cells (0.9 vs 0.2), all $q < 0.05$. *ADRB2*-H TNBC had higher T-cell inflamed score (95 vs -80), *IFNγ* score (-0.23 vs -0.37), MAPK activation score (-0.46 vs -1.7), all $q < 0.05$; and higher expression of immune checkpoint genes (*CD274, PDCD1, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, TNFSF14, TIGIT, BTLA, CEACAM1, CD47, CD274*; fold change: 1.6-3.7, all $q < 0.05$). *ADRB2*-H tumors had higher expression of genes related to inflammatory response, IFNγ response, IL6-JAK-STAT3 signaling (normalized enrichment score (NES): 1.9 – 2.1), while *ADRB2*-L had enrichment of MYC targets V1, MYC targets V2, E2F targets and G2M checkpoint (NES: 2.5 – 4.2), all FDR < 0.01. *ADRB2*-H TNBC had better OS (mOS: 23.6 vs 18.6 months; HR 0.81, 95% CI 0.73-0.89, $p < 0.0001$) compared to *ADRB2*-L. **Conclusions:** High *ADRB2* expression in TNBC is associated with better survival and an immune enriched TME, elevated immune checkpoints and other targetable vulnerabilities. Future studies are needed to investigate *ADRB2* as a potential stress biomarker and therapeutic target. Research Sponsor: NIH (NCATS and NCI); K08CA279766-01A1.

Enhanced efficacy of inavolisib combined with anti-PD-1 or anti-HER2 antibody in treating brain metastases from breast cancer.

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Background: The PI3K/AKT/mTOR signaling pathway is a crucial regulatory pathway involved in cell proliferation, survival, migration, and metabolism. This dysregulation can occur through various mechanisms, such as PIK3CA gene mutations and PTEN gene loss. The research of PI3K inhibitors has made significant progress in the treatment of ER-positive and HER2-negative breast cancer. Alpelisib is the only approved PI3K inhibitor for treating PIK3CA mutation-positive breast cancer. The SOLAR-1 trial demonstrated that Alpelisib combined with endocrine therapy significantly prolongs progression-free survival in these patients. However, despite improving PFS, the side effects of PI3K inhibitors pose limitations on their widespread application. Consequently, researchers are exploring next-generation PI3K inhibitors with improved safety and efficacy. Inavolisib is a novel, highly selective PI3Kα inhibitor that shows better tolerability and safety compared to existing PI3K inhibitors and has demonstrated promising antitumor effects in clinical trials. Building on this, our study aims to identify the optimal treatment regimen combining Inavolisib with various breast cancer therapies to effectively target brain metastases. **Methods:** We established a brain metastasis model in C57BL/6 mice by intracardiac injection of control (triple-negative) and hHER2+ Py8119 breast cancer cells. In addition to the Inavolisib monotherapy and vehicle control groups, Inavolisib was combined with a PD-1 antibody or albumin-bound paclitaxel in the triple-negative model. In the HER2+ model, Inavolisib was combined with Tucatinib, trastuzumab, or SHR-A1811 (an ADC drug targeting HER2). We monitored changes in body weight and survival rates in each group and assessed brain metastasis using IVIS small animal in vivo imaging. **Results:** In the triple-negative model, Inavolisib monotherapy or its combination with albumin-bound paclitaxel reduced intracranial tumor size but did not significantly extend mouse survival. Conversely, the combination of Inavolisib and PD-1 antibody significantly prolonged overall survival in triple-negative breast cancer mice. In the HER2+ breast cancer model, all three combination therapies reduced tumor burden and extended survival compared to monotherapy. However, overall, the combination with trastuzumab achieved unexpectedly good results, which were comparable to SHR-A1811 and superior to Tucatinib. **Conclusions:** Our findings suggest that the combination of the PI3K inhibitor Inavolisib with anti-PD-1 or anti-HER2 antibody therapy may offer an effective strategy for treating brain metastases in breast cancer. This discovery provides new insights and possibilities for improving treatment options in breast cancer brain metastasis. Further research is needed to validate the efficacy and safety of this combination therapy. Research Sponsor: None.

Efficacy and safety of RC48-ADC in triple-negative breast cancer subtypes: FUSCC-TNBC-umbrella trial results.

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Background: RC48-ADC is a novel HER2-targeting antibody-drug conjugate. This study evaluated RC48-ADC in pretreated triple-negative breast cancer (TNBC) patients with low HER2 expression, stratified by AR status. **Methods:** In this phase Ib/II trial, pretreated metastatic TNBC patients with low HER2 expression were enrolled: RL group (LAR subtype, n=20) and RO group (non-LAR subtype, n=20). All received RC48-ADC 2.0 mg/kg intravenously every 2 weeks. Primary endpoint: objective response rate (ORR). Secondary endpoints: progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and safety. **Results:** 40 heavily pretreated patients were enrolled (median 2 previous lines, range 1-7). In the overall population, best ORR was 35.0% (confirmed ORR: 32.5%), DCR 47.5%, median PFS 4.0 months. RL group showed better outcomes: best ORR 45.0% vs 25.0%, confirmed ORR 40.0% vs 25.0%, DCR 50.0% vs 45.0%, median PFS 4.9 vs 3.1 months. Median OS was not reached in RL group vs 16.6 months in RO group. Most common treatment-related adverse events (TRAEs) were AST increased (70% vs 40%) and ALT increased (65% vs 20%), mostly grade 1-2. Peripheral neuropathy occurred in 15% (RL) and 10% (RO) patients. Hematologic toxicities were mild. No treatment-related deaths occurred. **Conclusions:** RC48-ADC showed promising antitumor activity with manageable safety in pretreated TNBC patients with low HER2 expression, particularly in LAR subtype. The 35.0% ORR in heavily pretreated TNBC warrants further investigation in biomarker-selected populations. Clinical trial information: NCT03805399. Research Sponsor: None.

Efficacy and key safety outcomes of RC48-ADC in overall population and by subgroups.

Outcomes	Overall (n=40)	RL Group (n=20)	RO Group (n=20)
Efficacy			
Confirmed ORR, n (%)	13 (32.5)	8 (40.0)	5 (25.0)
Best ORR, n (%)	14 (35.0)	9 (45.0)	5 (25.0)
DCR, n (%)	19 (47.5)	10 (50.0)	9 (45.0)
Median PFS, months	4	4.9	3.1
Median OS, months	NR	NR	16.6
Best Response, n (%)			
CR	1 (2.5)	1 (5.0)	0 (0.0)
PR	13 (32.5)	8 (40.0)	5 (25.0)
SD	5 (12.5)	1 (5.0)	4 (20.0)
PD	21 (52.5)	10 (50.0)	11 (55.0)
Selected TRAEs, n (%)			
AST increased			
- Grade 1-2	22 (55.0)	14 (70.0)	8 (40.0)
- Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased			
- Grade 1-2	17 (42.5)	13 (65.0)	4 (20.0)
- Grade ≥3	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral neuropathy			
- Grade 1-2	3 (7.5)	2 (10.0)	1 (5.0)
- Grade ≥3	2 (5.0)	1 (5.0)	1 (5.0)

Artificial Intelligence-based tumor microenvironment and PD-L1 analysis using digital pathology to predict pembrolizumab response in metastatic triple-negative breast cancer.

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Background: The combination of pembrolizumab and chemotherapy improves survival in programmed death ligand 1 (PD-L1) positive metastatic triple-negative breast cancer (mTNBC). However, responses vary even among PD-L1 positive, and predictive biomarkers remain undefined. This study investigates the predictive biomarkers to pembrolizumab through digital pathology and artificial intelligence (AI)-based tumor microenvironment (TME) and PD-L1 analysis. **Methods:** We retrospectively analyzed 53 PD-L1 positive, mTNBC patients treated with pembrolizumab at Gangnam Severance Hospital (2017–2024). PD-L1 positivity was defined as a combined positive score (CPS) ≥ 10. Immune phenotypes and immune cell density in both tumor and stroma were analyzed in 67 H&E images using Lunit SCOPE IO, an AI-powered whole slide image analyzer. PD-L1 CPS was analyzed in paired PD-L1 staining images by both Lunit uIHCv2 analyzer and pathologists. Samples were categorized as pre-(pre) or post-treatment (post). Pre-samples were collected before any therapy exposure, while post-samples were obtained after recurrence following neo/adjuvant therapy. These features were analyzed for their association with pembrolizumab response and clinical outcome. **Results:** With a median follow-up of 13.2 months, the median age was 53 years, and 16 patients (22.5%) were *de novo* stage IV TNBC. AI-assessed PD-L1 positivity was seen in 52.2% (35/67) of cases, compared to 74.6% (50/67) by pathologist. Overall, AI-based PD-L1 positive cases had a median progression-free survival (mPFS) of 8.8 months (mo) vs 6.7 mo in PD-L1 negative (p = 0.028), while pathologist-reported cases showed 7.9 mo vs 6.3 mo, respectively (p = 0.17). AI-based PD-L1 positivity in pre-samples was associated with better PFS with pembrolizumab (mPFS 7.7 mo vs 4.4mo, HR 0.32, p = 0.014), while post-samples showed no significant association (mPFS 7.3 mo vs 6.4mo, HR 0.69, p = 0.4). Notably, post-samples (50.0%) had a higher proportion of cases with AI-based CPS ≥ 10 compared to pre-samples (36.4%), primarily driven by increased PD-L1-expressing macrophages, as revealed by AI-based cell composition analysis (22.7% vs 7.7%, p = 0.0007). When categorized by AI-based immune phenotype, notable differences were seen between pre/post-samples despite PD-L1 positivity. Post-samples showed a higher prevalence of the immune-desert phenotype, reflecting significant changes in the TME following prior therapy exposure (40.0% vs 20.0%, p = 0.06). **Conclusions:** This study highlights the role of the TME and PD-L1 assessed by AI in predicting pembrolizumab response in mTNBC. While PD-L1 positivity in pre-samples was associated with outcome, PD-L1 positivity in post-samples showed limited association with PFS, potentially influenced by immune desert phenotype and increased PD-L1-expressing macrophages. Research Sponsor: None.

Geographic access to triple negative breast cancer (TNBC) clinical trials: Are trials located near Black women?

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Background: Despite recent treatment advances, TNBC has a poor prognosis relative to other breast cancer subtypes. Black women in the U.S. are more likely to be diagnosed with TNBC, are diagnosed at more advanced stages, and have higher mortality even after controlling for socioeconomic variables than women of other races. Although clinical trials are essential to improving TNBC treatment, Black women are underrepresented. We investigated the geographic availability of TNBC clinical trials for Black women in the U.S. to elucidate potential trial access limitations. **Methods:** All trials registered on ClinicalTrials.gov as of 9/30/2024 were queried (N= 510,397). Phase II and III interventional treatment trials in active status in the U.S. including "breast" in the title or disease variable (n =449) were considered. We narrowed results to TNBC trials through keyword searches of title and disease variables (e.g., TNBC, HER2 negative and hormone receptor negative). We tabulated the number of trials per county and supplemented with 5-year population estimates (2018-2022) and county adjacency data from the U.S. Census Bureau to evaluate for geographic and demographic differences in TNBC trial availability. **Results:** We identified 108 active TNBC trials (58 metastatic [54%], 50 nonmetastatic [46%]), including 87 Phase II (81%) and 21 Phase III (19%). There were 1,230 U.S. study sites, of which 217 had one active TNBC trial (18%), 529 had 2-4 trials (43%), and 484 had ≥5 trials (39%). Most sites had metastatic and nonmetastatic offerings (700, 57%) while 450 sites had only nonmetastatic trials (37%) and 80 had only metastatic trials (7%). State-level differences in trial availability were observed (see Table). For example, 37% of Black and 34% of non-Black women 18+ in Alabama had no TNBC trials in their or neighboring counties while all women 18+ in nine states had a trial available in at least a neighboring county. **Conclusions:** A geographical analysis of active Phase II and III therapeutic TNBC clinical trials found uneven trial availability across the country. Most study sites had < 5 TNBC trials available; a third of sites had no metastatic trials, suggesting that many women may have difficulty finding an applicable trial even when near to a site. On a national scale, distance does not appear to be a primary reason for disparities in TNBC trial participation for Black and non-Black women. Nevertheless, millions of women live in areas without any trials, therefore expanding geographic reach is a necessary but insufficient approach to improve access. Research Sponsor: None.

Category (Number of Counties)	Black women 18+ in millions (%)	Non-Black women 18+ in millions (%)	Total in millions (%)
Counties with trial (748)	14 (82%)	88 (77%)	102 (78%)
Trials only in adjacent county (1452)	2 (12%)	21 (18%)	22 (17%)
No trials in county nor adjacently (944)	1 (6%)	6 (5%)	7 (5%)
Total (3144)	17 (100%)	115 (100%)	131 (100%)

Immunotherapy vs. chemotherapy run-in followed by pembrolizumab plus nab-paclitaxel in metastatic triple negative breast cancer (mTNBC): Results from a phase II study.

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Background: Pembrolizumab (pembro) with chemotherapy has shown survival benefit in PD-L1+ (CPS10+) mTNBC, but many responses are not durable, and patients with PD-L1 negative/low tumors do not benefit from the combination. Data from GeparNuevo and TONIC suggest that induction therapy can remodel the tumor immune environment and improve responses. We have conducted a trial with two run-in cohorts and mandatory serial tissue and blood collections in 50 mTNBC patients, comparing pembro vs. nab-paclitaxel (nab-P). **Methods:** Single-arm, single institution phase II study (NCT02752685) to evaluate safety and clinical activity of nab-P+pembro in PD-L1 unselected mTNBC, 0-2 prior lines of chemotherapy allowed. Patients (n = 50) were enrolled sequentially into two cohorts: chemotherapy run-in (cTNBC, nab-P before nab-P+pembro) and immunotherapy run-in (iTNBC, pembro before nab-P+pembro). Serial tumor biopsies assessed by IHC (Dako 22C3), quantitative multiplex immunofluorescence (qMIF), and gene expression (NanoString). Overall response rates assessed using irRECIST. Tumoral T- and myeloid-cell phenotypes, peripheral lymphocyte-to-neutrophil ratio (LNR), and monocyte-to-lymphocyte ratio (MLR) were correlated with overall response rate (ORR) and survival outcomes. **Results:** 50 patients enrolled and completed treatment, for 80% of patients: treatment was 1L for metastatic disease. Median follow-up is 19.9 months, clinical results for cTNBC and iTNBC cohorts shown in table. Across both cohorts higher LNR was associated with improved OS (R= 0.37, p= 0.0075), conversely, higher MLR was associated with poorer OS (R= -0.46, p= 0.00087). Tumor immune cell subpopulations showed no significant differences between iTNBC and cTNBC at baseline. Analyses of on-treatment samples will be presented at the meeting. PD-L1 expression, while not different at baseline, remained unchanged in cTNBC but increased significantly in iTNBC ($p<$ 0.02), possibly reflecting pembrolizumab-driven immune modulation. With the caveat of comparing sequential cohorts, the iTNBC cohort showed a trend for higher ORR (47% vs. 23%, p= 0.08) and longer median PFS (8.4 vs. 5.5 months, HR = 0.68, 95%CI: 0.37-1.24), with significantly longer OS (25.8 vs. 18 months, HR = 0.50, 95%CI: 0.26-0.98, p = 0.043) compared to cTNBC. **Conclusions:** Timing of pembro administration may influence PD-L1 expression and clinical outcomes in mTNBC. We show that the immunotherapy run-in strategy converts more PD-L1-negative/low into PD-L1-positive tumors, possibly rendering more patients eligible for chemo-immunotherapy and improving outcomes. Clinical trial information: NCT02752685. Research Sponsor: Merck & Co., Inc.

	cTNBC (n=30)	iTNBC (n=20)
PD-L1 CPS >/=10	5/23 (22%)	2/16 (12%)
PD-L1 CPS conversion (CPS<10 to CPS>/=10)	2/14 (14%)	4/13 (31%)
Confirmed ORR (CR+PR)	7/30 (23%)	9/19 (47%)
mPFS (months)	5.5	8.4
mOS (months)	18.0	25.8

Trop2-targeted PET/CT with ^{68}Ga-MY6349 for the diagnosis of primary and metastatic breast cancer and evaluation towards patient stratification in Trop2-targeted ADCs.

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Background: Trop2-targeted ADCs have demonstrated promising efficacy and have been approved in patients with HR+HER2- and triple-negative breast cancer (TNBC). However, not all patients within these subtypes benefit equally from such treatment, highlighting the urgent need for developing tools for patient selection and stratification. We have previously developed a novel PET/CT imaging agent (^{68}Ga-MY6349) that specifically targets Trop2, which has shown high specificity for Trop2 in preclinical and clinical studies (DOI: 10.1172/JCI185408). **Methods:** This study enrolled patients with newly diagnosed or previously treated breast cancer at the First Affiliated Hospital of Xiamen University between January 2024 and December 2024. All patients underwent paired ^{18}F-FDG PET/CT and ^{68}Ga-MY6349 PET/CT imaging. SUVmax derived from the two PET/CT modalities and pathological results were recorded to evaluate the tumor uptake pattern and lesion detectability of the two imaging modalities. **Results:** A total of 61 patients were prospectively enrolled, including 7 true-negative and 54 true-positive cases. Among the 562 true-positive lesions, ^{68}Ga-MY6349 uptake (SUVmax) was significantly associated with breast cancer subtypes ($P<0.001$, Kruskal-Wallis $H=34.9$). SUVmax values were highest in HR+/HER2- [7.2 (4.4–9.4)], followed by TNBC [5.2 (3.8–6.4)], HER2+ [4.8 (1.7–7.4)], and HR+/HER2+ [3.3 (2.1–8.1)]. In HR+/HER2- subtypes, ^{68}Ga-MY6349 demonstrated significantly higher uptake compared to ^{18}F-FDG [7.2 (4.4–9.4) vs. 3.6 (2.3–5.5), $P<0.001$]. However, no significant difference regarding tumor uptake was observed in other subtypes. In 27 patients with HR+/HER2- subtypes, ^{18}F-FDG PET/CT detected 139/208 lesions (missing 2 primary, 40 visceral and bone metastases, and 27 lymph node metastases), while ^{68}Ga-MY6349 PET/CT detected 202/208 lesions (missing 1 visceral and bone metastasis and 5 lymph node metastases). Interestingly, among 215 lesions in 16 TNBC patients, ^{18}F-FDG PET/CT detected 206 metastatic lesions (missing 9 lymph node metastases), whereas ^{68}Ga-MY6349 PET/CT detected all lesions. For HER2+ (7 patients with 74 lesions) and HR+/HER2+ (4 patients with 65 lesions) subtypes, the two tracers exhibited comparable lesion detectability. **Conclusions:** ^{68}Ga-MY6349 PET/CT demonstrated superior uptake and greater lesion detectability compared to ^{18}F-FDG PET/CT in patients with HR+/HER2- breast cancer. The high uptake of ^{68}Ga-MY6349 in HR+/HER2- and TNBC lesions may partially explain the favorable clinical outcomes observed with Trop2-targeted ADCs in these subtypes, suggesting its potential role for patient selection and stratification for Trop2-targeted therapies. However, the observed heterogeneity in uptake warrants further investigation to clarify its applications across different patient populations. Clinical trial information: NCT06188468. Research Sponsor: None.

Comprehensive characterization of interleukin-enhanced factor 2 (ILF2) in triple-negative breast cancer (TNBC).

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Background: While treatment and management of TNBC has improved, there is a need for novel prognostic biomarkers to better inform outcomes and guide therapeutic options. *ILF2* is a poorly characterized protein with pleiotropic functions that is highly expressed in TNBC. Here we evaluated the associations of *ILF2* with 1) genomic and transcriptomic data, 2) tumor microenvironment (TME), and 3) clinical outcomes in TNBC. **Methods:** 15,544 breast cancer (BC) samples, including 3,038 TNBC, were tested by NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). *ILF2*-high (H) and *ILF2*-low(L) TNBC were defined by respective quartiles. Immune cell fractions were estimated by WTS deconvolution (Quanti-seq). Real world overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact using Kaplan-Meier estimates. Statistical significance was determined by chi-square, Fisher's exact, and Mann-Whitney U test with p-values adjustments ($q < .05$). **Results:** *ILF2* expression (median Log2(TPM+1) was higher (all $q < .05$) in key subgroups: ductal compared to lobular carcinoma (6.4 vs 6.0); primary compared to metastatic BC (6.4 vs 6.3); African American compared to White (6.4 vs 6.3); basal compared to luminal A, luminal B, HER2 PAM50 subtypes (6.9 vs 5.8, 6.3, 6.3); and TNBC compared to HR+HER2+, HR-HER2+, HR+HER2- subtypes (6.7 vs 6.3, 6.4, 6.2). Biopsied tissues from primary TNBC (pTNBC) and metastatic TNBC (mTNBC) patients were stratified into *ILF2*-H and *ILF2*-L groups. In both mTNBC and pTNBC, *ILF2*-H groups had 1) higher percentage of young patients (age < 50) (pTNBC: 35.5% vs 19.8%; mTNBC: 28.1% vs 17.3%; all $q < .05$); 2) higher mutation frequency of *TP53* (pTNBC: 94.5% vs 79.6%; mTNBC: 92.4% vs 74.4%), but lower frequencies for *PIK3CA* (pTNBC: 5.1% vs 23.4%, mTNBC: 8.8% vs 27.4%), *CDH1* (pTNBC: *0.8% vs 6.1%*; mTNBC: 2.8% vs 12.2%; all $q < .05$); 3) higher infiltration of NK cells (pTNBC: 3% vs 2.6%; mTNBC: 2.8% vs 2.6%), but lower infiltration of M2 $M\varphi$ (pTNBC: 2.5% vs 3.3%; mTNBC: 2.6% vs 3.2%) and Tregs (pTNBC: 1.5% vs 1.9%; mTNBC: 1.4% vs 1.7%; all $q < .05$); 4) higher expression levels of immune checkpoint (*CD274, PDCD1LG2, CTLA4, LAG3, HAVCR2, FOXP3, IDO1, CD276*, FC: 1.2-3.1; all $q < .05$), stem cell genes (*CD44, NANOG, POU5F1, KLF4, ALDH1A1*, FC: 1.4-2.4; all $q < .05$), and drug efflux genes (*ABCC3, ABCC11, ABCC2, ABCB1, ABCG2, ABCC1*, FC: 1.1-4.5; all $q < .05$) compared to *ILF2*-L group. In pTNBC, *ILF2*-H had significantly shorter OS vs *ILF2*-L group (22.3 vs 28.9 months, HR 1.2 [95% CI 1-1.5], p = .03), but no significant differences were observed between mTNBC *ILF2* groups (HR 1.1 [95% CI 0.93-1.3], p = .2). **Conclusions:** *ILF2*-H TNBC patients showed differential genomic and transcriptomic alterations that relate to therapy resistance, immune suppressive TME, and shorter OS. Further studies are warranted to validate the effects of *ILF2* upregulation on therapeutic efficacy. Research Sponsor: The Fashion Footwear Association of New York (FFANY) Foundation; None.

Concurrent GLP1R-agonist use with chemoimmunotherapy for early-stage triple-negative breast cancer.

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a key class of drugs for treating type 2 diabetes mellitus (DM2) and obesity. GLP-1 is rapidly degraded by DPP4, which led to the development of DPP4 inhibitors (DPP4i). Prior work has shown GLP-1R in tumor cells activates key growth signaling and GLP-1RA likely dampen inflammation. This suggests that GLP-1R activation may influence response rates to chemoimmunotherapy. This study aims to investigate the impact of GLP-1RAs and DPP4i (GLP1 drugs) exposure on pathological complete response (pCR) rates for patients with early-stage triple negative breast cancer (TNBC) receiving neoadjuvant chemoimmunotherapy. **Methods:** Patients with early-stage TNBC diagnosed between July 1, 2021, and December 31, 2023, who received the KEYNOTE-522 regimen were identified at three institutions. Patients using GLP-1RAs and DPP4i at breast cancer diagnosis and throughout the neoadjuvant period, alone or with other diabetes medications, were included. Those who started or discontinued GLP-1 drugs during chemoimmunotherapy were excluded. Group comparisons were made using Chi-square and two-sample t-tests. Human TNBCs were analyzed by IHC and CosMx 6000-plex spatial transcriptomics. **Results:** Among 343 patients, 7.5% were using GLP-1 drugs. The pCR rate among patients exposed to GLP-1 drugs was 30.8% compared to 64.4% in those not exposed ($p = 0.001$). For patients using other classes of DM2 medications ($n = 46$), the pCR rate was 65.2%, while for those not taking any DM2 medications ($n = 271$), the pCR rate was 64.2%. In univariate analysis, patients exposed to GLP-1 drugs were significantly older than non-exposed (median age: 60 vs. 51 years; $p = 0.009$), had a higher BMI (35.0 vs. 28.9 kg/m^2; $p = 0.002$), and had higher rates of DM2, hypertension, and hyperlipidemia. In multivariate analysis, only age was associated with pCR (OR: 0.97, 95% CI: 0.96-0.99, $p = 0.007$). When comparing patients taking GLP-1 drugs with those using other DM2 medications, no significant differences were observed regarding age, BMI, or clinical T or N stage. To evaluate tumor-intrinsic factors that may influence treatment response, we examined TNBC specimens ($n = 84$) and identified GLP-1 receptor expression in tumor cells in 35.7% of cases and in the tumor microenvironment in 60.7% of cases. A spatial transcriptomics atlas of GLP-1 drug-exposed tumors (469,029 cells) provides evidence of GLP-1 pathway activity in both malignant and non-malignant cells of the tumor microenvironment. **Conclusions:** We observed significantly lower pCR rate among patients taking GLP1 drugs during neoadjuvant chemotherapy for TNBC. These effects were not observed with other diabetic medications. Detection of GLP1R expression in TNBC specimens indicates there may be direct and indirect effects of agonists to the GLP1 pathway on chemoimmunotherapy response rates. Research Sponsor: None.

HAI-score, an objective HER2 artificial intelligence method for accurate H-score estimation from IHC-stained breast cancer samples.

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Background: Accurate HER2 assessment is essential for breast cancer (BC) treatment, as it directs targeted therapy decisions and predicts patient prognosis. While immunohistochemistry (IHC) is widely used, its manual scoring is susceptible to inter-observer variability. RNAscope, an RNA in situ hybridization (ISH)-based technique, has shown to have a strong correlation with HER2 protein levels and has outperformed AQUA, a high-throughput quantitative immunofluorescence imaging system, in detecting HER2-low cases. However, RNAscope is constrained by its higher cost and technical complexity compared to IHC staining assays. To address this, we propose the HAI-Score, an objective, robust, accessible, non-tissue disruptive, and fast Artificial Intelligence method for evaluating the H-score from IHC images, validated using RNAscope values. **Methods:** The dataset comprises 526 tissue microarray (TMA) cores for RNAscope and IHC evaluations. The dataset includes 100 commercially available BC cores (from TissueArray.Com) and 426 cores from 243 patients at MD Anderson Cancer Center. We digitized TMA cores stained with HercepTest (Dako) (S1 dataset, n=566) and Ventana Pathway 4B5 (Roche) (S2 dataset, n=580) assays. Half of the images were randomly allocated for training and the remaining half were used for validation. A computer vision algorithm detects cell membranes using a specially designed image filter based on domain knowledge. Different visual features were then extracted from these detected cell membranes, including perimeter, normalized area, Feret diameter, fractal dimension, porosity, and staining intensities. These features were used to train a neural network to predict the HAI-Score. The ground truth was defined as HER2 RNA levels measured by RNAscope. We evaluated the HAI-Score accuracy by correlating it (Pearson, R^2) with RNA values and compared it to correlations from AHSQ (a state-of-the-art deep learning model), an expert pathologist, and FDA-approved HER2 IHC assays (HercepTest, Ventana PATHWAY). **Results:** HAI-Score yielded a correlation of 0.85 and an R^2 value of 0.711 on the testing dataset, which includes images from both the S1 and S2. This performance surpassed AHSQ, the H-score by a breast pathologist, and the scores of two FDA assays with RNA values (Table 1). **Conclusions:** HAI-Score provides an objective alternative to evaluate HER2 expression. It is strongly correlated with HER2 RNA levels and was superior to evaluations by an experienced breast pathologist. Following additional independent multi-site validation, HAI-Score could enable treatment personalization, optimize better surgical planning, and reduce overtreatment. Research Sponsor: National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Allergy and Infectious Diseases; the National Institute of Dental and Craniofacial Research; the National Library of Medicine; the National Instutute on Aging; the VA Research and Development Office through the Lung Precicision Oncology Program; the Office of the Assistant Secretary of Defense for Health Affairs through the Prostate Cancer Research Program; the Kidney Mapping and Atlas Project (KMAP); sponsored research agreements from Astrazeneca, Bristol Myers Squibb, the Prevent Cancer Foundation, Innovation in Cancer Informatics, and the Scott Mackenzie Foundatio; the National Institute of Diabetes and Digestive and Kidney Diseases; the Kidney Mapping and Atlas Project (KMAP); the VA Biomedical Laboratory Research and Development Service.

Comparison of methods with RNAscope using Pearson correlation and R^2.

Method	Pearson Correlation	R^2
Roche	0.58	0.33
Dako	0.76	0.57
Pathologist	0.76	0.58
AHSQ	0.83	0.69
HAI-Score	**0.85**	**0.71**

Impact of HER2-ultralow heterogeneity and optimal threshold on trastuzumab deruxtecan (T-DXd) efficacy in metastatic breast cancer: A national multicenter cohort study (HEROIC).

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Background: Trastuzumab deruxtecan (T-DXd) has been approved for patients (pts) with HER2-ultralow metastatic breast cancer (MBC). HER2 discordance commonly occurs between primary and metastatic lesions within the same patient; however, its incidence remains unknown in the HER2-ultralow era. Additionally, there is still controversy about which specimen to use to determine HER2-ultralow status and optimal threshold to guide T-DXd therapy. **Methods:** This national, multicenter cohort study included MBC pts treated with T-DXd (5.4 mg/kg) with HER2 status available for both primary tumors and matched metastases between January 2020 and October 2024 (NCT06551220). HER2 status was determined according to the DB-06 protocol. Pts were divided into three cohorts based on HER2 discordance patterns: cohort 1 (HER2-positive/low/ultralow in both primary and metastases), cohort 2 (HER2-positive/low/ultralow in primary and HER2-null in metastases), and cohort 3 (HER2-null in primary and HER2-positive/low/ultralow in metastases). Endpoints included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate, and clinical benefit rate. **Results:** From 24 centers nationwide, 3546 pts met the criteria and were included. The incidence of HER2 discordance between primary and matched metastases has changed across eras of HER2-positivity definitions: HER2-positive era (9.8%, $K = 0.78$), HER2-low era (25.0%, $K = 0.39$), and HER2-ultralow era (20.2%, $K = 0.16$). Among T-DXd-treated pts (n = 1052), a higher response rate was observed in cohort 1 (ORR = 55.7%) and cohort 3 (ORR = 53.1%) compared to cohort 2 (ORR = 13.0%). ORR is positively correlated with HER2 expression if metastatic lesions are used as the examined tissue (positive 62.9%, low 49.8%, ultralow 47.0%, null 13.0%). However, the correlation between ORR and HER2 expression is not significant when primary lesions were examined (positive 57.8%, low 41.5%, ultralow 54.4%, null 53.1%). Additionally, cohort 1 (mPFS = 11.6 mo, mOS = 30.7 mo) and cohort 3 (mPFS = 10.9 mo, mOS = 18.4 mo) exhibited significantly superior PFS and OS compared to cohort 2 (mPFS = 6.1 mo, mOS = 12.3 mo). Faint incomplete membrane staining percentage $\geq$5% in metastatic lesion was the best threshold to distinguish PFS (HR = 0.54, $P = 0.02$; mPFS, 11.4 vs 8.6 mo) and ORR (OR = 4.00, $P = 0.01$; 60% vs 27%) among HER2-ultralow MBC treated with T-DXd. **Conclusions:** A high HER2-ultralow discordance rate was observed between primary tumors and matched metastases. HER2 status in metastatic specimens more accurately predicts T-DXd efficacy compared to primary specimens. A staining threshold of $\geq$5% tumor cells in metastatic lesions may optimize T-DXd treatment in HER2-ultralow MBC. Therefore, re-evaluating HER2 status in metastatic lesions is recommended for T-DXd treatment decision. Research Sponsor: None.

Opioid use disorder among females with breast cancer: A comprehensive analysis of prevalence in the United States and associated factors.

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Background: Patients with breast cancer (BC) are frequently prescribed opioids for pain management, placing them at risk of opioid use disorder (OUD). This study analyzes the prevalence of OUD and identifies factors contributing to its risk among BC patients in the United States. **Methods:** We conducted a retrospective analysis using the National Inpatient Sample (NIS) database, a Healthcare Cost and Utilization Project (HCUP) component. Females with BC were identified through ICD-10 codes. The Cochran-Armitage trend test assessed OUD prevalence trends from 2016 to 2022. Multivariable regression models estimated the impact of multiple patient demographics and comorbidities on the presence of OUD. **Results:** Among 1,189,884 females aged≥18 with BC, 2.3% (27,500) had OUD. The mean age of OUD patients was 58.38 years, compared to 64.46 years in the non-OUD cohort. OUD prevalence was highest in those aged 18–50 years (3.8%), followed by 51–60 years (3.0%), and lowest in those > 60 years (1.7%). Between 2016 and 2020, OUD prevalence increased from 1.9% to 2.8%, followed by a decline to 2.4% in 2022 (p-trend < 0.01). Factors that were linked with higher OUD involved patients with neoplasm-related pain(NRP)(aOR 5.718, 95% CI 5.549-5.893, p < 0.01), on palliative care (aOR 1.397, 95% CI 1.353-1.443, p < 0.001), with metastasis (aOR 1.573, 95% CI 1.526-1.621, p < 0.01), depression (aOR 1.447, 95% CI 1.400-1.495, p < 0.01), bipolar disorder (aOR 2.173, 95% CI 2.038-2.317, p < 0.01), suicidality (aOR 3.228, 95% CI 2.938-3.546, p < 0.01), and anxiety (aOR 1.617, 95% CI 1.572-1.664, p < 0.01). Moreover, substance use such as cocaine (aOR 5.252, 95% CI 4.708-5.859, p < 0.01) and amphetamine (aOR 3.948, 95% CI 3.443-4.527, p < 0.01) was also associated with higher odds, while cannabis users (aOR 0.876, 95% CI 0.793-0.968, p < 0.01) had lower odds of OUD. Our study further found racial disparities, with reduced odds among Blacks (vs Whites, aOR 0.933, 95% CI 0.901-0.967, p < 0.01) and Hispanics (vs.Whites, aOR 0.866, 95% CI 0.827-0.906, p < 0.01). Socio-economic differences were also noted, with lower odds among those of the 26th-50th (vs. 0-25th, aOR 0.932, 95% CI 0.9-0.966, p < 0.01), 51st-75th (vs. 0-25th, aOR 0.951, 95% CI 0.918-0.986, p < 0.01), and 76th-100th (vs. 0-25th, aOR 0.916, 95% CI 0.882-0.951, p < 0.01) household income quartiles. **Conclusions:** This study showcases the significant prevalence and impact of OUD among BC patients, identifying socioeconomic and racial disparities, and key risk factors such as NRP, psychiatric comorbidities, and concurrent substance use, like cocaine and amphetamines. Interestingly, cannabis use was associated with a lower risk of OUD, which may reflect its role as an alternative pain management strategy. Overall, this study suggests the need to adopt crucial preventative measures against OUD in patients exhibiting these characteristics. Research Sponsor: None.

Treatment patterns, genomic characteristics, and outcomes among patients with metastatic lobular breast cancer.

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Background: Invasive lobular carcinoma (ILC) is characterized by loss of E-cadherin expression and accounts for 10-15% of breast cancer diagnoses. ILC differs from the more common invasive carcinoma of no special type in the pattern of metastatic spread and genomic characteristics; however, clinicopathologic characteristics among patients with metastatic ILC are not well described. Here, we present comprehensive treatment, genomic, and outcome data in a large single-center cohort of patients with metastatic ILC. **Methods:** Patients were identified for inclusion in this retrospective study if they had ILC histology on early-stage breast biopsy/surgical pathology and/or *CDH1* mutation on metastatic site biopsy; all patients were required to have MSK-IMPACT somatic next generation sequencing (NGS) data available. Clinicopathologic characteristics were abstracted from the EMR. The Kaplan-Meier method was used to estimate overall survival (OS). The log-rank test was used to compare OS by ILC subtype and by genetic mutations. Wilcoxon rank sum test and Kruskal-Wallis test were used to compare number of treatment lines by receptor status. **Results:** 654 patients were included, of whom 99.8% were female, 89% were white, and 96% non-Hispanic. 438 (67%) had recurrent disease whereas 212 (33%) had *de novo* metastatic disease. Among 307 with ILC histologic subtype data available, 139 (45%) had classic type, 65 (21%) had pleomorphic, 45 (15%) had mixed, and 58 (19%) had other ILC subtypes. 454 (87%) had hormone receptor-positive (HR+) disease, 45 (9.1%) had HER2+ disease, and 50 (9.5%) had triple negative disease at metastatic diagnosis. In the total cohort, median number of treatment lines for metastatic disease was 4 (IQR 2-7) and median number of chemotherapies was 2 (IQR 1-3). In the HR+ cohort, median number of endocrine therapies was 2 (IQR 1-3). Among patients with genomic data from a biopsy obtained within 2 months of metastatic diagnosis, 79% had a *CDH1* mutation, 48% had a *PIK3CA* mutation, 5.6% had an *AKT1* mutation, 11% had a *PTEN* mutation, 9.3% had an *ESR1* mutation, 17% had a *HER2* mutation, and median tumor mutation burden (TMB) was 4 (IQR 3-7); 17% had TMB ^{3}10. Median OS in the total cohort was 4.4 years (95%CI 4.1-4.8). OS did not differ significantly by ILC subtype (p= 0.8). OS differed significantly by *CDH1* mutation status (wt 5.3 years, 95%CI 4.1-6.6; mut 3.7 years, 95%CI 3.5-4.2, p= 0.01), *PIK3CA* status (wt 4.6 years, 95%CI 4.0-5.8; mut 3.4 years, 95%CI 3.1-3.9, $p<$ 0.001), and *PTEN* status (wt 4.2 years, 95%CI 3.7-4.5; mut 3.4 years, 95%CI 2.2-4.3, p= 0.008). OS did not differ significantly by *HER2*, *AKT1*, or *ESR1* mutation status. **Conclusions:** In a large single-center cohort of patients with metastatic ILC, OS did not vary by ILC subtype, but did differ significantly by *CDH1, PIK3CA,* and *PTEN* mutation status. This underscores the prognostic importance of NGS in metastatic ILC. Research Sponsor: None.

TPS1120 Poster Session

A phase III randomized trial of radiotherapy optimization for low-risk HER2-positive breast cancer (HERO): NRG-BR008.

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Background: Breast radiotherapy (RT) is the standard of care for patients with early-stage breast cancer (BC) who undergo breast-conserving surgery (BCS). However, the magnitude of benefit of RT is less clear in BCS patients with low-risk disease who receive effective systemic therapy. Among patients with early-stage HER2-positive (HER2+) BC, 10-year locoregional recurrence has been reported as low as 1.5% following BCS, adjuvant chemotherapy and HER2-targeted therapy, and RT. Given these exceedingly favorable outcomes, with the addition of HER2-directed therapy, we seek to evaluate the feasibility of omitting RT among patients with early-stage HER2+ BC following BCS and appropriate systemic therapy. **Methods:** This is a phase III randomized trial for patients ≥18 years with early-stage, node-negative, HER2+ (IHC/FISH) BC treated with BCS with negative margins and sentinel lymph node biopsy or axillary dissection. Patients undergoing primary surgery must have pathologic T1-2 (≤3 cm) N0 disease, whereas patients receiving neoadjuvant therapy must have clinical T1-2 (with radiographically T≤5 cm) N0 disease and exhibit a pathologic complete response (ypT0N0) at surgery (residual DCIS [ypTis] spanning ≤1 cm is permitted, and surgical margins are negative for DCIS). All patients must receive cytotoxic chemotherapy and HER2-targeted therapy, either in the adjuvant or neoadjuvant setting. Stratification is by age (<60; ≥60), tumor size (≤1 cm; >1 cm), estrogen-receptor status (positive; negative), and systemic therapy sequencing (adjuvant *v* neoadjuvant). Patients will be randomized to standard breast RT in addition to continuation of trastuzumab to complete one year of treatment (Arm 1), or trastuzumab alone (Arm 2). Endocrine therapy will be recommended for patients with hormone-receptor-positive tumors. The primary endpoint is the recurrence-free interval (RFI). Secondary endpoints include time to ipsilateral breast recurrence, locoregional recurrence, disease-free survival, and overall survival, in addition to the 7-year ipsilateral breast recurrence rate among those not receiving RT. A health-related quality of life sub-study will assess differences in patient-reported breast pain and worry. We estimate a 7-year RFI of 97.5% with RT and allow for a clinically acceptable decrement of 3.63% without RT (7-year RFI of 93.87%; HR 2.5) to establish omission of RT as non-inferior. NRG-BR008 aims to enroll 1,300 patients over 7.25 years, yielding 80% power to detect the non-inferiority of RT omission with a one-sided α=0.05. We expect to observe the required 38 RFI events within 4.5 years of additional follow-up. The NRG-BR008/HERO trial opened to accrual in March 2023. Accrual is 64/1,300 as of 1/23/24. NCT #: NCT05705401. Support: U10 CA180868, -180822, UG1 CA189867, U24 CA196067. Clinical trial information: NCT05705401. Research Sponsor: National Cancer Institute; U10CA180868; National Cancer Institute; U10CA180822; National Cancer Institute; UG1CA189867; National Cancer Institute; U24CA196067.

TPS1121 Poster Session

IND.241: A Canadian Cancer Trials Group liquid-biopsy informed platform trial to evaluate treatment in CDK4/6-inhibitor resistant ER+/HER2- metastatic breast.

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Background: The combination of a CDK4/6 inhibitor + endocrine therapy (CDK4/6i+ET) is standard first-line systemic treatment for patients with ER+/HER2-negative metastatic breast cancer (MBC). Beyond this initial therapy, there are numerous therapeutic agents available/ in development for subsequent lines of treatment. Circulating tumor DNA (ctDNA) via liquid biopsy is a promising, non-invasive approach for blood-based tumor genotyping, patient stratification and response assessment with the potential to enhance biomarker-driven strategies and aid in development of new therapeutics. **Methods:** IND.241 is a master protocol platform design consisting of independent substudies monitoring patients with ER+/HER2- MBC prior to progression (PD) on CDK4/6i+ET and investigating novel agents or drug combinations in $2^{nd}/3^{rd}$ lines after progression on CDK4/6i+ET. The primary objective of the novel drug/combination substudies is to centrally interrogate ctDNA (Tempus xF+, a 523-gene liquid biopsy panel) and evaluate whether biomarker selection improves ORR or CBR as assessed by RECIST 1.1. Secondary objectives include safety and toxicity profile for each drug/combination, PFS, and OS. The monitoring substudy (Substudy A) enrolls patients currently on CDK4/6i+ET treatment and aims to characterize the molecular profile, clinical features, and ctDNA dynamics of acquired resistance. This platform trial enables creation and maintenance of a tissue and data bank including clinical data, genomics, and radiomics from all substudies to evaluate surrogates of treatment outcomes and potential biomarkers of response, resistance, and disease progression. Patients with specific biomarkers detected in ctDNA will be enrolled into corresponding biomarker positive cohorts of substudies. Patients with no substudy-specific biomarkers are randomized to biomarker negative cohorts of available substudies. Treatment substudies follow a 2-stage design. Currently, the monitoring substudy A is actively accruing. Substudy B is evaluating lunresertib (PKMYT1 inhibitor) + gemcitabine in patients +/-CCNE1 overexpression / amplification. Substudy C is evaluating niraparib (PARP inhibitor) + fulvestrant (ET) in patients +/- alterations in BRCA1/2 (germline/somatic) or PALB2 (germline). These latter two substudies have now closed to accrual, with efficacy and safety evaluation ongoing. Substudy D, which has recently been added, is evaluating lunresertib + camonsertib (ATR inhibitor) in patients +/- CCNE1 overexpression/amplification, FBXW7 or PPP2R1A alterations. Additional substudies are in development for inclusion in this platform trial. Clinical trial information: NCT05601440. Research Sponsor: Repare Therapeutics; GSK.

TPS1122 Poster Session

Phase II study evaluating 68Ga-FAPI PET uptake heterogeneity as a predictor of T-DXd treatment response in HER2-positive breast cancer brain metastases.

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Background: Breast cancer is a leading cause of metastasis to the central nervous system (CNS). Approximately 30% of patients with HER2-positive breast cancer develop brain metastases, which are associated with a poor prognosis and limited treatment options. T-DXd has shown promise in treating brain metastases from HER2-positive breast cancer. However, up to 10% patients showed brain metastasis progression at the initial evaluation of treatment and may require radiotherapy or neurosurgery immediately. Identifying predictors of treatment response and determining the timing for local therapy intervention is crucial for personalized medicine. Heterogeneity in tumor metabolism, as assessed by (68Ga)–labeled fibroblast-activation protein inhibitor (68Ga-FAPI) PET-CT which displays the activity of cancer-associated fibroblasts (CAFs) in the tumor microenvironment, with good sensitivity and specificity in brain metastasis imaging, may serve as a biomarker for treatment response. This study aims to investigate the predictive value of 68Ga-FAPI PET uptake heterogeneity for T-DXd treatment response in HER2-positive breast cancer brain metastases. **Methods:** This open-label, single-center, phase II clinical trial will investigate the heterogeneity of brain metastasis and analyze the difference between stable and active brain metastasis evaluated by 68Ga-FAPI uptake in HER2-positive MBC. Patients with HER2-positive metastatic breast cancer and confirmed brain metastases by MRI were enrolled; at least one measurable intracranial lesion ($\geq$ 1.0 cm) that has not previously been treated with radiation. Radiotherapy or neurosurgery is allowed with an interval $\geq$ 4 weeks. Patients will receive T-DXd treatment and undergo 68Ga-FAPI PET-CT scans before and after two cycles of treatment. The primary endpoint is the difference in baseline heterogeneity index by 68Ga-FAPI PET-CT between cerebral lesions achieving ORR and those that do not. Secondary endpoints include 68Ga-FAPI PET-CT value changes (SUVmax, SUVmean) at baseline and after treatment; difference in baseline heterogeneity index for PFS, CBR and OS; difference of baseline heterogeneity index, SUVmax and SUVmean between active or stable brain metastasis; 68Ga-FAPI PET-CT value changes (heterogeneity index, SUVmax, SUVmean) at baseline and 2 cycles after T-DXd treatment of whole body metastasis lesions. The study plans to enroll 50 patients and is actively enrolling. Clinical trial information: NCT06797622. Research Sponsor: CSCO-LingHang Oncology Research Foundation (Y-2022HER2AZQN-0378).

TPS1123 **Poster Session**

SOLTI-2201 ACROSS-TROP2 trial: A phase II study to identify predictive biomarkers of sacituzumab govitecan benefit and to understand resistance mechanisms in HR+/HER2- advanced or metastatic breast cancer.

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Background: Sacituzumab Govitecan (SG) is a TROP2-directed antibody-drug conjugate (ADC) linked to a topoisomerase I inhibitor via a hydrolysable CL2A linker. It is approved for the treatment of metastatic triple-negative breast cancer (mTNBC) patients who have undergone at least two prior systemic therapies, including one for advanced disease, and of hormone receptor-positive (HR+)/HER2-negative metastatic breast cancer (mBC) patients after endocrine therapy (ET) and two systemic treatments. Currently, no biomarkers, including TROP2 protein expression, have been identified to predict SG response, highlighting the need to explore biomarkers of efficacy and to identify key resistance mechanisms to the drug. The ACROSS-TROP2 study aims to address this unmet medical need. **Methods:** ACROSS-TROP2 (NCT06236269) is a phase II, open-label, single-arm trial investigating SG in HR+/HER2-negative mBC patients. The study initially planned to enroll 50 pre- or post-menopausal female or male participants who progressed during or after treatment with CDK4/6 inhibitors and received up to one prior chemotherapy or ADC regimen for metastatic disease. Due to high recruitment rates and promising findings demonstrating ADC benefits in earlier treatment lines (Bardia et al., NEJM 2024), a protocol amendment was introduced to expand the sample size to 100 patients. Participants will receive SG at 10 mg/kg via IV infusion on Days 1 and 8 of each 21-day cycle until disease progression (PD). Fresh tumor biopsies will be obtained at baseline, after 2–3 weeks of treatment (C2D1), and at PD. The primary endpoint is to measure changes in the CelTIL score—a composite of tumor cellularity and tumor-infiltrating lymphocytes—between baseline and C2D1 biopsies, as CelTIL is associated with long-term efficacy. Secondary endpoints include overall response rate, progression-free survival, duration of response, time to response, safety, and tolerability. Correlative analyses of molecular markers in tissue and blood will be conducted to correlate biological findings (e.g., CelTIL, Ki67, TROP2, PD-1/PD-L1, PAM50) with clinicopathological data, evaluate the predictive value of early dynamic changes in ctDNA, identify genomic alterations linked to treatment response and resistance, and explore changes from baseline to PD to identify mechanisms of resistance. A paired t-test will assess whether the mean change in CelTIL score is statistically different from zero. The study has been approved in Spain and is actively enrolling participants at 10 sites within the SOLTI network. Previously presented at ESMO Breast 2024, FPN: 265TiP, Eva Ciruelos et al. - Reused with permission. Clinical trial information: NCT06236269. Research Sponsor: None.

TPS1124 Poster Session

LITESPARK-029: A phase 2, randomized, open-label study of belzutifan plus fulvestrant in participants with estrogen receptor–positive, HER2-negative unresectable locally advanced or metastatic breast cancer after progression on previous endocrine therapy.

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Background: Endocrine-based therapy (ET), with or without cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), prolongs PFS and OS in participants (pts) with metastatic hormone receptor–positive (HR+) and human epidermal growth factor receptor 2–negative (HER2–) breast cancer. After PD on first-line therapy, next-line therapy options provide limited PFS gains, in part due to resistance mechanisms (eg, hyperactive FOXA1). The transcription factor hypoxia-inducible factor 2α (HIF-2α), a major target of FOXA1, regulates key components of angiogenesis and subsequent development of metastasis. Preclinical studies show suppression of tumor growth with an HIF-2α antagonist, particularly when combined with fulvestrant. Belzutifan, an HIF-2α inhibitor, is approved for the treatment of pts with advanced renal cell carcinoma following a PD-(L)1 inhibitor and vascular endothelial growth factor tyrosine kinase inhibitor. LITESPARK-029 (NCT06428396) evaluates belzutifan + fulvestrant vs everolimus + fulvestrant or exemestane in pts with estrogen receptor–positive (ER+)/HER2– unresectable locally advanced or metastatic breast cancer. **Methods:** This phase 2, randomized, active-controlled, open-label, multicenter study is enrolling pts (≥18 y) with locally confirmed ER+/HER2– unresectable, locally advanced or metastatic disease who have had radiographic PD on ≥12 mo of ET + CDK4/6i therapy in the noncurative setting or received ≥2 lines of ET in the noncurative setting including CDK4/6i where the CDK4/6i was discontinued due to intolerance (not due to progression). Pts must also be eligible for additional ET with everolimus plus either fulvestrant or exemestane per local investigator assessment, have an ECOG PS of 0 or 1, and provide a new or recent core biopsy for central determination of ER and HER2 status. Prior treatment with chemotherapy, antibody-drug conjugates, or PARP inhibitors in the noncurative setting is prohibited. Pts are randomized 1:1 to receive oral belzutifan 120 mg once daily + fulvestrant 500 mg on days 1 and 15 of cycle 1 and on day 1 of all subsequent 28-day cycles or oral everolimus 10 mg once daily + fulvestrant (as above) or oral exemestane 25 mg once daily until PD or unacceptable toxicity. Randomization is stratified by treatment with prior ET + CDK4/6i therapy ($<$ 18 mo duration before PD vs ≥18 mo duration before PD or no PD). Tumor imaging is performed at screening, Q8W from randomization through week 56, and Q12W thereafter. The primary endpoint is PFS per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints include PFS rate per RECIST v1.1 by BICR at 6 and 12 mo, OS, ORR per RECIST v1.1 by BICR, clinical benefit (CR, PR, or stable disease for ≥24 weeks), and safety. The study start date was July 2024. Clinical trial information: NCT06428396. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS1125 Poster Session

ALISertib in combination with endocrine therapy in patients with hormone receptor-positive (HR+), HER2-negative (HER2–) recurrent or metastatic breast cancer: The phase 2 ALISCA-Breast1 study.

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Background: Despite the many available treatments for patients (pts) with HR+, HER2– recurrent/metastatic breast cancer (MBC), optimal treatment after progression on CDK4/6 inhibitors (CDK4/6i) is unclear. One possible CDK4/6i resistance mechanism is increased expression of Aurora kinase A (AURKA), a key mitosis regulator associated with poor prognosis. Further implicated in CDK 4/6i resistance, high c-Myc or RB1 loss of function (LOF) are associated with transcriptional co-regulation or synthetic lethality, respectively, with AURKA. Alisertib is a highly selective, reversible, ATP-competitive, orally administered, small-molecule AURKA inhibitor with antiproliferative activity in HR+ BC-derived cell lines and BC xenograft models. Models with elevated AURKA or c-Myc expression, or RB1 LOF show greater alisertib sensitivity. Alisertib had activity in phase 1 and 2 trials, including objective response rates (ORRs) of 19.6–20% and median progression-free survival (PFS) of 5.4–5.6 months alone or with fulvestrant in pts with HR+/HER2–, endocrine-resistant MBC. The most common treatment-related grade ≥3 adverse events (AEs) were neutropenia, anemia, and leukopenia. **Methods:** ALISCA-Breast1 (NCT06369285) is a randomized phase 2 study. Primary objective: to determine the optimal alisertib dose administered with endocrine therapy (ET) based on AEs and serious AEs per CTCAE v5.0 and efficacy (ORR, duration of response, disease-control rate, PFS, overall survival). Secondary objectives: to identify biomarkers of efficacy and alisertib pharmacokinetics (PK). Key inclusion criteria: ≥18 years; ECOG performance status 0 or 1; confirmed HR+, HER2–, recurrent/metastatic breast adenocarcinoma not amenable to curative therapy; available tumor tissue for biomarker analyses; progression on or after ≥2 prior ET lines in recurrent/metastatic setting; prior CDK4/6i with ET in recurrent/metastatic setting. Key exclusion criteria: prior chemotherapy in recurrent/metastatic setting; prior AURKA-specific or pan-Aurora-targeted agents; unstable brain metastases. Eligible pts will be randomized 1:1:1 to alisertib 30 mg, 40 mg, or 50 mg orally twice daily on days 1–3, 8–10, and 15–17 every 28 days, plus physician's choice of anastrozole, letrozole, exemestane, fulvestrant, or tamoxifen not previously used in recurrent/metastatic setting or progressed upon in adjuvant setting; ≤50 pts will be enrolled per arm in the USA and Europe. All pts will undergo sparse PK sampling. Tumor tissue will be centrally assessed for biomarkers, including *RB1, MYC, TP53, ESR1,* PI3K/AKT pathway, *HER2* and *AURKA* genomic alterations/expression levels. The study will determine the optimal alisertib dose to combine with ET and may identify biomarker(s) defining pts with the greatest benefit from alisertib-based therapy. Clinical trial information: NCT06369285. Research Sponsor: Puma Biotechnology Inc.

TPS1126 **Poster Session**

Integrating gene signatures to guide HR+/HER2- MBC therapy in a diverse cohort (INSIGHT).

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Background: Black women with breast cancer (BC) have a 40% higher mortality rate compared to Non-Hispanic White (NHW) women. Worse outcomes have been observed among Black women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) BC despite comparable systemic therapies. Gene expression profiling has been used in early-stage BC to provide prognostic and predictive information beyond standard immunohistochemical classifications. BluePrint, an 80-gene molecular subtype signature, and MammaPrint (Agendia), a 70-gene risk of distant recurrence signature, further classify HR+/HER2- BC into luminal A, luminal B, HER2-enriched, and basal-type tumors. Non-Luminal A (Luminal B, HER2-enriched, and Basal-type) tumors are more aggressive and are associated with worse survival compared to Luminal A tumors. Our preliminary data demonstrate that non-Luminal A tumors are overrepresented in Black women (11% Black vs. 5% White). The role of molecular subtyping in guiding therapy for patients with HR+/HER- MBC is not defined. Retrospective studies have shown that non-Luminal A HR+/HER2- tumors derive less benefit from endocrine therapy (ET). We hypothesize that patients with non-Luminal A, HR+/HER2- MBC progressing on ET +/- CDK4/6 inhibition derive more benefit from chemotherapy than ET in the second line. Furthermore, the impact of the intervention will be more pronounced in Black women compared to NHW women. INSIGHT is a randomized phase II study evaluating the anti-tumor effect of capecitabine versus physician's choice ET as second line for patients with non-Luminal A HR+/HER2- MBC (NCT05693766). **Methods:** In this study, patients progressing on 1st line ET +/- a CDK4/6i are enrolled. Archival primary or metastatic tumor samples are analyzed using MammaPrint and BluePrint. Patients with non-Luminal A tumors are randomized (1:1) to receive physician's choice ET versus capecitabine, stratified by molecular subtype and race. Disease assessments are performed every three months. The primary endpoint is progression free survival (PFS). Secondary endpoints include overall response rate, clinical benefit rate, overall survival, and patient reported outcomes. The study has 80% power to detect a minimal hazard ratio of 0.5 in 5-year PFS with one-sided α = 0.05. Exploratory correlative studies are planned. This trial enriches for racial/ethnic minority patients through collaborations with the University of Texas Southwestern and the University of Alabama at Birmingham, health systems that serve large minority populations. Seven of the 64 planned patients have been enrolled. Clinical trial information: NCT05693766. Research Sponsor: Susan G. Komen.

TPS1127 Poster Session

ELCIN: Elacestrant in women and men with CDK4/6 inhibitor (CDK4/6i)-naïve estrogen receptor-positive (ER+), HER2-negative (HER2-) metastatic breast cancer (mBC)—An open-label multicenter phase 2 study.

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Background: Endocrine therapy (ET) plus a CDK4/6i is the mainstay treatment in first-line ER+/HER2- mBC; however, a subset of patients are unable to tolerate CDK4/6i, and resistance to ET emerges. Intrinsic resistance mechanisms include alterations in the PI3K/AKT/mTOR or cell cycle pathways; acquired resistance mechanisms include estrogen receptor gene 1 mutations (*ESR1*-mut), which emerge in up to 50% of patients during prolonged aromatase inhibitor therapy in mBC. In the phase 3 EMERALD trial, elacestrant significantly prolonged PFS vs standard-of-care (SOC) ET and was associated with a manageable safety profile in patients with ER+/HER2- mBC previously treated with ET+CDK4/6i, leading to its approval as the first clinically available oral SERD. Elacestrant significantly reduced the risk of progression or death vs SOC ET by 30% in the overall population (HR 0.70; 95% CI 0.55-0.88; P=0.002) and by 45% in patients with *ESR1*-mut tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard, 2022]. Preclinical studies demonstrated that elacestrant is equally active in both in vitro and in vivo models of ER+/HER2- breast cancer, regardless of prior exposure to CDK4/6i. Based on preclinical models and clinical efficacy data, elacestrant may improve clinical outcomes in CDK4/6i-naïve patients and provide a convenient all-oral treatment option if combined with CDK4/6i. The ELCIN trial will evaluate efficacy and safety of elacestrant in patients with ER+/HER2- mBC who received prior ET and no prior CDK4/6i in the metastatic setting. **Methods:** ELCIN (NCT05596409) is an open-label, multicenter, single-arm phase 2 trial. Eligible patients are women or men with ER+/HER2− mBC who received 1-2 lines of prior ET and no prior CDK4/6i or chemo in the metastatic setting. Patients must have measurable disease per RECIST v1.1 or a mainly lytic bone lesion (for bone disease only), ECOG PS ≤1, adequate bone marrow and organ function, and no active or newly diagnosed CNS metastases or visceral crisis. Patients will receive elacestrant 345 mg once daily. The primary objective is investigator-assessed PFS. Secondary objectives are ORR, DoR, CBR, OS, PROs-QoL, and safety. Exploratory objectives include elacestrant efficacy according to *ESR1*-mut status, changes in biomarkers, including allele mutation frequencies (cfNAs), and relationship between efficacy endpoints. Status: ELCIN has a planned sample size of 60 patients; recruitment is ongoing worldwide. Clinical trial information: NCT05596409. Research Sponsor: Menarini Group.

TPS1128 Poster Session

SIMRISE: A randomized phase III trial evaluating SIM0270 in combination with everolimus versus treatment of physician's choice in patients with ER+/HER2- advanced breast cancer, previously treated with CDK4/6 inhibitors.

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Background: CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have demonstrated sustained benefits in the first-line treatment of HR+/HER2- advanced breast cancer(aBC). However, effective ET options are limited for patients who progressed after the treatment of ET in combination with CDK4/6i. SIM0270 in combination with everolimus exhibited promising anti-tumor activities in a Phase I study. **Methods:** SIMRISE is an ongoing randomized, open label, Phase III trial designed to evaluate SIM0270 in combination with everolimus versus the treatment of physician's choice (TPC) for patients with ER+/HER2- aBC progressed on previous ET and CDK4/6i. A total of 460 patients will be enrolled across approximately 50 sites in China. Patients are randomized in a 1:1 ratio to receive either SIM0270 + everolimus or TPC (exemestane + everolimus or fulvestrant). Stratification factors include: visceral metastasis (yes or no); prior fulvestrant (yes or no); baseline ESR1 status (mutation detected or not detected). Key eligibility criteria include: ER+/HER2- aBC patients having measurable disease per RECIST 1.1 or bone only disease with at least one predominant lytic bone lesion or mixed lytic-blastic lesion; postmenopausal women and pre-/perimenopausal women or men receiving luteotropic hormone releasing hormone agonist(LHRHa) therapy per local prescribing information; patients must have received at least one line and no more than two lines of ET; recurrence while on or within 12 months of completion of adjuvant ET for ≥24 months is considered as first-line ET, or first line ET in advanced setting for ≥6 months. Patients must have previously received CDK4/6i combined with ET for ≥6 months; one line chemotherapy for aBC is allowed. The Primary endpoint is progression-free survival (PFS) as assessed by blinded independent review committee (BIRC). The secondary endpoints include PFS (assessed by investigators), overall survival (OS), objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR), time to progression (TTP), safety, pharmacokinetics (PK) and patients-reported outcomes (PRO). The analysis of primary endpoint will use a stratified log-rank test at an overall of 0.05 significance level (two-sided). Futility analyses are planned, and an independent data monitoring committee will be in place. Clinical trial information: NCT06680921. Research Sponsor: Simcere Zaiming Pharmaceutical Co., Ltd.

TPS1129 **Poster Session**

ADELA: A double-blind, placebo-controlled, randomized phase 3 trial of elacestrant (ELA) + everolimus (EVE) versus ELA + placebo (PBO) in ER+/HER2- advanced breast cancer (aBC) patients with *ESR1*-mutated tumors progressing on endocrine therapy (ET) + CDK4/6i.

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Background: ET+CDK4/6i is standard-of-care (SOC) in 1L ER+/HER2- aBC; however, tumors eventually develop resistance. Constitutive activation in the PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. *ESR1* mutations are a common type of acquired resistance that emerges in 40-50% of patients in the metastatic setting after prolonged aromatase inhibitor exposure. There is an unmet need for novel therapeutic approaches to overcome resistance mechanisms and improve outcomes in patients with ER+/HER2- aBC with *ESR1*-mutated tumors progressing after ET+CDK4/6i. ELA is a next-generation oral SERD that binds to ER-alpha, inducing its degradation. In EMERALD, ELA improved PFS vs SOC ET in patients with *ESR1*-mutated tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard 2022]. Differences were notable among patients who received prior ET+CDK4/6i ≥12 mo; median PFS with ELA was 8.6 mo vs 1.9 mo with SOC ET (HR 0.41; 95% CI 0.26-0.63) [Bardia 2024]. Crosstalk between ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating ELA+EVE (a mTORC1 inhibitor). In ELEVATE phase 1b (NCT05563220), ELA+EVE demonstrated ORR 22% and CBR at 24 weeks 72% in patients with ER+/HER2- aBC progressing after ET+CDK4/6i; ELA 345 mg + EVE 7.5 mg was identified as the RP2D [Rugo ESMO 2024]. Safety was consistent with the known profile of EVE+SOC ET. ADELA compares ELA+EVE vs ELA+PBO in ER+/HER2- aBC patients with *ESR1*-mutated tumors progressing on ET+CDK4/6i. **Methods:** ADELA (NCT06382948) is an international, multicenter, double-blind, placebo-controlled phase 3 trial. Eligible patients are adults (≥18 yrs) with ER+/HER2- aBC and *ESR1*-mutated tumors, previously treated with 1-2 lines of ET for aBC, and evidence of disease progression on prior ET+CDK4/6i for aBC after ≥6 mo. Patients receiving CDK4/6i-based adjuvant therapy are eligible (disease progression must be confirmed after ≥12 mo of treatment but <12 mo following CDK4/6i completion). Other criteria include adequate organ function and ECOG PS 0-1. Exclusion criteria include prior chemotherapy for aBC and active uncontrolled/symptomatic brain metastasis. Patients will be randomized 1:1 to 28-d cycles of ELA 345 mg + EVE 7.5 mg QD or ELA 345 mg + PBO QD until disease progression or unacceptable toxicity. Patients will receive dexamethasone mouthwash during the first 8 wks. Stratification factors are presence of visceral metastases (yes vs no) and duration of prior CDK4/6i (≥12 mo vs <12 mo). The primary objective will be to evaluate PFS based on blinded independent review committee. Secondary endpoints include investigator-assessed PFS, OS, ORR, CBR, DoR, TTR, best percentage change in tumor burden, safety, and HRQoL. Status: Planned enrollment is 240 patients; recruitment is ongoing. Clinical trial information: NCT06382948. Research Sponsor: Menarini Group.

TPS1130 **Poster Session**

Dauntless-1, a phase 2 clinical trial to evaluate PMD-026, a first-in-class pan-RSK inhibitor, combined with fulvestrant to overcome resistance to CDK4/6 inhibitors in advanced or metastatic HR+/HER2- breast cancer.

Sandra Elaine Dunn, Hung T. Khong, Muralidhar Beeram, Robert Wesolowski, Hyo S. Han, Nicolaos Jay Palaskas, Aarthi Jayanthan, Martin Sebastian Olivo, Brian Barnett; Phoenix Molecular Designs, Vancouver, BC, Canada; Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, AZ; START Center for Cancer Care, San Antonio, TX; Ohio State University Comprehensive Cancer Center, Columbus, OH; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Ronald Reagan UCLA Medical Center, Los Angeles, CA

Background: Resistance to CDK4/6 inhibitors (CDK4/6i) is common for many patients with HR+/HER2- advanced or metastatic breast cancer, therefore new strategies are urgently needed to overcome this challenge. Ribosomal S6 kinases (RSK1-4) are implicated in breast cancer growth and resistance, and they are activated by the PI3K and MAPK pathways, which are linked to CDK4/6i resistance. As a convergence point of these pathways, RSK drives resistance by promoting the G2/M phase of the cell cycle and bypassing G1/S control. Inhibiting RSK with PMD-026, a first-in-class oral small molecule inhibitor, halts G2/M progression and blocks growth in CDK4/6i-resistant models, including those cross-resistant to abemaciclib and palbociclib. RSK also complexes with estrogen receptor alpha (ERα), enhancing transcription and tumor growth. PMD-026 disrupts this interaction, showing activity in both ESR1 wild-type and mutant HR+/HER2- models, making it a promising partner for endocrine therapies. It synergizes with fulvestrant and oral SERDs, achieving significant growth inhibition in pre-clinical models, including a 7000-fold improvement with fulvestrant in soft agar assays. Nuclear translocation of RSK is a key driver of breast cancer in mice and serves as a biomarker for RSK signalling activity. In the Phase 1/1b monotherapy study, PMD-026 was generally well-tolerated, and it reduced the risk of progression or death in patients by 93% in a subset of RSK2 high metastatic breast cancer patients. **Methods:** Dauntless-1 is a Phase 2a study for locally advanced or metastatic HR+/HER2- breast cancer patients previously treated with a CDK4/6i in combination with endocrine therapy (NCT04115306). It is designed to prospectively enroll RSK2+ (≥50% nuclear staining with ≥2+ staining intensity) patients to evaluate PMD-026 in combination fulvestrant. Fulvestrant will be dosed per the package insert (500 mg IM, Day 1 and 15 of the first 28-day cycle, then Day 1 of every cycle thereafter) in combination with PMD-026 at the RP2D (200 mg, PO, Q12h), determined in the dose-finding portion of the study. The combination regimen will have a safety lead-in cohort of 6 patients. The SRC will review the safety data after the sixth patient has been treated for at least 28 days. If determined to be safe, up to 14 additional patients will receive the combination for a total of 20 patients. A Bayesian safety monitoring rule will be used to evaluate the rate of DLTs during expansion. Primary objectives will be safety, pharmacokinetics, and progression free survival. Secondary objectives include duration of response, overall response and overall survival. Exploratory objectives will evaluate PMD-026 in the context of mutations (ESR1, PIK3CA, AKT1, p53, KRAS) at baseline using ctDNA. Clinical trial information: NCT04115306. Research Sponsor: None.

TPS1131 Poster Session

OPERA-01: A randomized, open-label, phase 3 study of palazestrant (OP-1250) monotherapy vs standard-of-care for ER+, HER2- advanced or metastatic breast cancer patients after endocrine therapy and CDK4/6 inhibitors.

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Background: Endocrine therapy(ET) resistance is a major challenge in treating estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (MBC); estrogen receptor (ESR1) mutations are an important mechanism of resistance. The standard of care (SOC) first-line treatment for ER+, HER2− MBC is ET plus a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Despite the benefit of ET and CDK4/6i, disease progression and acquired resistance to the combination remain a challenge. Novel, more effective ETs that can overcome resistance are needed to improve outcomes and delay time to chemotherapy. Palazestrant (OP-1250) is a novel oral, complete estrogen receptor antagonist (CERAN) and selective ER degrader (SERD) that acts by blocking both transcriptional activation function domains, AF1 and AF2, regardless of ESR1 mutation status. As monotherapy, palazestrant showed a tolerable safety profile, favorable pharmacokinetics and encouraging antitumor efficacy in heavily-pretreated patients during phase 1/2 studies, regardless of *ESR1* mutation status (NCT04505826; Lin et al. ESMO 2023 MO382). **Methods:** OPERA-01 (NCT06016738) is a multicenter, randomized, open-label, phase 3 clinical trial comparing the efficacy and safety of palazestrant as a single agent to SOC ET (fulvestrant, anastrozole, letrozole, or exemestane) in patients with ER+, HER2− MBC that relapsed or progressed on 1-2 prior lines of ET, including a CDK4/6i. Adult patients are eligible with a diagnosis of evaluable ER+, HER2− inoperable locally advanced or MBC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Prior treatments must include 1 or 2 prior lines of ET with the last ET duration of ≥6 months; must have received and have disease progression on CDK4/6i with ET for MBC. Prior chemotherapy for MBC is not allowed. The study included a dose selection phase, where participants were randomized to 90 mg qd or 120 mg qd palazestrant or SOC; enrollment in this phase is complete. After the dose selection of palazestrant, the study will continue with the selected dose compared to SOC ET at a 1:1 randomization. Overall, 510 patients will be randomized to palazestrant or SOC ET during the study. The primary endpoint of progression-free survival will be assessed by blinded independent central review in patients with and without *ESR1* mutations (dual primary endpoint). Secondary endpoints include overall survival, antitumor activity (objective response rate, clinical benefit rate, and duration of response), safety, exposure and patient-reported outcomes in patients with and without *ESR1* mutations. Study recruitment began in November 2023. Clinical trial information: NCT06016738. Research Sponsor: Olema Oncology.

TPS1132 **Poster Session**

Immunologic targeting of native and mutated ESR1 receptor for treatment of hormone receptor expressing metastatic breast cancer.

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Background: Hormone receptor positive (HR+) HER2 negative metastatic breast cancer (MBC) remains a difficult clinical problem. Endocrine therapies have remained the mainstay of therapy for decades and despite combination with targeted agents and development of novel targeted therapies, the 5-year survival rate of MBC remains low. Resistance to ET can occur due to the development of point mutations in the estrogen receptor alpha type I (ESR1), which constitutively activates the receptor, making it resistant to anti-estrogen. We produced a peptide library of the entire wild type (WT) ESR1 and identified four promiscuous peptide epitopes that routinely drive a CD4 Th1 response in healthy donors and breast cancer patients. Additionally, we created overlapping peptides around each known ESR1 mutation site and pulsed them on type I polarized dendritic cells (DC1) also resulting in an increased CD4 Th1 response. We hypothesize that ER alpha receptor can serve as a target for the immune response and ESR1 mutations that develop in HR+ breast cancer patients can be utilized as a neoantigen that will drive CD4 Th1 responses and antibodies that can be developed as an immune based therapy for patients with HR+ MBC. Combining DC1 vaccination with novel endocrine therapies such as Elacestrant, we expect an increase in ESR1 degradation and enhanced antigen presentation leading to an expanded immune and clinical response. **Methods:** In this open pilot study, up to 18 patients with HR+ HER2 negative, ESR1 mutated MBC with measurable or evaluable disease will be enrolled to determine the feasibility and safety of the combination of DC1 vaccines and Elacestrant. Prior use of elacestrant is exclusionary. Eligible patients will undergo apheresis of peripheral blood to collect and create DC1 vaccines. DC1 will be pulsed with ESR1 WT and mutated peptides. Patients will be injected in their groin nodes (or accessible tumor if available) weekly with these pulsed DC1 (20-50 million) for eight consecutive weeks. They will alternate between WT ESR1 DC1s and mutated ESR1 DC1s. Patients will receive combination of DC1 vaccinations and Elacestrant at 345 mg orally daily concurrently during vaccination and continued after. After the initial vaccination series, patients will undergo radiological assessment of their disease, and if no evidence of progression they will receive booster DC1s every four weeks x 3 doses. The primary objective of this pilot study is safety and feasibility. Secondary objectives include preliminary efficacy, biomarkers assessment, safety and patient reported outcomes. Tumor tissue and blood samples will be collected for correlative analyses including ctDNA and changes in variant allele frequency of ESR1 during treatment. The study is open at H. Lee Moffitt Cancer Center. Clinical trial information: NCT06691035. Research Sponsor: V Foundation.

TPS1133 Poster Session

Adaptive designed eniluracil + capecitabine phase 2 trial in advanced or metastatic breast cancer patients.

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Background: Ethynyl-uracil (eniluracil or 6422), an irreversible inhibitor of the dihydropyrimidine dehydrogenase enzyme that metabolizes 5-FU to catabolites, eliminates the formation of 5-FU catabolites and catabolite side effects while exposing cancer cells to more 5-FU and more cancer killing 5-FU anabolites. The combination of a single 40 mg day 1 dose of 6422 followed by Day 2 Capecitabine (6422+Cap) on a 7 day on + 7 day off schedule (7+7) of Capecitabine (Cap) is being evaluated. The dose of Cap used in 6422+Cap will be approximately 15% of the therapeutic dose of Cap used in clinical practice for breast cancer. A Phase 1B study in patients with refractory gastrointestinal (GI) cancer has been completed. The Maximum Tolerated Dose of Cap in 6422+Cap was determined to be 225 mg BID. The Recommended Phase 2 Dose Range of Cap in 6422+Cap was determined to be from 75 mg BID to 225 mg BID. based on the FDA's Optimal Design Guidance and Project Optimus initiative to define the dose-response relationship for both safety and efficacy. Since FDA believed that determining the optimal dosage regimen following the Principles of Project Optimus would be extremely difficult for 6422+Cap in GI cancer given the standard combination chemotherapeutic treatments, the target population was changed to breast cancer patients. FDA also determined that a Phase 1B study in breast cancer would not be required given the GI cancer Phase 1B data. **Methods:** Several Project Optimus focused Phase 2 designs were evaluated. Based on guidance from the FDA, an adaptive, 3 arm, 30 patients/arm, phase 2, open-labelled, randomized trial was selected which would compare 2 regimens of 6422+Cap vs. standard dose of Cap alone. The study would initially enroll patients into 2 treatment arms. The 2 arms are: a 1000 mg/m2 BID monotherapy Cap control group and a 6422+Cap regimen of 40 mg on day 1 followed by day 2 Cap dose of 150 mg BID on 7+7 schedule. Upon completing the enrollment and evaluation of 9-10 patients in each of the first 2 arms, an interim analysis will be conducted to determine the Cap dose to be used in the 6422+Cap 3rd arm. Depending on the interim results, Cap dose in the 3rd arm will either be increased to 225 mg BID or decreased to 75 mg BID. Patients with triple-negative or HR positive/HER2 negative, advanced or metastatic breast cancer are eligible for the study. Patients should have measurable disease in accordance with RECIST 1.1. Patients with stable brain metastases are eligible. The primary endpoint of the study is Objective Response Rate. This will be assessed based on the null hypothesis that the endpoint in each 6422+Cap arm is less than or equal to the monotherapy arm. Additionally, safety will be assessed by the incidence and severity of adverse events across treatment groups. The pharmacokinetics of Cap, 5-FU, and the FBAL catabolite will be evaluated using population PK analysis. Currently 3 patients have been enrolled in the study. Clinical trial information: NCT06568692. Research Sponsor: Processa Pharmaceuticals Inc.

TPS1134 Poster Session

DATO-Base: A phase II study of DATOpotamab deruxtecan for patients with breast cancer brain metastases or leptomeningeal disease.

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Background: Approximately half of patients with metastatic TNBC and one fifth of those with estrogen receptor (ER)+/HER2-negative metastatic breast cancer (MBC) eventually develop breast cancer brain metastases (BCBM), with an adverse prognostic effect. Intracranially penetrant systemic therapies in HER2-negative MBC are very limited. In this setting, antibody-drug conjugates (ADCs) have shown promise, with impressive intracranial activity observed with trastuzumab deruxtecan. Datopotamab deruxtecan (Dato-DXd) is a novel anti-Trop2 ADC with robust antitumor activity in HER2-negative MBC. In the TROPION-Breast01 phase 3 trial, Dato-DXd outperformed chemotherapy for ER+/HER2-negative MBC, and promising early-phase data was also reported in triple-negative MBC. Preclinical data in tumor models found favorable intracranial penetration for Dato-DXd, and encouraging clinical data were reported in patients with lung cancer brain metastases. Based on the relevant unmet need and the promising preclinical and clinical data seen with Dato-DXd, there is a strong rationale in testing Dato-DXd for patients with HER2-negative MBC and BCBM or leptomeningeal disease (LMD). **Methods:** DATO-Base is an ongoing, open label, multicenter, investigator-initiated phase II trial for patients with HER2-negative MBC with active BCBM and/or LMD. Eligible participants are women and men with HER2-negative active (newly diagnosed/untreated or treated/progressive) brain metastases or LMD. Patients are enrolled in one of three cohorts: Cohort A (n = 24) for HR+/HER2-negative BCBM; Cohort B (n = 24) for triple-negative BCBM; Cohort C (n = 10) for HER2-negative LMD (any ER status). Patients in Cohort A require prior treatment with at least one line of endocrine treatment in the metastatic setting; no prior treatment is required for Cohorts B and C. Prior treatment with approved or investigational ADCs is allowed. Participants receive Dato-DXd 6 mg/kg IV on day 1 of each 21-day cycle until progression, unacceptable toxicity, withdrawn consent, noncompliance, or death. The primary endpoint for Cohorts A and B is intracranial objective response rate per RANO-BM criteria. Patients in each cohort will be enrolled based upon Simon two-stage designs: if ≥1/9 patients respond, a total of 24 patients will be enrolled. Cohort C is exploratory, with description of overall survival and exploratory endpoints. Blood and cerebrospinal fluid is being collected at baseline, C2D2, and at progression for translational studies. The trial was activated in December 2023, with enrollment ongoing. Clinical trial information: NCT06176261. Research Sponsor: None.

TPS1135 Poster Session

The efficacy and safety of eutideron, etoposide, and bevacizumab in patients with brain metastases from breast cancer.

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Background: Brain metastases (BM) from breast cancer (BC) are a significant therapeutic challenge, with limited systemic treatment options capable of crossing the blood-brain barrier (BBB). Median overall survival (OS) ranges from 4 to 16 months, influenced by molecular subtype and treatment modality. Triple-negative and HER2-positive subtypes are associated with higher BM incidence. There is a crucial need to explore systemic therapies that address both intracranial and extracranial disease. Eutideron, a novel small-molecule inhibitor with robust CNS penetration, has demonstrated activity against metastatic BC models involving the brain. Early clinical studies suggest its efficacy in advanced BC, with intracranial activity and manageable toxicity. Combining eutideron with etoposide, a cytotoxic agent, and bevacizumab, an anti-VEGF monoclonal antibody, may enhance therapeutic outcomes. Bevacizumab, known for reducing BM-associated edema and improving quality of life, has shown promise in combination regimens but has not been evaluated alongside eutideron and etoposide. This Phase II trial investigates this novel three-drug regimen in patients with recurrent BC and measurable BM. **Methods:** This open-label, single-arm Phase II trial evaluates the efficacy and safety of eutideron, etoposide, and bevacizumab in female patients aged ≥18 years with recurrent metastatic BC and measurable BM. Eligible patients had an ECOG performance status of 0–2, life expectancy ≥12 weeks, and progressed untreated or previously treated BM not requiring immediate local treatment. Baseline brain MRIs confirmed at least one measurable CNS lesion per RANO-BM criteria. The treatment regimen includes eutideron (30 mg/m^2/day, IV, Days 1–5 of a 21-day cycle), etoposide (30 mg/m^2/day, IV, Days 1–3 of a 21-day cycle), and bevacizumab (10 mg/kg, IV, Days 1 and 21 of each cycle). After 4–6 cycles, responders continued bevacizumab maintenance until progression or intolerable toxicity.Primary endpoint: CNS Objective Response Rate (CNS-ORR) per RANO-BM. Secondary endpoints: CNS Clinical Benefit Rate, CNS Progression-Free Survival, Overall Survival, and systemic ORR by RECIST 1.1. Safety was monitored using CTCAE v5.0. The trial, targeting 43 patients across Chinese centers, aims to inform future strategies for BC patients with BM. Clinical trial information: NCT05781633. Research Sponsor: None.

TPS1136 Poster Session

Trial in progress: A study of Bria-OTS cellular immunotherapy in metastatic recurrent breast cancer.

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Background: Metastatic breast cancer is almost always fatal. Objectives: Primary: To evaluate the safety of BC1 cell line immunotherapy in patients with advanced late-stage metastatic breast cancer; Secondary: To evaluate the tumor response to BC1 cellular immunotherapy; Exploratory: To evaluate progression-free (PFS) and overall survival (OS); To evaluate the immune responses elicited by BC1 cellular immunotherapy; To evaluate patient and tumor characteristics that may be predictive of responses to HLA-matched cellular immunotherapy; To evaluate time to subsequent therapy; and To evaluate PFS 2 on subsequent therapy. **Methods:** Study Population: Patients with metastatic recurrent breast cancer after progression on prior therapies. Key Inclusion Criteria: Histologically-confirmed metastatic breast cancer after failure of standard therapies; ≥18 years old; Expected survival of >4 months; Adequate performance status (ECOG ≤2); Adequate hematologic and organ function; Clinically stable with resolution of toxicities from previous treatment to baseline with the exception of alopecia. Key Exclusion Criteria: Concurrent anti-cancer treatment or concurrent cancer; Anti-cancer treatment within 3 weeks of first treatment; History of hypersensitivity to study therapies; New York Heart Association stage 3-4 cardiac disease; Moderate-severe pleural or pericardial effusion; Pregnant or nursing; HIV+; Known immunodeficiency or ongoing treatment with immunosuppressive therapy >10 mg/day prednisone equivalent; Severe psychiatric or other clinically progressive major medical problems. Study Design: This is an open-label study. Phase 1: BC1 cell line alone; Phase 2, Bria-OTS regimen with check point inhibitor (CPI). Phase 1: Patient 1: 20 million cells BC1 intradermally q2 wks x 8 wks (4 doses); Patient 2: 40 million cells of BC1; Patient 3: 60 million cells BC1. If no DLT with BC1 monotherapy, the combinational phase of the study will begin with BC1 and the Bria-OTS regimen q3 wks + CPI. During the Phase 1 combination and Phase 2 expansion phases, all patients will be treated with BC1 cells as part of the Bria-OTS regimen, which includes cyclophosphamide 300 mg/m^2 2-3 days prior to BC1 cell inoculation, and concurrent peg-interferon 0.6 mcg s.c. on the day of BC1 cell inoculation. Imaging studies: At screening, after monotherapy phase, before combination phase, and q9 weeks thereafter for 6 months, then q12 weeks. Patients who had PD but with clinical benefit may continue treatment. Subjects will continue to be followed for time on subsequent therapy (PFS2) and survival q3 mos. for 2 years. The phase 1 monotherapy part of the study has enrolled and treated 3 patients. Clinical trial information: NCT06471673. Research Sponsor: BriaCell Therapeutics Corp.

TPS1137 **Poster Session**

Trial in progress: ENCORE—Multicenter prospective registry of sequential antibody drug conjugates (ADCs) in HER2 negative metastatic breast cancer (MBC) (TBCRC-067).

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Background: Antibody-drug conjugates (ADCs) have demonstrated substantial improvement in progression free survival (PFS) and overall survival (OS) in phase III clinical trials in patients with metastatic triple negative breast cancer (mTNBC) and hormone receptor positive/HER2-negative (HR+/HER2-) metastatic breast cancer (MBC), offering an effective new treatment strategy. Several outstanding questions impact the use of these drugs clinically, and prospective real-world data is needed. First, it is important to understand the safety and efficacy of these agents in a real-world population with diverse patient characteristics. Second, it is critical to understand the safety and efficacy of these ADCs in sequence. Third, it is essential to identify biomarkers that can help clarify mechanisms of response and resistance to ADCs, which may inform future sequencing and treatment strategies. **Methods:** This is a multicenter prospective registry study of patients with HER2-negative MBC who are treated with sequential ADCs per standard of care (SOC) with the goal to understand the safety and efficacy of sequential ADCs in a real-world setting (NCT06774027). A total of 100 participants with HER2-negative MBC will be enrolled in this study, either prior to starting their first ADC per SOC (cohort 1 = HR+/HER2-; cohort 2 = mTNBC) or prior to starting their second ADC per SOC (cohort 3 = HR+/HER2-; cohort 4 = mTNBC). The dual primary endpoints are real-world progression free survival (rwPFS) of ADC1 and rwPFS of ADC2. Secondary endpoints include overall response rate (ORR), duration of response (DOR), best overall response (BOR), disease control rate (DCR), and real-world overall survival (rwOS), and safety for each ADC. Exploratory endpoints include translational correlates of response/resistance to ADCs (e.g., circulating tumor DNA, circulating tumor cells, and tissue spatial correlates) and patient-reported outcomes (PROs). rwPFS and rwOS will be estimated by the Kaplan-Meier method. Statistics will be descriptive. Enrollment to start in the first quarter of 2025. Clinical trial information: NCT06774027. Research Sponsor: Gilead.

TPS1138 Poster Session

Update on phase III pivotal trial of Bria-IMT + CPI vs physician's choice in advanced metastatic breast cancer (BRIA-ABC).

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Background: The SV-BR-1-GM breast cancer cell line activates anti-tumor immunity by expressing tumor associated antigens and secreting GM-CSF which enhances dendritic cell activation and promotes adaptive (T-cell mediated) and innate (dendritic and NK cell) immune responses. The cells are also engineered to optimize immune recognition through pt specific HLA antigen matching. SV-BR-1-GM acts through direct antigen presentation and CD4+ T-cell activation and, when combined w/ checkpoint inhibitors (CPIs), has demonstrated clinical benefit in 54 heavily pretreated metastatic breast cancer (MBC) pts. In pts w/ disease progression following CPI therapy, similar or improved progression free survival (PFS) compared to their prior treatment regimen. Disease control following antibody drug conjugates was observed in 40%of pts. Clinical benefit was seen in 5 out of 8 pts w/ untreated intracranial metastases. CD8+ Immuno-PET imaging suggests systemic activation, w/ increased CD8+ tumor infiltrating lymphocytes at both primary and metastatic tumor sites, as well as lymphoid organs. Optimized sequencing of CPI w/ SV-BR-1-GM and its latest phase 3 formulation have shown enhanced clinical outcomes, including improved overall survival (OS) (median 13.4 mos), PFS (3.6 mos), and clinical benefit rate (CBR; 61%).These findings have informed refinements to the ongoing pivotal, registration enabling Phase 3 trial, designed to optimize pt selection and treatment sequencing strategies. **Methods:** This ongoing multicenter, randomized, open label Phase 3 trial evaluates Bria-IMT + CPI vs. Treatment of Physician's Choice (TPC) in MBC pts lacking approved curative therapies. Pts are randomized 1:1:1 to Bria-IMT + CPI, TPC, or Bria-IMT monotherapy (discontinued after 150 enrollments to prioritize combination arms). The Bria-IMT regimen consists of: Day -2: Cyclophosphamide 300 mg/m^2, Day 0: 20M irradiated SV-BR-1-GM cells, Day 2/3: 0.1 mcg pegylated α interferon at each inoculation site. CPI infusion is administered Day -3 to 3. Cycles q3w. TPC regimens follow site specific SOC. Imaging q6w (first 2 cycles), then q8w. Eligibility includes all MBC subtypes, including CNS mets, and permits prior CPI therapy ($>$21 days pre-treatment). There will be 100 sites across the U.S., Canada, and ex-North America w/ an enrollment target of 404. The trial is currently active at 59 sites with 217 sub investigators. To date, 67 pts screened: 46 randomized (median age 56 yrs [34–83], median 6 [2–13] prior lines of therapy. The primary endpoint is OS, with an interim analysis at 144 events targeting a hazard ratio of 0.6. Secondary endpoints: PFS, overall response rate, CBR, CNS event free survival, and TWiST. Safety analyses ongoing; pt reported outcomes assess subjective treatment impact. Clinical trial information: NCT03328026. Research Sponsor: BriaCell Therapeutics Corp.

TPS1139 Poster Session

Efficacy and safety of disitamab vedotin in combination with RC148 versus albumin-bound paclitaxel ± toripalimab for patients with HR-negative HER2-low-expressing unresectable locally advanced or metastatic breast cancer: An open-label, randomized, controlled phase II study.

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Background: Patients (pts) with hormone receptor (HR)-negative and HER2-low-expressing (defined as IHC 1+, or IHC 2+/ISH-) advanced breast cancer have poor prognosis and more effective treatment options are needed. Disitamab vedotin (DV) is a novel humanized anti-HER2 antibody conjugated with monomethyl auristatin E (MMAE) via a cleavable linker. DV alone or in combination with a PD-1 inhibitor showed encouraging antitumor activities with manageable safety in pts with HER2-low-expressing (IHC 1+, or IHC 2+/ISH-) advanced or metastatic breast cancer, gastric cancer and other solid tumors (Wang J., et al., *Cancer Commun*, 2024; Wang Y., et al., *eClinicalMedicine*, 2024). RC148 is a bispecific monoclonal antibody directed against programmed death receptor-1 and vascular endothelial growth factor receptor. DV+RC148 combination is expected to exert a synergistic antitumor effect by improving the tumor immune microenvironment. We aim to evaluate the efficacy and safety of DV plus RC148 versus albumin-bound paclitaxel ± toripalimab in pts with HR-negative HER2-low-expressing advanced breast cancer in this randomized phase II trial (NCT06642545). **Methods:** The key eligibility criteria are pts aged 18 years or older with unresectable stage III or stage IV breast cancer, negative HR status, low HER2 expression (defined as IHC1+, or IHC2+/ISH-), no previous chemotherapy for locally recurrent or metastatic disease, and no disease recurrence within 6 months after treatment completion (within 12 months if using taxanes) if with radical treatment. Pts who previously received anti-HER2 therapy or immunotherapy are excluded (except pts receiving neoadjuvant/adjuvant PD-[L]1 inhibitors 12 months prior to recurrence or progression). Pts will be randomized (stratified by PD-L1 expression status: positive or negative) in a ratio of 1:1 to receive DV (2.0 mg/kg) plus RC148 (20 mg/kg) intravenously once every two weeks or to receive albumin-bound paclitaxel (125 mg/m^2 day 1 and day 8) ± toripalimab (240 mg day 1) intravenously every three weeks until occurrence of disease progression or intolerable toxicity. The primary endpoint is objective response rate (ORR) in all pts per investigator's assessment according to RECIST v1.1. The secondary endpoints are ORR in the PD-L1-positive pts; investigator-assessed progression-free survival, disease control rate, duration of response, and overall survival in all pts and the PD-L1-positive pts. This study was initiated in August 2024. Clinical trial information: NCT06642545. Research Sponsor: RemeGen Co., Ltd.

TPS1140 **Poster Session**

A phase II trial to assess the impact of β2 adrenergic receptor (β2-AR) blockade in metastatic triple negative breast cancer (mTNBC).

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Background: In PD-L1+ mTNBC patients (pts), the standard of care treatment is chemotherapy and pembrolizumab (P) in the first-line setting. Our group and others have demonstrated that chronic β2-AR signaling suppresses $CD8^+$ cytotoxic T lymphocytes (CTL) function, drives their exhaustion, and increases the number of immunosuppressive myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) in the tumor microenvironment (TME), thus supporting tumor proliferation. Consequently, abrogation of β-AR signaling using the pan β-blocker propranolol or $\beta\text{-AR}^{-/-}$ knockout mice increased the intratumoral frequency of CTLs and elevated the CTL:Treg ratio (Bucsek et al. Cancer Res. 2017; PMID: 28819022). Similarly, mouse tumor models also demonstrated decreased exhaustion markers (PD1, TIM3, LAG3) on CTLs when β-AR was blocked, via propranolol (Qiao G et al. Cancer Immunol Res. 2021, PMID: 33762351). Confirming this phenomenon, we have shown, in a prospective clinical trial in metastatic melanoma, that β-AR blockade with propranolol significantly increased response to P with an objective response rate (ORR) of 78%, as opposed to 30-40% with P alone (Gandhi et al. Clin Cancer Res 2021, PMID: 33127652). Moreover, clinical β-AR blockade was associated with higher immune infiltration in the TME (Hiller JG, Clin Cancer Res 2020, PMID: 31754048). Therefore, we hypothesize that using propranolol with chemotherapy and P should improve response for pts with newly metastatic PD-L1+ TNBC. **Methods:** This is a phase II single-arm, non-randomized multi-center study. Pts are women ≥18 yrs with PD-L1+ mTNBC, who will receive propranolol, chemotherapy (paclitaxel, nab-paclitaxel, gemcitabine-carboplatin) and P in the upfront setting: chemotherapy on days 1, 8 and P on day 1 every 3 weeks in addition to propranolol 30 mg BID, with intra-pt propranolol dose-escalation by 10 mg BID weekly to a total of 80 mg BID as tolerated by blood pressure and heart rate as natural biomarkers for dose. Treatment will continue until disease progression per RECIST. The primary endpoint is ORR, defined as complete or partial response. The secondary endpoint is safety, 6-month progression-free and overall survival. As an exploratory endpoint, changes in TME and blood immune markers will be assessed. In stage 1, n1=23 evaluable pts will be enrolled. If ≥ 13/23 responses are observed, then the study will continue to enroll another n2=14 pts for a total of n=37, otherwise will be suspended for futility. If ≥ 24/37 responses are observed, then the proposed therapy will be considered promising. Pre- and 6-week post-treatment tumor biopsies and blood samples will be analyzed for changes in stress-induced biomarkers (epinephrine, norepinephrine, and frequency of CTL, MDSC, Treg) and exhaustion markers (PD1, TIM3, LAG3). The study is currently open and has accrued one patient. Clinical trial information: NCT05741164. Research Sponsor: NIH (NCI).

TPS1141 Poster Session

Emiltatug ledadotin (Emi-Le): A B7-H4-directed dolasynthen antibody-drug conjugate (ADC) being investigated in phase 1 dose expansion in patients with triple negative breast cancer who received at least one prior topoisomarase-1 inhibitor ADC.

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Background: Breast cancer is the leading cause of cancer death for women worldwide, with triple-negative breast cancer (TNBC) considered one of the more aggressive breast cancers, accounting for ~15% of all cases. Unfortunately, there remains an unmet medical need for effective and well-tolerated treatments for advanced/metastatic TNBC; in heavily pretreated patients, standard-of-care single-agent chemotherapy has limited efficacy, with response rates of ~5%, PFS ~7 weeks. Emiltatug ledadotin (Emi-Le; XMT-1660) is a B7-H4-directed Dolasynthen ADC designed with a precise, target-optimized drug-to-antibody ratio (DAR 6) and a proprietary auristatin F-HPA microtubule inhibitor payload with controlled bystander effect. The FDA has granted Emi-Le two Fast Track designations for the treatment of adult patients with breast cancer, including patients with TNBC who have previously been treated with topoisomerase-1 inhibitor (topo-1) ADCs. Initial dose escalation clinical data from the ongoing Phase 1 trial at doses ranging from 38.1-67.4 mg/m2 per cycle demonstrated a 23% confirmed response rate in patients with B7-H4 high TNBC who were heavily pretreated all of whom received at least one prior topo-1 ADC. **Methods:** Based on encouraging clinical activity and tolerability data in the initial dose escalation data, the expansion portion (EXP) of the Phase 1 trial has been initiated and is actively enrolling patients. EXP has a Simon 2-stage design and will evaluate two doses in patients with advanced/metastatic TNBC who have received 1-4 prior lines of systemic therapy, including at least one topo-1 ADC. Patients will be evaluated for B7-H4 expression prospectively by IHC and will be stratified into B7-H4 TPS "high" and B7-H4 TPS "low" cohorts. The first EXP dose is 67.4 mg/m2 Q4W. Dose exploration is ongoing to identify a potential second higher EXP dose. The protocol includes the option for multiple additional indications, including HR+/HER2- breast cancer, endometrial cancer, ovarian cancer, and ACC-1. Clinical trial information: NCT05377996. Research Sponsor: Mersana Therapeutics.

TPS1142 Poster Session

TBCRC 058: A randomized phase II study of enzalutamide, enzalutamide with mifepristone, and treatment of physician's choice in patients with androgen receptor-positive metastatic triple-negative or estrogen receptor-low breast cancer (NCT06099769).

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Background: Triple-negative breast cancer (TNBC) refers to a heterogenous group of breast cancers (BC) that lack expression of ER, PR, and HER2. Despite recent advances with immunotherapy (IO) and antibody-drug conjugates (ADCs), TNBC remains the most aggressive subtype, characterized by a high risk of recurrence and a short overall survival in the metastatic setting. BCs with low levels of ER and PR expression (1-10%) clinically behave like TNBC, and clinical management follows the TNBC treatment (tx) paradigm. We and others have identified a subset of ER/PR/HER2 negative breast cancers (BC) that express the androgen receptor (AR). Enzalutamide (enza), an AR-antagonist, has demonstrated activity in AR+ metastatic TNBC (Traina et al, JCO 2018). Activation of the glucocorticoid receptor (GR) has been implicated as a mechanism of resistance to AR inhibition in prostate and BC (Kach et al, Sci Transl Med 2015). Advanced TNBC remains an area of unmet need, particularly in patients who are ineligible for or progress following a checkpoint inhibitor. This randomized study will evaluate the efficacy of enza or enza plus the GR antagonist mifepristone (mif) as compared to physician's choice chemotherapy (TPC). **Methods:** This is a randomized phase II trial; 201 patients (pts) will be randomized 1:1:1 to enza, enza with mif, or TPC (carboplatin, paclitaxel, eribulin, or capecitabine). The primary endpoint (endpt) is progression free survival (PFS), and the trial is designed to test the hypothesis that PFS in the pooled enzalutamide arms is superior to TPC; there is 80% power to detect a hazard ratio (HR) of 0.70, corresponding to increase in PFS from 3.5 months (mos) with TPC to 5.0 mos with enza-based tx. Secondary endpts include pairwise comparisons of PFS among the 3 arms and evaluation of response rate, clinical benefit rate, duration of response, overall survival, safety/toxicity, and patient-reported outcomes by arm. Exploratory endpts include correlation of tumor and circulating markers (constitutively active AR variants in circulating tumor cells and circulating tumor cell DNA) with tx response. Eligible pts must have: ECOG 0-2, metastatic ER/PR low or negative, HER2 0-2+ (FISH not amplified) (BC), measurable or evaluable disease (dz) per RECIST v1.1, $<$ 3 prior lines of chemotx, any # prior endocrine txs, no prior anti-AR tx or CYP17 inhibition, no prior mif. Pts with PD-L1+ BC must have received prior IO if not contraindicated. Tumors must have AR $>$10%, normal organ function, no history of brain mets. As of 1/23/25, 11 of 201 pts have begun protocol-specified tx. Clinical trial information: NCT06099769. Research Sponsor: Breast Cancer Research Foundation; TBCRC; Astellas; Corcept; The TaTa Sisterhood Foundation; Pfizer.

TPS1143 Poster Session

AXALAP: Phase Ib study of axatilimab in combination with olaparib in *BRCA1/2* and *PALB2*-associated metastatic HER2-negative breast cancer (BC).

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Background: Poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) have revolutionized the treatment of patients (pts) with germline *BRCA1/2* (gBRCA)-associated HER2-negative BC. However, resistance eventually occurs in almost all pts. Tumor-associated macrophages (TAMs), a key component of the BC tumor microenvironment, are highly immunosuppressive and associated with poor clinical outcomes. In preclinical immunocompetent models of BRCA-associated BC, PARP inhibition induces suppressive CSF-1R+ TAMs, contributing to resistance, so that combining anti-CSF-1R therapy with PARPi significantly enhances progression free survival (PFS) compared to PARPi monotherapy (190d vs 92d). Axatilimab (SNDX-6352; Ab969.g2), a humanized IgG4 monoclonal antibody targeting CSF-1R, reduces TAMs, potentially slowing tumor growth and enhancing anti-tumor immunity. In the Phase I SNDX-6352-0502 study for advanced solid tumors, axatilimab showed tolerability at the highest dose (6 mg/kg), with biomarker modulation observed at doses as low as 1 mg/kg. Axatilimab is FDA-approved for chronic graft-versus-host disease (cGVHD). **Methods:** AXALAP (NCT06488378) is a non-randomized open-label, proof-of-concept phase 1 study designed to evaluate axatilimab 1mg/kg or 3mg/kg every 2 weeks in combination with olaparib 300 mg twice daily in pts with somatic or germline *BRCA1/2*- and *PALB2*-associated HER2-negative metastatic BC. Patients must be PARPi naïve, or have not progressed on prior PARPi, and have received up to 2 prior lines of chemotherapy for metastatic disease. Pts will receive a two-week lead-in of olaparib monotherapy, followed by combined olaparib and axatilimab. Pts will undergo mandatory tumor biopsies pre-treatment, after the 2-week olaparib lead-in, and after 2 cycles of olaparib/axatilimab, with an optional biopsy at time-of-progression. Primary objectives are to establish the maximum tolerated dose (MTD) and recommended phase 2 dose and to assess the safety and tolerability of axatilimab and olaparib. Secondary objectives include assessment of changes in CSF-1R+ CD163+ macrophage levels after olaparib monotherapy and after 2 cycles of combination treatment at the MTD; to determine the objective response rate and the median PFS of the combination per RECIST 1.1 criteria. The MTD will be determined by Bayesian Optimal Interval (BOIN) design. Pts will be treated in cohorts of 3 with a maximum of 10 at each dose. If the MTD is identified as 3mg/kg, we will complete enrollment of 10 pts at 1 mg/kg to assess biological effectiveness and clinical efficacy of the lower dose. We expect to treat up to 20 pts, who will receive study treatment until development of unacceptable toxicity or disease progression. Enrollment began on 5/2024 at Dana-Farber Cancer Institute and the trial will also open at Beth Israel Deaconess Medical Center and Mayo Clinic-Rochester. Clinical trial information: NCT03604692. Research Sponsor: Incyte; U.S. National Institutes of Health; U.S. National Institutes of Health.